Sharon Kimble
(S.E.N.,R.G.N.)

# *Herbal Hormones*

Version - 2016-1
Version - 1.0.8713

Version 1.0.8713– – Document LaTeXed – 1st January 2016
[git] • Branch: Version_1 @ a8a068f • Release: 1.0 (2016-01-01)

# Contents

Chapter 1

# Preface

## Disclaimer

The author of this ebook has used her best efforts in preparing this ebook and the information contained in it. This book is distributed as is, without warranty of any kind, either express or implied, respecting the contents of this ebook, including but not limited to implied warranties for the ebook's quality, performance, or fitness for any purpose. The author and any dealers and distributors shall not be liable to the purchaser or any other person or entity with respect to liability, loss, or damages caused or alleged to have been caused directly or indirectly by this ebook. This document is provided as is.

The author takes no responsibilities for any problems, damages, or loss of sanity resulting from improper usage of herbals. If you are in any doubt, do NOT take the tablets, or whatever but post a question to your relevant newsgroup or refer to a competent medical doctor or endocrinologist. Messing about with something you do not understand may seriously damage your health. YOU HAVE BEEN WARNED.

## This document

This document started life as a chapter in "Universal Hormones 2015" but was soon removed and developed here.

# Acknowledgements

Thanks to all the people, too many to list individually, who contributed to my research for this ebook. Any errors or omissions are nobodies fault except my own, but I would also refer you back to the disclaimer.

# Creative Commons



# Please note . . .

Certain sections of side-effects text will be highlighted like this -

**common**
**moderate**
**warning**
**danger**
**overdose**

These represent the five categories of side-effects and their warnings, in descending order of importance.

**other possible side-effects**

*In some places you may see a little* ***black text on boxed green background*** *round a word or two, these show that they are a common side-effect.*

*You may also see* ***black text on boxed magenta background*** *which shows a moderately common side-effect.*

*Or* ***black text on boxed blue background*** *is a warning that something is amiss and needs attending to.*

*A* ***black text on boxed red background*** *shows a dangerous side-effect which should be notified extremely soon, if not now, to your local GP, Doctor, Endocrinologist, or Hospital.*

*A* ***black text on boxed violet background*** *shows an overdose. Speak to your local GP, Doctor, Endocrinologist, or Hospital As Soon As Possible, if not sooner!*

*Possible* ***other side-effects*** *are shown in a tan-coloured box like this one.*

Pharmaceutical drugs are highlighted as black underlined text on a pale yellow stripe.

# About the author

My name is Sharon Kimble, and I am a retired Registered General Nurse and State Enrolled Nurse, living in the United Kingdom.

I have approached this subject with the idea and question of 'What information would I want to know about this herbal preparation if I were going to start taking it?'

Sharon Kimble
My email address
1st January 2016

I have for a long time stated that herbal hormones are a waste of time and money, however I have changed my views slightly with regard to Pueraria. Have a look and see :).

I have also included my own thoughts and comments on each herb in a section labelled "Commentary", which is indexed in the "General Index" under the heading of "Commentary".

Chapter 2

# README FIRST

This chapter gives a quick introduction to the most important parts of *"Herbal Hormones"*. The rest of the book is basically a verbose version of this chapter. You should start by reading this chapter, as it summarises all the herbs, giving their name, uses, and common side-effects. For more detailed information you can read their main entries.

If you want to know more about herbalism and how it works, you can read the Introduction. Or you can jump right in and read your favourite herb in this chapter and then click on the herbs name at the end of its section to jump straight to its main entry.

If you want to know more about the coloured boxes of the side-effects, then jump to Please note . . . .

If you want to see the difference between *side-effects* and *adverse effects*, then jump to Side-effects vs. Adverse effects.

Whatever, I hope you read it and enjoy what you're learning. If you have any questions you can email me on my email address at the end of Chapter 1, and I'll endeavour to help.

# Alfalfa

## Uses

Alfalfa is used for kidney conditions, bladder and prostate conditions, and to increase urine flow. It is also used for high cholesterol[1], asthma, osteoarthritis, rheumatoid arthritis, diabetes, upset stomach, and a bleeding disorder called thrombocytopenic purpura. People also take alfalfa as a source of vitamins A, C, E, and K4; and minerals calcium, potassium, phosphorous, and iron.

## Common side-effects

Alfalfa seeds and sprouts can be contaminated with such pathogens as Salmonella enterica and Escherichia coli (Van Beneden, Keene, and Strang, 1999), (Mahon, Ponka, and W. N. Hall, 1997), (CDC, 1997), (Christy, 1999). Most healthy adults exposed to salmonella or Escherichia coli will have symptoms such as

- **diarrhoea**,
- **nausea**,
- **abdominal cramping**, and
- **fever**

that are self-limiting. The E. coli infection can lead to haemolytic uremiac syndrome with kidney failure or death in children or the elderly. The Food and Drug Administration (FDA) issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts (Christy, 1999). Ingestion of dried alfalfa preparations[2] is generally without important side effects in healthy adults (Drugs.com, 2009).

## Further information

This can be found at Alfalfa

[1] a fatty substance known as a lipid and is vital for the normal functioning of the body

[2] a mixture made for medicinal use

# American Ginseng

## Uses

American ginseng is used for low iron in the blood (anaemia), insomnia[3], diabetes, nerve pain, erectile dysfunction (ED), fever, hangover symptoms, attention deficit-hyperactivity disorder (ADHD), blood and bleeding disorders, cancer, painful joints, dizziness, headaches, convulsions, fibromyalgia, atherosclerosis[4], memory loss, and as an anti-aging aid.

## Common side-effects

All medicines may cause side effects, but many people have no, or minor, side effects. Check with your doctor if any of these most common side effects persist or become bothersome -

- **Agitation, diarrhoea,**
- **headache, nervousness, trouble sleeping**.

## Further information

This can be found at American Ginseng

# Angelica

## Uses

Loss of appetite, peptic discomforts such as mild spasms of the gastrointestinal tract, feeling of fullness, flatulence[5] (herbalgram, 1990a).

## Common side-effects

- **Sensitive to sunlight** and
- **sensitive to UV radiation** (ABC, 2000).

[3] difficulty in going to sleep or in getting enough sleep

[4] hardening of the arteries

[5] flatulence is passing gas from the digestive system out of the back passage. It's more commonly known as "passing wind", or "farting"

### Further information

This can be found at Angelica.

## Anise

### Uses

Anise has been used as a flavouring in alcohols, liqueurs, dairy products, gelatins, puddings, meats, and candies, and as a scent in perfumes, soaps, and sachets. The oil has been used to treat lice, scabies, and psoriasis. Anise frequently is used as a carminative[6] and expectorant[7]. Anise also is used to decrease bloating[8] and settle the digestive tract in children. In high doses, it is used as an anti-spasmodic and an antiseptic[9] and for the treatment of cough, asthma, and bronchitis.

### Common side-effects

Safe to use in small doses (unknown, 2015c).

### Further information

This can be found at Anise.

## Asian Ginseng

### Uses

Treatment claims for Asian ginseng are numerous and include the use of the herb to support overall health and boost the immune system. Traditional and folk uses of ginseng include improving the health of people recovering from illness; increasing

[6] relieving flatulence

[7] promoting or facilitating the secretion or expulsion of phlegm, mucus, or other matter from the respiratory tract

[8] abdominal distension due to swallowed air or intestinal gas

[9] prevents infection by inhibiting the growth of infectious agents

a sense of well-being[10] and stamina; improving both mental and physical performance; treating erectile dysfunction, hepatitis[11] C, and symptoms related to menopause; and lowering blood glucose and controlling blood pressure.

### Common side-effects

A common side effect of Asian ginseng may be

- **insomnia**, along with other side effects which can include
- **nausea**,
- **headaches**,
- **nose bleeds**,
- **high blood pressure**,
- **low blood pressure**, and
- **breast pains**. Some people have experienced
- **diarrhoea** and
- **skin eruptions** (unknown, 2014h).

### Further information

This can be found at Asian Ginseng.

## Basil

### Uses

Basil has long been considered an anti-depressant. It makes an excellent tea that acts on the adrenal cortex, and it can help the body stimulate hormones[12] that regulate the body's natural response to stress. For this reason, many people believe that basil has uplifting properties. Basil may also be able to improve memory, and it is often utilised to overcome the effects of jet lag. Basil has been commonly found in a variety of treatments for diarrhoea, intestinal parasites, fevers, and skin infections. It is also thought to imitate oestrogen,

[10] The state of feeling healthy, happy, and content. Well-being is affected by things such as physical and mental health, income, education, social support, attitude, values, stress, security, and other qualities of life

[11] A group of diseases in which the liver becomes enlarged and inflamed, causing fever, nausea, vomiting, abdominal pain, and dark urine

[12] a group of chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be manufactured

and may help regulate the menstrual cycle. In addition, basil may stimulate the immune system and lower the uric acid content that is responsible for arthritis and gout. Basil can also be used to treat the pain and inflammation of arthritis (herbwisdom, 2015a).

### Common side-effects

Because basil can enhance the effectiveness of insulin and blood glucose-lowering medications, people with diabetes and those using such medication should use the herb with caution and only under the guidance of a professional health care provider (Resource, 2015b).

### Further information

This can be found at Basil.

## Black Cohosh

### Uses

Modern day use of black cohosh is most commonly for menopausal symptoms but also Premenstrual Syndrome (PMS) and irregular periods (Resource, 2015c).

### Common side-effects

Side effects with black cohosh are generally mild and rare. They include

- **stomach upsets** and
- **nausea**. Other side effects that have been noted are
- **low blood pressure**,
- **headache**,
- **dizziness** (Resource, 2015c).

The most common side effects are -

- **vomiting**, or
- **skin rashes**.

### Further information

This can be found at Black Cohosh.

# Borage

## Uses

Borage seed oil is used for skin disorders including eczema[13], seborrheic dermatitis[14], and neurodermatitis[15]. It is also used for rheumatoid arthritis (RA), stress, PMS, diabetes, attention deficit-hyperactivity disorder (ADHD), acute respiratory distress syndrome (ARDS), alcoholism, pain and inflammation, and for preventing heart disease and stroke.

Borage flower and leaves are used for fever, cough, and depression (WMD, 2009a).

## Common side-effects

- **Nausea**,
- **cramping**,
- **bloating** and
- **headache** are side effects that Borage can cause, although they are relatively mild (herbwisdom, 2015c).

### Further information

This can be found at Borage.

# Caraway

## Uses

Caraway seems to be a natural treatment for dyspepsia[16], hysteria, and similar disorders. Also it is believed to be an effective stomachic[17] (Resource, 2015e).

[13] Eczema is a term for a group of medical conditions that cause the skin to become inflamed or irritated

[14] Seborrheic dermatitis, or seborrhea, is a common skin disease that causes a red, itchy rash with white scales

[15] Neurodermatitis is a chronic skin condition in which the skin becomes inflamed and is extremely itchy

[16] painful, difficult, or disturbed digestion, which may be accompanied by symptoms such as nausea and vomiting, heartburn, bloating, and stomach discomfort

[17] serves to tone the stomach, improving its function and increasing appetite

### Common side-effects

Caraway oil can cause

- **belching**,
- **heartburn**[18], and nausea when used with peppermint oil. It can cause
- **skin rashes** and
- **itching** in sensitive people when applied to the skin.

### Further information

This can be found at Caraway.

## Chaste tree/berry

### Uses

Modern uses of chaste tree berry include reduction of PMS, menstrual cramps[19] and other pre-menopausal symptoms.

Acne, benign prostatic hyperplasia (BPH), fibrocystic breast disease, impotence, female infertility, lactation, menopausal symptoms, menstrual irregularities, PMS, progesterone insufficiency (medscape, 2015b).

### Common side-effects

Generally regarded as safe; mild and reversible adverse effects[20] include -

- **itching**,
- **rash**,
- **headache**,
- **fatigue**,
- **acne**, and
- **menstrual disturbances**.
- **cramping**,

[18] a burning sensation in the chest that can extend to the neck, throat, and face

[19] spasmodic contractions of the uterus, such as those occurring during menstruation, usually causing pain in the abdomen that may radiate to the lower back and thighs

[20] An unwanted side-effect

- **diarrhoea**,
- **hair loss**,
- **stomach pain**,
- **tiredness**.

### Further information

This can be found at Chaste Tree/Berry

## Cranberry

### Uses

urinary tract infection (UTI) (prevention), urinary deodoriser for incontinent patients, type 2 diabetes, chronic[21] fatigue syndrome, scurvy, pleurisy, as a diuretic[22], antiseptic, antipyretic[23], and cancer (medscape, 2015c).

### Common side-effects

- **Upset stomach**,
- **nausea**, and/or
- **vomiting**,
- **diarrhoea** (drugs.com, 2015d).

### Further information

This can be found at Cranberry.

[21] constant

[22] a substance that promotes the production of urine

[23] something that reduces fever or quells it

# Damiana

## Uses

Damiana has both diuretic and antiseptic properties and has been used as an herbal treatment for UTIs such as bladder and urethra[24] inflammation. Damiana is a mild laxative[25] and can be useful in the treatment of constipation. It's used in folk medicine to treat asthma and bronchitis, particularly in Indian herbal medicine (Resource, 2015h).

## Common side-effects

Damiana is relatively safe in regular doses although the long-term effects of its use have not been tested (Resource, 2015h).

### Further information

This can be found at Damiana.

# Dill

## Uses

Dill herb is used for prevention and treatment of diseases and disorders of the gastrointestinal tract, kidney and urinary tract, for sleep disorders, and for spasms.

## Common side-effects

Side effects from the consumption of dill are very rare.

### Further information

This can be found at Dill.

[24] the organ that carries the urine out of the bladder and outside your body

[25] substances that loosen stools and increase bowel movements

# Dong quai

## Uses

Stimulate normal menstrual flow, prevent cramping, PMS, and menopausal symptoms.

Anaemia, constipation, dysmenorrhoea[26], hypertension, psoriasis, rheumatism, skin depigmentation, ulcers (medscape, 2015e).

## Common side-effects

- **Sensitivity in the sun**,
- **nausea**,
- **dizziness** and
- **headaches**.

## Warning

Because dong quai may act like oestrogen in the body, you should not take it with hormone medications except under your doctor's supervision (unknown, 2015d).

### Further information

This can be found at Dong Quai.

# Fennel

## Uses

Fennel is often used for colic, flatulence, irritable bowel, kidneys, spleen, liver[27], lungs, suppressing appetite, breast enlargement, promoting menstruation[28], improving digestive system, milk flow and increasing urine flow. Fennel is also commonly used to treat

[26] painful menstrual periods

[27] A large organ located in the right upper abdomen. It stores nutrients that come from food, makes chemicals needed by the body, and breaks down some medicines and harmful substances so they can be removed from the body

[28] the periodic discharge from the vagina of blood and tissues from a nonpregnant uterus

amenorrhoea[29], angina, asthma, anxiety, depression, heartburn, water retention, lower blood pressure, boost libido, respiratory congestion, coughs and has been indicated for high blood pressure and to boost sexual desire.

### Common side-effects

- **Mild rash**,
- **itching** (Drugs.com, 2014).

### Further information

This can be found at Fennel.

## Fenugreek

### Uses

Appetite stimulant[30], atherosclerosis, constipation, diabetes, dyspepsia/gastritis, fevers, kidney ailments, hyperlipidemia/hypertriglyceridemia, lactation promotion, local inflammation (topical) (medscape, 2015g).

### Common side-effects

Possible side effects of fenugreek when taken by mouth include

- **wind**,
- **bloating**, and
- **diarrhoea**. Fenugreek can cause
- **skin irritation**.

### Further information

This can be found at Fenugreek.

[29] absence of menstruation

[30] temporarily increase alertness and energy

# Hops

## Uses

Anxiety, insomnia and other sleep disorders, restlessness, tension, excitability, ADHD, nervousness, and irritability (medscape, 2015h).

## Common side-effects

Possibly **contact dermatitis** (medscape, 2015h).

### Further information

This can be found at Hops.

# Kudzu

## Uses

Few uses backed up by clinical data[31].

## Common side-effects

No side-effects have been reported in clinical studies when kudzu is taken by mouth (webmd, 2009).

### Further information

This can be found at Kudzu.

# Liquorice

## Uses

Arthritis, bronchitis, dry cough, peptic ulcers, gastritis, infections (bacterial/viral), prostate cancer, sore throat, systemic lupus erythematosus (SLE), upper respiratory inflammation (herbwisdom, 2015k).

[31] facts and information

### Common side-effects

- **Muscle pain** or
- **numbness in the arms and legs**.

### Further information

This can be found at Liquorice.

## Marijuana

### Uses

Decrease intraocular pressure, analgesia, anti-emetic[32] effects, appetite stimulant (medscape, 2015i).

### Common side-effects

Use of marijuana can cause

- **dry mouth**,
- **nausea**,
- **vomiting**,
- **dry or red eyes**,
- **heart and blood pressure problems**,
- **lung problems**,
- **impaired mental functioning**,
- **headache**,
- **dizziness**,
- **numbness**,
- **panic attacks**,
- **hallucinations**,
- **flashbacks**,
- **depression**, and
- **sexual problems**.

### Further information

This can be found at Marijuana.

[32] causing vomiting

# Milk thistle

## Uses

Alcoholic liver disease, appetite stimulant, gallbladder problems, hepatic cirrhosis, chronic hepatitis, hepatotoxic[33]ity (chemical/drug-induced), jaundice, pleurisy, prostate cancer, spleen diseases (medscape, 2015j).

## Common side-effects

Milk thistle is generally regarded as safe. Side effects are usually mild and may involve -

- **Stomach upset**,
- **diarrhoea**,
- **nausea and vomiting**,
- **rash (from touching milk thistle plants)**.
- **abdominal bloating**,
- **abdominal fullness or pain**,
- **anorexia**,
- **dyspepsia**,
- **flatulence**.

### Further information

This can be found at Milk Thistle.

# Pueraria

## Uses

Menopausal symptoms, like low libido, and osteoporosis, aging, breast enhancement, improving your skin, and weight loss, and antioxidant[34] properties, and also as an insecticide[35].

[33] damaging to the liver

[34] a substance that in small amounts will inhibit the oxidation of other compounds. Also see Free radicals and antioxidants

[35] a substance used to kill insects

### Common side-effects

Possibly making the menstrual cycle longer.

## Further information

This can be found at Pueraria.

# Red clover

### Uses

Hot flashes[36]/flushes, PMS, Lowers cholesterol, helps prevent osteoporosis, reduces possibility of forming blood clots and arterial plaques[37], can limit development of BPH. Breast enhancement and breast health. Improve urine production, circulation of the blood and secretion of bile. They also act as detergent, sedative[38] and tonic[39]. Red clover has the ability to loosen phlegm and calm bronchial spasms. The fluid extract[40] of red clover is used as an anti-spasmodic[41] and alterative[42] (herbwisdom, 2015n).

### Common side-effects

- **headache**,
- **nausea**, and
- **rash**.

## Further information

This can be found at Red Clover.

[36]A sudden, temporary onset of body warmth, flushing, and sweating (often associated with menopause)

[37]accumulations of blood cells, fats, and other substances that may build up in blood vessels, possibly reducing or blocking blood flow

[38]a drug that calms a patient, easing agitation and permitting sleep

[39]patent medicine that claims to have tonic properties

[40]A substance made by soaking an herb in a liquid that removes specific types of chemicals. The liquid can be used as is or evaporated to make a concentrate or a dry extract for use in capsules or tablets

[41]preventing spasms

[42]causing alteration

# Sage

## Uses

Aiding digestion, Alzheimer's disease, asthma, bacterial and fungal infections, biliousness, bites, calming and stimulating the nervous system, candida, colds, coughs, dental abscesses, diarrhoea (infantile), dysmenorrhoea, encouraging healing, excessive menstrual bleeding, flatulent dyspepsia, gastrointestinal upset, gingivitis, glossitis, headache (nervous), hot flashes (menopausal sweats) hyperhidrosis, improving memory, indigestion, infected gums, intestinal infection, insect bites, irregular and scanty periods, joint paint, kidney problems, lack of appetite, lethargy, liver complaints, lungs or stomach haemorrhaging, measles, mouth ulcers, night sweats, oral inflammation, palsy, perspiration (excessive), pharyngitis, phthisis[43], quinsy, reducing lactation, rheumatism, rhinitis, skin, throat, mouth and gum infections, soothing the digestive tract, stimulating upper digestive secretions, intestinal mobility, bile flow, and pancreatic function, stings, stomatitis[44], strengthening the nervous system, throat infections, typhoid fever, uvulitis, vaginal discharge. Taken internally or as a gargle or mouthwash; galactorrhoea[45], hyperhydrosis, inflammations of the mouth, tongue or throat.

## Common side-effects

- **stomach discomfort**,
- **nausea**,
- **vomiting** or
- **abdominal discomfort**.

## Further information

This can be found at Sage.

[43] a name for any disease that causes wasting of the body, but the term is especially applied to pulmonary tuberculosis

[44] an inflammation of the lining of any of the soft-tissue structures of the mouth. Stomatitis is usually a painful condition, associated with redness, swelling, and occasional bleeding from the affected area

[45] milky secretion from the breasts

# Saw palmetto

## Uses

BPH. Increasing breast size, improving sexual vigour and as an aphrodisiac[46]. Stimulating hair growth, colds, coughs, irritated mucous membranes, sore throat, asthma, chronic bronchitis, migraines and cancer. Prostate cancer. Nutritive tonic, relieving the symptoms of menstruation, improving muscle tone and muscle building.

## Common side-effects

- **headache**,
- **nausea**,
- **dizziness**
- **vomiting**,
- **constipation**,
- **diarrhoea**.

### Further information

This can be found at Saw Palmetto.

# Soy

## Uses

Menopausal vasomotor symptoms[47], osteoporosis, decrease risk[48] of breast cancer, cardiovascular disease (medscape, 2015m)

## Common side-effects

- **stomach pain**,
- **loose stool**,
- **diarrhoea**,
- **nausea**,

[46] a substance that, when consumed, increases sexual desire

[47] having to do with the narrowing and widening of blood vessels

[48] The chance or probability that a harmful event will occur. In health, for example, the chance that someone will develop a disease or condition

- **bloating**,
- **constipation**.

### Further information

This can be found at Soy.

## Wild yam

### Uses

Relaxing muscles, soothing nerves and relieving pain. Uterine tonic. Menstrual cramps. Allaying colic and flatulence caused by muscle spasms; for poor circulation and neuralgia; for the inflammatory stage of rheumatoid arthritis; and for abdominal and intestinal cramping. Wild Yam can be very beneficial for nervousness, restlessness and other nervous conditions. As a stimulant for increased bile flow, it helps to relieve hepatic congestion, bilious colic, gallstones, kidney and gallbladder problems and rheumatic conditions (herbwisdom, 2015r).

### Common side-effects

None known.

### Further information

This can be found at Wild Yam.

Chapter 3

# Introduction

## Complementary and alternative medicine

complementary and alternative medicine (CAM) refers to healing approaches and therapies that are not based on principles of mainstream, conventional medicine -

- Complementary[49] medicine refers to unconventional practices used with mainstream medicine,
- Alternative medicine refers to unconventional practices used instead of mainstream medicine,
- Integrative medicine is health care that uses all appropriate therapeutic approaches - conventional and alternative - within a framework that focuses on the therapeutic relationship and the whole person.

CAM has been widely used in the US for decades. Almost 40% of adults use some form of CAM, most often to treat pain or anxiety or to modify cholesterol levels. Use is also common among patients with chronic pain, cancer, hepatitis C, or other intractable conditions. The most frequently used therapies include medicinal herbs (see Dietary supplements) and other plant-derived supplements (botanicals), mind-body practices, and massage therapy.

Some CAM therapies are now offered in hospitals and are sometimes reimbursed by insurance companies. Some traditional medical schools, including 45 North American medical schools in the Consortium of Academic Health Centres for Integrative Medicine, provide education about CAM and integrative medicine.

Broad, philosophic differences distinguish conventional and alternative approaches to healing (see Differences Between Conventional and Alternative Medicine).

[49] A group of diverse medical and health care systems, practices, and products that are used together with conventional medicine

Because patients worry about being criticised, they do not always volunteer information about their use of CAM to physicians. Therefore, it is very important for doctors to specifically ask their patients about CAM use in an open, nonjudgmental way. Learning about patients' use of CAM can strengthen rapport, build trust, and provide an opportunity to discuss CAM's benefits and risks. Doctors may also identify and avoid potentially harmful interactions between drugs[50] and CAM therapies or nutritional supplements, monitor patient progress, guide patients to certified or licensed CAM practitioners, and learn from patients' experiences with CAM.

## Definition of health

> Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO, 1948).

This definition was established by the World Health Organisation in 1948 and has not been amended since then, it has stood the test of time.

Looking more up to date, the Oxford Dictionary states that health is -

> The state of being free from illness or injury (Press, 2015).

The British Medical Journal broadened the definition to bear in mind the increased burden of chronic conditions world-wide. Their definition is -

> The level of functional or metabolic efficiency of a living organism. In humans it is the ability of individuals or communities to adapt and self-manage when facing physical, mental or social challenges (Huber et al., 2011).

Health is a resource for everyday life, not the object of living, and is a positive concept emphasising social and personal resources as well as physical capabilities. Health is a fundamental human right, recognized in the "Universal Declaration of Human Rights" of 1948.

The definition that I am going to use is the oldest, being the World Health Organisation one of 1948.

[50] Any substance (other than food) that is used to prevent, diagnose, treat, or relieve symptoms of a disease or abnormal condition. Also, a substance that alters mood or body function or that can be habit-forming or addictive, especially a narcotic

## Definition of illness

**Disease based** - Dysfunction of organs or biochemical processes.

**Symptom and individual based** - Imbalance of body, mind, and spirit.

## Method of treatment

External interventions (eg, drugs, surgery, radiation therapy).

Support and strengthening of patients' inherent capacity for self-healing.

## What are complementary therapies?

Here's one simple definition: those medical practices that fall outside conventional Western medicine. Complementary therapies include mind-body therapies, in which the power of the mind or the spirit is harnessed to heal the body. They also encompass touch therapies, which involve massage and other forms of physical manipulation performed by practitioners to promote healing. And they comprise physical agents that are eaten, inhaled or rubbed on the skin.

A specific complementary therapy may contain any or all of these elements. For example, aromatherapists use essential oils, which are inhaled or rubbed on the skin and are often used in massage. The process of heating and inhaling these oils includes a meditative component that many people think of as mind-body therapy.

Some people prefer the term alternative medicine to complementary therapies, and the abbreviation CAM is being used increasingly. Another term is complementary and alternative health care (CAHC). These terms refer to the same spectrum of medical options. The words used reflect the different attitudes and experiences of the people speaking. The term complementary therapies implies that these treatments are used with conventional medicine. Still others use the term integrative medicine to strongly state the importance they place on integrating elements of conventional and complementary medicines into a more unified approach (CATIE, 2011d).

Knowledge based on individual stories rather than hard data is called anecdotal information. This information can be collected and shared by practitioners or the people using the treatments. Anecdotal information is an important component of both complementary and conventional medicine. In conventional medicine, such observation may reveal new uses for existing treatments or identify unforeseen side effects.

In complementary medicine, anecdotal information is often recorded and compiled to form a base of information about the likely outcome[51] of a treatment. Anecdotal information has limitations. It is based on the experience of individuals; how these experiences apply to others is often difficult to judge.

Although much of Western medical practice was developed from anecdotal information, the current standard for a Western medical treatment is a double-blind[52] placebo-controlled[53] trial. In such a study, a group of people with the same medical condition believe they are being given the same treatment. Placebo[54]s are used by some trial participants, but no-one knows who is getting the real treatment. The study is called double-blind because even the doctors and researchers who collect the results are not told which participants received placebos. This method is intended to eliminate biases based on the expectations of researchers and participants and to gather statistical evidence[55] about how often we can expect the treatment to work. Some complementary therapies can and are being tested in double-blind placebo-controlled trials. Unfortunately, various factors often hamper complementary therapies trials:

- **Money** - Practitioners and producers of complementary therapies rarely have the financial resources of a drug company. Even when they do, most complementary medicines can't be patented, so there is less financial incentive to pay for trials.

[51] A specific endpoint measured in a clinical trial. Examples include weight loss, cholesterol levels, severe toxicity, worsening of disease, and death

[52] Describes a clinical trial in which neither the re- searcher nor the patient knows which of several possible therapies the patient is receiving

[53] Refers to a method of studying a drug or dietary supplement in which a placebo (an inactive ingredient) is given to one group of participants, and the drug or dietary supplement being tested is given to a second group of participants. Results from the two groups are compared to see if the drug or dietary supplement being tested works better than the placebo

[54] An inactive substance or treatment that has no effect on the body and that ideally looks, smells, and tastes the same as, and is given the same way as, the active drug or treatment being tested. The effects of the active substance or treatment are compared to the effects of the placebo

[55] Information used to support the use of a particular screening procedure, treatment, or preventive measure. In medicine, evidence needed to determine effectiveness is provided by laboratory research, clinical trials, and other studies

- **Skepticism** - Western scientists skilled in performing controlled clinical trials[56] are often skeptical about complementary medicines. Due to this skepticism, trials of complementary therapies do not build a researcher's prestige in the same way that a typical drug trial might.
- **History** - Complementary therapy practitioners and users have not participated in many controlled clinical trials. As well, practitioners schooled in medical systems with established bodies of knowledge (such as traditional Chinese medicine) may see little need to re-examine these therapies to comply with Western medical standards. Western medical researchers, on the other hand, may see little need to study complementary therapies when a Western medical treatment exists.
- **Pure substance** - A controlled trial requires a purified, consistent dose of the treatment. In the case of some complementary therapies, this purified form is not available. In others, practitioners and users believe the therapy is most effective in its natural "unpure" state.

Some solutions to these problems are emerging. Governments are now more willing to dedicate resources to the study of complementary therapies. For example, the federal government of Canada has targeted funding for research on natural health products through the Canadian Institutes of Health Research and through the Natural Health Products Directorate. Other research funds are also targeting complementary therapy research. In some cases, trial methods may need to be adapted to study complementary therapies effectively. All of these efforts will require collaboration between Western scientists and complementary therapy practitioners to produce reputable results (CATIE, 2011c).

## Regulation of Natural Health Products in Canada

In response to growing concerns about the regulatory environment for herbal remedies, Health Canada developed a new regulatory framework for natural health products, which came into effect January 1, 2004.

This framework is the product of extensive consultation with a range of stakeholders. Previously natural health products were sold as either drugs or foods under the Foods and Drugs Act and Regulations. The new Natural Health Products Regulations call for improved labelling, good manufacturing practices, product and site licensing, and provision for a full range of health claims that will be supported by evidence.

[56] a particular type of clinical research that compares one treatment with another

The products that fall within the new Regulations include herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids and essential fatty acids. All natural health products in Canada require a product licence before being marketed.

Obtaining a product license requires detailed information on the product submitted to Health Canada, including medicinal ingredients, source, potency, non-medicinal ingredients and recommended use. Once a product has been assessed by Health Canada, the product label bears a product licence number preceded by the distinct letters NPN, or, in the case of a homeopathic medicine, by the letters DIN-HM. The product licence number on the label informs consumers that the product has been reviewed and approved by Health Canada for safety and efficacy[57].

With improved, standardised[58] labelling, consumers are able to make more informed decisions about the natural health products they buy. Labels are required to specify directions for use, the recommended use or purpose (health claim), medicinal and non-medicinal ingredients, and any cautions, contra-indications or known adverse reactions associated with the product (CATIE, 2011b).

## Differences Between Conventional and Alternative Medicine

| Factor | Conventional medicine | Alternative medicine |
|---|---|---|
| Definition of health | A condition of physical, mental, and social well-being and the absence of disease and other abnormalities | Optimal balance, resilience, and integrity of the body, mind, and spirit and their interrelationship |
| Definition of illness | Organ dysfunction, disordered biochemical processes, or undesirable symptoms | Symptom and individual based: Imbalance of body, mind, and spirit |
| Concept of life force | Life processes that are based on known physical biochemical events | A nonphysical, scientifically inaccessible life force that unites mind and body, interconnects all living beings, and is the underpinning of health (often called vitalism) |
| Understanding of consciousness | Results only from physical processes in the brain | Not localized to the brain; can exert healing effects on the body |
| Method of treatment | Any evidence-based intervention, including drugs, surgery, radiation therapy, electrical treatments, medical devices, physical therapy, exercise and nutritional and lifestyle interventions | Support and strengthening of patients' inherent capacity for self-healing |
| Reliance on scientific evidence | Strict reliance on established principles of scientific evidence | Flexible use of scientific evidence; treatments often based on tradition and/or anecdotal support instead |

[57] capacity for producing a desired result or effect

[58] A process manufacturers may use to ensure batch-to-batch consistency of their products and to provide a measure of quality control. Dietary supplements are not required to be standardised in the United States. Some manufacturers use the term incorrectly or to mean different things and the presence of the word "standardised" on a supplement label does not necessarily indicate a level of product quality

## Efficacy

In 1992, the Office of Alternative Medicine in the National Institutes of Health (NIH) was formed to study the efficacy and safety of alternative therapies. In 1998, this office became the National Center for Complementary and Alternative Medicine (NCCAM). Other NIH offices (eg, National Cancer Institute) also fund some CAM research.

There are 3 types of support for CAM therapies -

- Use over periods of time ranging from decades to centuries,
- Evidence of established physiologic mechanisms of action[59] (eg, modification of -aminobutyric acid [GABA] activity in the brain by valerian),
- Efficacy as shown in clinical trials.

A substantial amount of information about CAM is available in peer-reviewed journals, evidence-based reviews, expert panel consensus[60] documents, and authoritative textbooks; much of it has been published in languages other than English (eg, German, Chinese). However, most CAM therapies have not been tested in definitive clinical trials and probably will not be for the following reasons -

- Industry has no financial incentive to fund research,
- CAM therapies may be difficult to study using conventional methodology,
- Manufacturers of CAM products do not have to prove disease-specific efficacy.

Thus, the FDA allows marketing of dietary supplement[61] s and use of CAM devices but significantly[62] restricts efficacy claims. Generally, manufacturers of dietary supplements can claim benefit to the body's structure or function (eg, improves cardiovascular health) but not benefit for treating disease (eg, treats hypertension).

## Research

Designing studies of CAM therapies poses challenges beyond those faced by researchers of conventional therapies -

[59] the means by which a substance (such as a dietary supplement) is able to produce an effect in the body

[60] a general agreement

[61] A product that is intended to supplement the diet. A dietary supplement contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their components; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is identified on the front label of the product as being a dietary supplement

[62] In medicine, a mathematical measure of difference between two or more groups receiving different treatments that is greater than what might be expected to happen by chance alone

- Therapies may not be standardised. For example, there are different systems of acupuncture, and the contents and biologic activity of extracts made from the same plant species vary widely (chemical identification and standardisation of active ingredients is not considered part of CAM),
- Diagnoses may not be standardised; use of many CAM therapies (eg, traditional herbal medicine, homeopathy, acupuncture) is based on the patient's unique characteristics rather than on a specific disease or disorder,
- Double- or single-blinding is often difficult or impossible. For example, patients cannot be blinded[63] as to whether they are practicing meditation. Reiki practitioners cannot be blinded as to whether or not they are using energy healing,
- Outcomes are difficult to standardise because they are often specific to the individual rather than objective and uniform (as mean arterial pressure, Hb A 1c level, and mortality are),
- Placebos may be difficult to devise because identifying the effective component of a CAM therapy may be difficult. For example, in massage, the effective component could be touching, the specific area of the body massaged, the particular massage technique used, or time spent with the patient.

From a conventional research perspective, use of a placebo control is particularly important when subjective outcomes (eg, pain, nausea, indigestion) are used and when disorders that are intermittent, self-limited, or both (eg, headaches) are being studied; such end points and disorders are often the targets of CAM therapies. However, CAM systems interpret placebo effects as nonspecific healing effects that arise out of the therapeutic interaction and are inseparable from specific treatments. In practice, alternative therapies are intended to optimise the patient's capacity for self-healing (placebo response) as well as treatment-specific effects. Thus, many CAM practitioners strive to enhance the quality of the healing environment and therapeutic relationship. Studying the effective components of a CAM therapy without undermining the integrity of that therapy in a research setting remains a methodologic challenge.

[63] a process used in clinical trials to assign individuals to the control group (to receive the standard treatment) or the test group (to receive the new treatment under study) without the individuals or the researchers knowing to which group they have been assigned. Blinding helps ensure that information collected in the study is true and not biased (flawed). In a single-blinded study, the individuals do not know whether the standard treatment or a new treatment is being given. In a double-blinded study, neither the individuals nor the researchers know which treatment is being given

## Safety

Although the safety of most CAM therapies has not been studied in clinical trials, many of these therapies have a good safety record. Many CAM therapies (eg, nontoxic[64] botanicals, mind-body techniques such as meditation and yoga, body-based practices such as massage) have been used for thousands of years with no evidence of harm, and many seem to have no potential for harm. However, there are some safety considerations, including the following -

- Use of an alternative approach to treat a life-threatening disorder that can be effectively treated conventionally (eg, meningitis, diabetic ketoacidosis, acute leukemia) - perhaps the greatest risk of CAM, rather than the risk of direct harm from a CAM therapy,
- Toxicity from certain herbal preparations (eg, hepatotoxicity from pyrrolizidine alkaloids, Atractylis gummifera, chaparral, germander, greater celandine, Jin Bu Huan, kava, pennyroyal, or others; nephrotoxicity from Aristolochia; adrenergic[65] stimulation from ephedra),
- Contamination (eg, heavy metal contamination of some Chinese and Ayurvedic herbal preparations; contamination of other products, such as PC-SPES and some Chinese herbs, with other drugs),
- Interactions between CAM therapies (eg, botanicals, micronutrients, other dietary supplements) and other drugs (eg, induction of cytochrome P-450 [CYP3A4] enzymes by St. John's wort, resulting in reduced activity of antiretrovirals, immunosuppressants, and other drugs), particularly when the drug has a narrow therapeutic index[66],
- As with any physical manipulation of the body (including mainstream techniques such as physical therapy), injury (eg, nerve or cord damage due to spinal manipulation in patients at risk, bruising in patients with bleeding disorders).

Current alerts about harmful dietary supplements are available at the FDA web site. Historically, the FDA did not tightly regulate the production of dietary supplements. However, new FDA regulations now require compliance with manufacturing practices that guarantee quality and safety of supplements.

[64] capable of causing death or serious debilitation

[65] working on adrenaline (epinephrine) or noradrenaline (norepinephrine)

[66] The ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment. The larger the therapeutic index, the safer the drug is

To help prevent injuries due to physical manipulations, patients should look for CAM practitioners who graduated from accredited schools and are professionally licensed. Rates of complications[67] are very low when chiropractic or acupuncture is provided by practitioners with full credentials.

## Categories

Five categories of alternative medicine are generally recognized (see Types of Alternative Medicine) -

- Alternative whole medical systems,
- Mind-body medicine,
- Biologically based practices,
- Manipulative and body-based practices,
- Energy medicine.

The name of many therapies only partially describes their components.

## Types of Alternative Medicine

- **Whole medical systems** - All-encompassing approaches, including theory and practice (eg, explanation of disease, diagnostics, therapy)
- **Ayurveda** - Aims to restore balance within the body.
  Uses diet, massage, herbs, meditation, therapeutic elimination, and yoga.
- **Homeopathy**
  - **Based on the law of similars** - A substance that causes certain symptoms when given in large doses is used in minute doses to cure the same symptoms.
- **Naturopathy** - Aims to prevent and treat disease by promoting a healthy lifestyle, treating the whole person, and using the body's natural healing abilities.
  Uses a combination of therapies, including acupuncture, counseling, exercise therapy, guided imagery, homeopathy, hydrotherapy, medicinal herbs, natural childbirth, nutrition, physical therapies, and stress management.
- **Traditional Chinese medicine** - Aims to restore proper flow of life force (qi) in the body by balancing the opposing forces of yin and yang within the body.
  Uses acupuncture, massage, medicinal herbs, and meditative exercise (qi gong).

[67] In medicine, an illness or condition that occurs while a patient has a disease. The complication is not a part of the disease, but may be a result of the disease or may be unrelated

- **Mind-body medicine** - Use of behavioral, psychologic, social, and spiritual techniques to enhance the mind's capacity to affect the body and thus to preserve health and prevent or cure disease.
- **Biofeedback** - Uses electronic devices to provide patients with information about biologic functions (eg, BP, muscle activity) and to teach patients to control these functions.
- **Guided imagery** - Uses mental images to help patients relax or to promote wellness or healing of a particular condition (eg, cancer, psychologic trauma).
- **Hypnotherapy** - Puts patients into a state of relaxation with attentive and focused concentration to help them change their behavior and thus improve their health.
- **Meditation** - Involves intentional self-regulation of attention or a systematic mental focus on particular aspects of inner or outer experience.
- **Relaxation techniques** - Aim to elicit a psychophysiologic state of hypoarousal by reducing sympathetic nervous system activity and BP, easing muscle tension, slowing metabolic processes, or altering brain wave activity.
- **Biologically based practices** - Use of naturally occurring substances (eg, particular foods, micronutrients) to affect health.
- **Biologic therapies** - Uses substances naturally occurring in animals (eg, shark cartilage [to treat cancer], S -adenosyl- l -methionine [SAMe], glucosamine [to treat osteoarthritis]) to treat disease.
- **Chelation therapy** - Uses a drug to bind with and remove a hypothesised excess or toxic amount of a metal or mineral in the body.
- **Diet therapies** - Use specialised dietary regimens (eg, Gerson therapy, macrobiotic diet, Ornish diet, Pritikin diet) to treat or prevent a specific disease (eg, cancer, cardiovascular disorders) or to generally promote wellness.
- **Herbalism** - Uses plants and plant extracts to treat disease and promote wellness.
  *This is the one that's really of use to us.*
- **Orthomolecular medicine** - Uses substances that occur naturally in the body (eg, hormones, vitamins), often in doses higher than the recommended daily amount, to treat disease and promote wellness.
- **Manipulative and body-based practices** - Focused primarily on the body's structures and systems (eg, bones, joints, soft tissues[68]).
  Based on the belief that the body can regulate and heal itself and that its parts are interdependent.

[68] A group or layer of cells in a living organism that work together to perform a specific function

- **Chiropractic** - Involves manipulating the spine, other joints, and soft tissue to restore normal spinal neuromuscular function.
  Also involves prescribing exercises and ergonomic measures.
- **Massage** - Involves manipulating tissues to promote wellness and to reduce pain and stress.
- **Postural re-education** - Uses movement and touch to help patients become more aware of their body, relearn healthy posture, and move more easily.
- **Reflexology** - Involves applying manual pressure to specific areas of the foot that theoretically correspond to different organs or systems of the body.
- **Structural integration** - Involves manipulating and stretching the fascia to reestablish healthy bone and muscle alignment.
- **Energy medicine** - Manipulation of the body's energy fields (biofields) with the intent to affect health.
  Based on the belief that a universal life force or subtle energy resides in and around the body.
- **Acupuncture** - Stimulates specific points on the body, usually by inserting thin needles into the skin and underlying tissues to unblock the flow of qi along energy pathways and thus restore balance in the body.
- **External qi gong** - Involves master healers using the energy of their own biofield to bring the patient's energy into balance.
- **Magnets** - Placing magnets on the body to reduce pain.
- **Pulsed electrical field** - Placing injured body parts in an induced electrical field to facilitate healing.
- **Reiki** - Involves practitioners channeling energy through their body and into a patient's body to promote healing.
- **Therapeutic touch** - Uses the therapist's healing energy, usually without touching the patient, to identify and repair imbalances in the patients biofield.

# Dietary supplements

Dietary supplements are the most commonly used of all complementary and alternative therapies, primarily because they are widely available and can be bought without consulting a health care practitioner.

The FDA regulates dietary supplements differently from drugs. The FDA regulates only quality control and good manufacturing processes but does not ensure standardisation of the active ingredients or efficacy.

## Definition

The Dietary Supplement Health Education Act (DSHEA) of 1994 defines a dietary supplement as -

> **Any product (except tobacco)** - in pill, capsule, tablet, or liquid form - containing a vitamin, mineral, herb or other plant product, amino acid, or other known dietary substance that is intended as a supplement to the normal diet.

In addition, certain hormones, such as dehydroepiandrosterone (DHEA, a precursor to androgens and oestrogens) and melatonin, are regulated as dietary supplements and not as prescription drugs.

## Labelling

The DSHEA requires that the product label identify the product as a dietary supplement and notify the consumer that the claims for the supplement have not been evaluated by the FDA. The label must also list each ingredient by name, quantity, and total weight and identify plant parts from which ingredients are derived (see the DSHEA legislation at www.fda.gov/RegulatoryInformation/Legislation/default.htm ). Manufacturers are permitted to make claims about the product's structure and function (eg, good for urinary tract health) but cannot make or imply claims for the product as a drug or therapy (eg, treats UTIs).

## Safety and efficacy

Most people who use dietary supplements assume that they are good for health generally, are safe and effective for treating specific conditions, or both because dietary supplements are natural (ie, derived from plants or animals) and because some are supported by centuries of use in traditional systems of medicine. However, the FDA does not require manufacturers of dietary supplements to prove safety or efficacy (although supplements must have a history of safety). Most supplements have not been rigorous[69]ly studied. For most, evidence suggesting safety or efficacy comes from traditional use, in-vitro[70] studies, certain case report[71]s, and animal studies. However, manufacturers and distributors of supplements

[69] accurate, precise, and without deviation from standards

[70] outside the body

[71] A detailed record of the diagnosis, treatment, and follow- up of an individual patient. Case reports also contain some information about the patient (such as age, gender, and ethnic origin)

now must report serious adverse events[72] to the FDA through the MedWatch system. There are a few supplements (eg, fish oil, chondroitin/glucosamine, saw palmetto) now proved to be safe and useful complements to standard drugs.

Evidence concerning the safety and efficacy of dietary supplements is increasing rapidly as more and more clinically based studies are being done. Information about such studies is available at the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM) web site ( nccam.nih.gov/research/clinicaltrials ).

## Purity and standardization

Lack of regulation and government monitoring also means that supplements are not monitored to ensure that they contain the ingredients or amount of active ingredient the manufacturer claims they contain. The supplement may have unlisted ingredients, which may be inert or harmful (eg, natural toxins, bacteria, pesticides, lead or other heavy metals), or it may contain variable amounts of active ingredients, especially when whole herbs are ground or made into extracts. Consumers are at risk of getting less, more, or, in some cases, none of the active ingredient, if the active ingredient is even known. Most herbal products are mixtures of several substances, and which ingredient is the most active is not always known. The lack of standardisation means not only that products from different manufacturers may vary, but also that different batches produced by the same manufacturer may differ. This product variability is a particular source of difficulty in conducting rigorous scientific trials and comparing the results among different trials. However, some supplements have been standardised and may include a designation of standardisation on the label.

New regulations governing supplement production in the US include rules for Good Manufacturing Practices (GMPs). These rules strengthen standards for keeping manufacturing facilities and equipment clean and raw materials pure and uncontaminated. GMPs also ensure proper labeling, packaging, and storage of the finished product.

## Other concerns

Additional areas of concern include -

[72] An unwanted medical problem that occurs during treatment. Adverse events may be unrelated to the treatment or they may be caused by the therapy or procedure. For example, an adverse event may be caused by the toxic effects of a particular drug or dietary supplement or by an interaction with another therapy. Also called adverse effect and side effect

- Use of dietary supplements instead of conventional drugs,
- Stability of supplements (especially herbal products) once manufactured.

### Toxicity

#### Interactions between supplements and drugs

Most information about these concerns comes from sporadic individual reports and some references.

Despite these concerns, many patients strongly believe in the benefits of supplements and continue to use them with or without a doctor's involvement. Patients may not think to disclose or may wish to conceal their use of dietary supplements. For this reason, the outpatient history should periodically include explicit questions about past and new use of CAM therapies, including dietary supplements. Many doctors incorporate some supplement use into their practice; their reasons include proven benefit of the supplement, a desire to ensure that supplements are used safely by patients who will use supplements anyway, and the doctor's belief that the supplements are safe and effective. There are few data to guide patient counselling regarding supplement safety. But some experts believe that the overall number of problems due to dietary supplements is rare compared with the overall number of doses taken and that the supplement, if correctly manufactured, is likely to be safe. As a result, these experts advise purchase of supplements from a well-known manufacturer, and many recommend buying supplements made in Germany because there they are regulated as drugs and thus oversight is stricter than in the US.

## Alternative Whole Medical Systems

Alternative medical systems are complete systems with explanation of disease, diagnosis, and therapy.

### Homeopathy

Developed in Germany in the late 1700s, homeopathy is based on the principle that like cures like. A substance that, when given in large doses, causes a certain set of symptoms is believed to cure the same symptoms when it is given in minute doses. The minute dose is thought to stimulate the body's healing mechanisms. Treatments are based on the patient's unique characteristics, including personality and lifestyle, as well as symptoms and general health.

Remedies used in homeopathy are derived from naturally occurring substances, such as plant extracts and minerals. Extremely low concentrations are prepared in a specific way. The more dilute the homeopathic remedy, the stronger it is considered to be.

Some solution[73]s are so dilute that they contain no molecules of the active ingredient. There is no compelling, scientific explanation for how these dilutions could work.

## Evidence

Efficacy of homeopathic remedies for various disorders has been studied. No study has clearly shown efficacy for any specific homeopathic remedy, although some studies have shown positive results (eg, one well-conducted, randomised[74], placebo-controlled clinical study showed a therapeutic benefit greater than placebo in the treatment of diarrhoea in children). Homeopathy is commonly incorporated into health care practices in Europe and India.

## Uses

Homeopathy has been used to treat various disorders, such as allergies, rhinitis, digestive problems, musculoskeletal pain, and vertigo. The effect of homeopathic solutions on joint pain and tenderness and quality of life[75] in fibromyalgia is being studied.

## Possible adverse effects

Homeopathy is well-tolerated and has few risks; rarely, an allergic or toxic reaction occurs.

Unlike herbal and nutritional supplements, homeopathic remedies are regulated by the FDA as drugs; they are available over the counter or by prescription. Because so little active ingredient is left after dilution, active ingredients are tested before dilution. Homeopathic remedies have been temporarily exempted from limits on the amount of alcohol (the usual diluent) that they can contain. However, the label is required to list the following -

- Manufacturer,

[73] A liquid in which another substance has been dissolved or mixed

[74] When referring to an experiment or clinical trial, the process by which animal or human subjects are assigned by chance to separate groups that compare different treatments or other therapies. Randomization gives each participant an equal chance of being assigned to any of the groups

[75] the overall enjoyment of life, a sense of well-being, and the ability to carry out routine activities

- The label "homeopathic",
- At least one indication,
- Instructions for safe use,
- Unless specifically exempted, the active ingredient and degree of dilution.

Conventional clinicians should not assume that a homeopathic remedy taken by a patient is biologically inactive. Patients often use the term homeopathic erroneously in reference to a dietary supplement they are taking. Also, the FDA allows many medicinal herbs to be registered and labeled as homeopathic if they undergo a particular pharmaceutical process.

## Traditional Chinese Medicine

Originating > 2000 years ago, traditional Chinese medicine is based on the theory that disease results from improper flow of the life force (qi). The movement of qi is restored by balancing the opposing forces of yin and yang, which manifest in the body as heat and cold, external and internal, and deficiency and excess. Various practices (eg, acupuncture, diet, massage, medicinal herbs, meditative exercise called qi gong) are used to preserve and restore qi and thus health.

### Evidence

Chinese medicine traditionally uses formulas containing mixtures of herbs to treat various disorders. Traditional formulas can be studied; for example, efficacy in the treatment of irritable bowel syndrome has been shown. One herb, used by itself, may not be as effective and may have side effects. Nevertheless, current conventional research favours study of single herbs. For example, Tripterygium wilfordii (thunder god vine) has demonstrated anti-inflammatory[76] properties and clinical efficacy in treating RA, and Astragalus may benefit patients with lung cancer. Various Chinese herbs have been studied as treatments for hepatitis and hepatic fibrosis. Some studies suggest efficacy, but data are limited.

### Possible adverse effects

One problem is the standardisation and quality control of Chinese herbs. Many are unregulated in Asia; they may be contaminated with heavy metals from polluted ground water or may be adulterated with drugs such as antibiotics or corticosteroids. However, high-quality products are available through certain manufacturers that comply with FDA Good Manufacturing Practices.

[76] a substance or treatment that reduces inflammation or swelling

# Mind-Body Medicine

Mind-body medicine is based on the theory that mental and emotional factors influence physical health through a system of neuronal, hormonal, and immunologic connections throughout the body. Behavioral, psychologic, social, and spiritual techniques are used to preserve health and to prevent or cure disease.

Because scientific evidence supporting the benefits of mind-body medicine is abundant, many of these approaches are now considered mainstream, although they remain underused. Techniques such as biofeedback, guided imagery, hypnotherapy, meditation, and relaxation are used in the treatment of chronic pain, coronary artery disease, headaches, insomnia, and incontinence and as aids during childbirth. These techniques are also used to help patients cope with disease-related and treatment-related symptoms of cancer and to prepare patients for surgery. Efficacy of mind-body medicine in patients with asthma, hypertension, or tinnitus is not as clear.

## Biofeedback

For this technique, electronic devices are used to provide information to patients about biologic functions (eg, heart rate, BP, muscle activity, skin temperature, skin resistance, brain surface electrical activity).

### Uses

With the help of a therapist or with training, patients can then use information from biofeedback to modify the function or to relax, thereby lessening the effects of conditions such as pain, stress, insomnia, and headaches. Biofeedback is also used in patients with faecal or urinary incontinence, chronic abdominal pain, tinnitus, Raynaud's syndrome, or attention or memory disorders (eg, attention-deficit/hyperactivity disorder, traumatic brain injury). Generally, biofeedback does not seem to be useful in asthma; a possible exception is heart rate variability biofeedback, which may help reduce asthma symptoms and drug use and improve pulmonary function.

## Guided imagery

Mental images, self-directed or guided by a practitioner, are used to help patients relax (eg, before a procedure) and to promote wellness and healing (to try to effect physical changes - eg, by mobilising the immune system). The images can involve any of the senses.

### Uses

Imagery used with relaxation techniques (muscle relaxation and deep breathing) may help reduce pain and improve quality of life in patients with cancer. Imagery has also been used in patients with psychologic trauma.

## Hypnotherapy

Hypnotherapy is derived from western psychotherapeutic practice. Patients are put into an advanced state of relaxation. They become absorbed in the images presented by the hypnotherapist and are relatively distracted from but not unconscious of their surroundings and the experiences they are undergoing. Some patients learn to hypnotise themselves.

### Uses

Hypnotherapy is used to treat pain syndromes, phobias, and conversion disorders and has been used with some success to manage smoking cessation and weight loss. It can reduce pain and anxiety during medical procedures in adults and children. It may be useful in irritable bowel syndrome, headaches, asthma, and some skin disorders (eg, warts, psoriasis). It may help lower BP. Hypnotherapy helps control nausea and vomiting (particularly anticipatory) related to chemotherapy and is useful in palliative cancer care. Some evidence suggests that hypnotherapy helps lessen anxiety and improve quality of life in patients with cancer.

## Meditation

In meditation, patients regulate their attention or systematically focus on particular aspects of inner or outer experience. The most highly studied forms of meditation are transcendental meditation (TM) and mindfulness meditation. Although research is incomplete, results to date suggest that meditation could work via at least 2 mechanisms:

- Producing a relaxed state that counters excessive activation of neurohormonal pathways resulting from repeated stress,
- Developing the capacity for metacognitive awareness (the ability to stand back from and witness the contents of consciousness), thus theoretically helping patients not react to stress automatically (with highly conditioned, learned patterns of behaviour) and helping them tolerate and regulate emotional distress better.

Most meditation practices were developed in a religious or spiritual context; their ultimate goal was some type of spiritual growth, personal transformation, or transcendental experience. However, studies suggest that as a health care intervention, meditation can often be beneficial regardless of a person's cultural or religious background.

### Uses

Meditation has been used to relieve anxiety, pain, depression, stress, insomnia, and symptoms of chronic disorders such as cancer or cardiovascular disorders. It is also used to promote wellness.

### Relaxation Techniques

Relaxation techniques are practices specifically designed to relieve tension and strain. The specific technique may be aimed at

- Reducing activity of the sympathetic nervous system,
- Lowering BP,
- Easing muscle tension,
- Slowing metabolic processes,
- Altering brain wave activity.

Relaxation techniques may be used with other techniques, such as meditation, guided imagery, or hypnotherapy.

## Biologically Based Practices

Biologically based practices use naturally occurring substances and include biologic therapies (eg, shark cartilage to treat cancer, glucosamine to treat osteoarthritis), diet therapies, herbalism, see Dietary supplements, orthomolecular medicine, and chelation therapy.

### Diet Therapy

Diet therapy uses specialised dietary regimens (eg, Gerson therapy, macrobiotic diets, Pritikin diet) to treat or prevent a specific disorder (eg, cancer, cardiovascular disorders) or generally promote wellness. Some diets (eg, Mediterranean diet) are widely accepted and encouraged in traditional western medicine. The Ornish diet, a very low-fat vegetarian diet, can help reverse arterial blockages that cause coronary artery disease and may help prevent or slow the progression of prostate and other cancers. Some people following a macrobiotic

diet have reported cancer remission, but a well-controlled clinical study has not been conducted. Because it usually takes months or years for benefits to be realized, diet therapy is more likely to be effective if started early.

# Manipulative and Body-Based Practices

Manipulative and body-based practices include chiropractic, massage therapy, postural reeducation, reflexology, and structural integration.

## Chiropractic

In chiropractic, the relationship between the structure of the spine and function of the nervous system is thought to be the key to maintaining or restoring health. The main method for restoring this relationship is spinal manipulation. Chiropractors may also provide physical therapies (eg, heat and cold, electrical stimulation, rehabilitation strategies), massage, or acupressure and may recommend exercises or lifestyle changes.

### Uses

Chiropractic provides short-term relief of low back pain, but continuing adjustments may not provide additional benefit. Thus, the usefulness of chiropractic for chronic back pain is unclear. Chiropractic is sometimes useful in treating headache disorders (although data are inconsistent) and nerve impingement syndromes; it has also been used to treat neck pain. The usefulness of manipulation for conditions not directly related to the musculoskeletal system has not been established.

### Possible adverse effects

Serious complications resulting from spinal manipulation (eg, low back pain, damage to cervical nerves, damage to arteries in the neck) are rare. Spinal manipulation is not recommended for patients with osteoporosis or symptoms of neuropathy (eg, paresthesias, loss of strength in a limb). Whether it is safe for patients who have had spinal surgery or stroke or who have a vascular disorder is unclear.

### Massage Therapy

In massage therapy, body tissues are manipulated to promote wellness and reduce pain and stress. The therapeutic value of massage for many musculoskeletal symptoms and stress is widely accepted. Massage has been shown to help relieve the following -

- Muscle soreness,
- Pain due to back injuries,
- Fibromyalgia,
- Anxiety, fatigue, pain, nausea, and vomiting in cancer patients.

Massage therapy is reported to be effective in treating low birth weight infants, preventing injury to the mother's genitals during childbirth, relieving chronic constipation, and controlling asthma.

Massage can cause bruising and bleeding in patients with thrombocytopenia or bleeding disorders. Therapists must avoid putting pressure on bones affected by osteoporosis or metastatic cancer.

### Reflexology

This variant of massage therapy relies on manual pressure applied to specific areas of the foot; these areas are believed to correspond to different organs or body systems via meridians. Stimulation of these areas is believed to eliminate the blockage of energy responsible for pain or disease in the corresponding body part. Reflexology may help relieve anxiety in patients with cancer.

## Energy Medicine

Energy medicine intends to manipulate subtle energy fields (also called biofields) thought to exist in and around the body. All energy therapies are based on the belief that a universal life force or subtle energy resides in and around the body. Qi gong, which is used in traditional Chinese medicine, is an energy therapy.

### Acupuncture

Acupuncture, a therapy within traditional Chinese medicine, is one of the most widely accepted alternative therapies in the western world. Specific points on the body are stimulated, usually by inserting thin needles into the skin and underlying tissues. Stimulating these specific points is believed to unblock the flow of qi along energy pathways (meridians) and thus restore balance; > 350 defined points are located along the meridians. The procedure is generally not painful but may cause a tingling sensation. Sometimes stimulation

is increased by twisting or warming the needle. Acupuncture points may also be stimulated by pressure (called acupressure), lasers, ultrasound, or a very low voltage electrical current (called electroacupuncture) applied to the needle.

## Evidence and uses

Research has shown that acupuncture releases various neurotransmitters (eg, endorphins) that act as natural painkillers. Reasonable evidence supports the efficacy of acupuncture as a pain reliever, an antinauseant, and an anti-emetic. However, in many studies, results of sham acupuncture are comparable to those of actual acupuncture; the relative efficacy of sham and actual acupuncture is still not clear.

Acupuncture relieves nausea and vomiting related to surgery and chemotherapy. When used with anti-emetic drugs, acupuncture has an additive effect. Acupuncture also helps relieve nausea and vomiting during pregnancy. Acupuncture has been used to relieve pain after surgical or dental procedures. As part of a comprehensive treatment plan (sometimes as adjunctive[77] treatment), acupuncture may be useful in treating addiction, carpal tunnel syndrome, fibromyalgia, headache, low back pain, osteoarthritis, and xerostomia (in patients with advanced cancer) and in stroke rehabilitation.

Preliminary evidence suggests that acupuncture may relieve vasomotor symptoms in men taking gonadotropin analogs for prostate cancer. The evidence for relieving symptoms and improving pulmonary function in patients with asthma and for relieving pain or improving function in patients with RA is mixed. Acupuncture is ineffective for smoking cessation and weight loss.

## Possible adverse effects and contraindications

Adverse effects are rare if the procedure is done correctly. Worsening of symptoms (usually temporary) and vasovagal symptoms are the most common. Because acupuncture can cause fainting and drowsiness (although rarely), patients should be supine at least for their first treatment and should not drive or do any tasks that require alertness after treatment until they know how it affects them. Infection is extremely rare; most practitioners use disposable needles.

[77] an accessory or auxiliary agent or measure

Acupuncture is contraindicated in patients with severe bleeding disorders. Electroacupuncture is contraindicated in patients with a pacemaker or an implanted defibrillator. Acupuncture at certain points may stimulate uterine contractions, and in traditional Chinese medicine, it is used to modulate labour. Only specially trained practitioners should use acupuncture in pregnant women.

## Magnets

Energy therapy may rely on magnetic (alternating- or direct-current) fields.

### Evidence and uses

Magnets, in particular, are a popular treatment for various musculoskeletal disorders, although multiple studies have shown no effectiveness, especially for pain relief, one of their most common applications.

Preliminary evidence suggests that static (permanent) magnets may help relieve pain in patients with osteoarthritis. However, the evidence that electromagnets may reduce pain and improve physical function is more consistent than that for static magnets. Using pulsating electromagnetic fields to speed healing of nonunion fractures is well-established.

### Possible contraindications

Possible contraindications for magnets include pregnancy (effects on the foetus are unknown) and use of implanted cardiac devices, an insulin pump, or a drug given by patch.

## Therapeutic Touch

Therapeutic touch, sometimes referred to as laying on of hands, uses the therapist's healing energy to identify and repair imbalances in a patient's biofield. Usually, practitioners do not touch the patient; instead, they move their hands back and forth over the patient. Therapeutic touch has been used to lessen anxiety and improve the sense of well-being in patients with cancer, but these effects have not been rigorously studied. In the US, nurses have introduced therapeutic touch into ICUs and other hospital settings.

### Reiki

Reiki, which originated in Japan, is a similar technique; in Reiki, practitioners channel energy through their hands and transfer it into the patient's body to promote healing. Practitioners are thought to have special healing powers, which are required for these treatments.

## Herbalism

Here we talk about the main subject of this ebook, Herbalism.

Herbal therapies are medically active substances harvested from plants. They may come from any part of the plant but are most commonly made from leaves, roots, seeds or flowers. They are eaten, drunk, smoked, inhaled or applied to the skin.

Herbal therapies are part of virtually every medical system. Many drugs now used by conventional Western doctors originated as herbal medicines. Practitioners involved in the medical systems discussed earlier use herbs extensively. So do herbalists, who practise outside these systems. A European healing tradition, sometimes called the "wise woman" tradition, also focuses primarily on herbal healing.

Herbal medicines are often viewed as a balanced and moderate approach to healing. Pharmaceutical drugs derived from plants are made by isolating the chemicals that have a medical effect and concentrating them in the medication. Herbal therapies, on the other hand, contain all the chemical components of a plant, as they occur naturally. This important part of herbal medicine may explain why some herbs - used by experienced practitioners for centuries - have not performed well in modern clinical trials when their active chemicals were isolated from the rest of the plant.

Herbal therapies are available at herbal and health food stores and, increasingly, are being sold in drugstores and grocery stores. Buyers' clubs are another option for buying herbs and other nutritional and complementary therapy products. These clubs allow people to pool their money to obtain bulk products at lower wholesale costs. Then members purchase products through the club at a reduced rate, often through the mail.

Herbal medicines are often promoted as a gentle and non-toxic approach to good health. This does not mean herbal therapies never cause side effects or never interact with other pharmaceutical and herbal treatments. Learn enough about any herbal therapy to ensure that the dose is safe and effective. Learn about possible side effects and watch for signs of drug interactions. It is also important to inform

your doctor, pharmacist and complementary therapist about all of the medications and health products you are taking - prescription and non-prescription - including herbs and supplements (CATIE, 2011a).

Many plants contain compound[78]s that directly or indirectly affect hormones or hormone activity in the body. Since phytoestrogens [79] are far weaker than their animal counterparts, they can be used effectively to manage overabundant or deficient amounts of oestrogen. The molecular structure of phytoestrogens is so similar to those in animals that they readily bind with oestrogen receptors, in some cases even more readily than the actual animal steroids. Because the plant steroids are so much less "reactive," though, they occupy the receptor while only performing some (or none) of the job. The animal oestrogen is swept on in the bloodstream to either bind with some other receptor, a blood protein, or ultimately to be destroyed in the liver or excreted from the body altogether. In this way, plant hormones can be used to "block" the direct activity of free, unbound oestrogen in the body. If there is a deficiency the small amount of stimulation from the plant hormones can cause a mild oestrogenic[80] effect and in this way act as an oestrogen supplement.

Endocrine disrupting compounds, also known as EDCs[81], alter the function of the endocrine system and consequently cause adverse health effects. Phytoestrogens, natural plant compounds abundantly found in soy and soy products, behave as weak oestrogen mimics or as antioestrogens. They are considered to be EDCs, and have some beneficial effects on health, including reducing the risk of breast cancer and improving metabolic parameters. However, the supporting evidence that consumption of phytoestrogens is beneficial is indirect and inconsistent. Lifetime exposure to oestrogenic substances, especially during critical periods of development, has been associated with the formation of malignancies and several anomalies of the reproductive systems. Phytoestrogen consumption in infants, through soy-based formulas, is of particular concern.

[78] in pharmacy, a substance that contains more than one ingredient

[79] Compounds found in plants that can mimic the effects of oestrogen in the body (medical-dictionary, 2014)

[80] having the properties of, or properties similar to, an oestrogen

[81] These are defined as substances that *"interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism)"* (Crisp and Clegg, 1998)

Prospective[82] epidemiological[83] studies for the evaluation of the effect of phytoestrogens alone, and in combination with other oestrogenic chemicals, are lacking, yet possible adverse effects should not be taken lightly (Bar-El, 2010).

Plant-derived phytoestrogens and oestrogens in Hormone Replacement Therapy (HRT) have overlapping yet sometimes divergent effects on the incidence[84] of breast cancer and osteoporosis. Using human MCF-7 breast carcinoma and G-292 osteosarcoma cell lines[85], it was investigated whether the phytoestrogens genistein and daidzein affect reporter gene transcription via the oestrogen receptors (ERs) ER$\alpha$ and ER$\beta$1 as well as whether they affect the expression of oestrogen-responsive genes in MCF-7 cells and the secretion of the cytokine IL-6 from G-292 cells. The results showed that genistein and daidzein potently trigger transactivation with ER$\beta$1 from oestrogen response element-reporter genes (EC50s of 1.7-16 nM) although they were 400- to 600-fold less potent than 17$\beta$-estradiol (E2) (EC50 of 0.02-0.04 nM). E2 was the only potent activator of ER$\alpha$ (EC50 of 0.1-0.4 nM). The rank order potency (E2 > genistein > daidzein) is maintained in MCF-7 cells as well as G-292 cells with both receptor subtypes, with a strong receptor selectivity of the phytoestrogens for ER$\beta$1 over ER$\alpha$. Genistein and daidzein increased the expression of oestrogen-responsive genes in MCF-7 cells. Daidzein, like E2, inhibited IL-1$\beta$ and hormone-mediated IL-6 secretion from G-292 cells. The results provide a basis for understanding how dietary phytoestrogens protect bone without increasing the risks for breast cancer (Chrzan, 2007). Note should be taken of the highlighted line which means that phytoestrogens are a very weak form of oestrogen, which could be better said that they aren't worth taking!

Some people have tried the, so-called, "herbal hormones" i.e. herbal substances that purport to have the same effect as medically prescribed hormones but with fewer problems or side effects. These are phytoestrogens, which are sometimes referred to as natural or herbal hormones, and are naturally occurring substances extracted from plants. Looked at under the microscope their molecules look a lot like oestrogens that normally are produced in a woman's body. But they also resemble some anti-oestrogens, like the breast-cancer drug tamoxifen.

---

[82] under observation, following over a period of time

[83] the associative relationships between the fre- quency of occurrence of a disease and its determinants, its predisposing and precipitating causes

[84] The number of new cases of a disease diagnosed in a specific group of people during a specific period of time. For example, the annual incidence of childhood cancer is 14.6 cases per 100,000 children aged birth to 14 years

[85] Cells of a single type that have been adapted to grow and divide in the laboratory and are used in research

Some of the herbs that folk have tried include a variety of extracts from -

- Alfalfa at page 61,
- American Ginseng at page 75,
- Angelica at page 108,
- Anise at page 118,
- Asian Ginseng at page 133,
- Basil at page 155,
- Black Cohosh at page 160,
- Borage at 190,
- Caraway at page 206,
- Chaste Tree/Berry at page 212,
- Cranberry at page 225
- Damiana at page 243,
- Dill at page 248,
- Dong Quai at page 254,
- Fennel at page 275,
- Fenugreek at page 285,
- Hops at page 297,
- Kudzu at page 305,
- Liquorice at page 313,
- Marijuana at page 335,
- Milk Thistle at page 352,
- Pueraria at page 380,
- Red Clover at page 389,
- Sage at page 401,
- Saw Palmetto at page 413,
- Soy at page 428,
- Wild Yam at page 445.

amongst others, as a means of physically feminizing themselves (MacRae and Pattison, 2002).

Prompted by numerous advertisements that included claims about the benefits of soy for ending or lessening hot flushes, the North Central Cancer Treatment Group Clinic based at Mayo Clinic in the USA, studied 177 breast cancer survivors. The results of this study were released on 28th February, 2000.

The flushes, which also affect women undergoing chemotherapy or tamoxifen treatment for breast cancer, can be accompanied by palpitations and feelings of anxiety, and can be very disruptive to life, the study said.

> "Despite optimistic hopes that this soy phytoestrogen product would alleviate hot flushes, the scientific data from this study demonstrated that it did not help,"

said Charles Loprinizi, one of the authors of the study.

The conclusion of the study based at the Mayo Clinic found that the 177 breast cancer survivors who took soy pills did not experience any noticeable changes: the oestrogen-like substance found in soybeans is not effective in stopping or decreasing hot flushes - disputing advertised claims for such products.

Additionally, herbal hormone regimens when used together with traditional pharmaceutical programmes do obstruct, and not heighten feminization. These weak oestrogen-like molecules do not augment, but compete with the pharmaceutical regimen. Phytoestrogens exert their effects primarily through binding to oestrogen receptors (ER). There are two variants of the oestrogen receptor, alpha (ER-$\alpha$) and beta (ER-$\beta$) and many phytoestrogens display somewhat higher affinity for ER-$\beta$ compared to ER-$\alpha$ (TGC, 2015). Or in other words, taking herbals and prescribed-oestrogen both at the same time means that they are going to be fighting for the same oestrogenic-receptors in your body, and you only have a finite number of the receptors, once they are being used they won't share with some other oestrogen that just happens along, its all or nothing!

Phytochemicals concentration and profiles are affected by biotic and abiotic factors linked to plant genotype, crop management, harvest season, soil quality, available nutrients, light, and water. Soil health and biological fertility play a key role in the production of safe plant foods, as a result of the action of beneficial soil microorganisms, in particular of the root symbionts arbuscular mycorrhizal fungi. They improve plant nutrition and health and induce changes in secondary metabolism leading to enhanced biosynthesis of health-promoting phytochemicals, such as polyphenols, carotenoids, flavonoids, phytoestrogens, and to a higher activity of antioxidant enzymes (Sbrana, 2014).

The use of herbs is a time-honoured approach to strengthening the body and treating disease. Herbs, however, contain components that can trigger side effects and that can interact with other herbs, supplements, or medications. For these reasons, you should take herbs with care, preferably under the supervision of a health care provider in the field of botanical medicine (unknown, 2014i).

Also, herbals might interact with some other medication you are taking that has been prescribed for you, which is not a good situation to be in. Also, you may be receiving other chemicals as part of the herbal substance, and these 'may' be harmful to you i.e. you could have a violent reaction to them, at the worst you could go into anaphylactic shock (a potentially fatal condition). Is it worth the risk? Only you can decide.

## Herbal health products and supplements

- **What are herbal health products and supplements?** - A botanical is a plant or part of a plant that people use to try to stay healthy, or to treat health conditions and illnesses. An herbal health product or supplement (also called a botanical product) is a type of dietary supplement that contains one or more herbs.
  Herbal health products and supplements are available in many forms, including in tea bags, capsules, tablets, liquids, and powders. Examples of common herbal health products and supplements include black cohosh, echinacea, garlic, ginkgo, saw palmetto, and St. John's wort.
- **Are herbal health products and supplements safe?** - Herbs aren't necessarily safer than the ingredients in over-the-counter (OTC) and prescription medicines just because they come from nature. Although herbal health products and supplements are advertised as "natural," their ingredients aren't necessarily natural to the human body. They may have strong effects on your body. They can also cause unpleasant health effects (also called adverse effects). Researchers have studied the benefits and risks of some herbal health products and supplements, but others need to be studied more.
- **Are herbal health products and supplements regulated by the U.S. Food and Drug Administration[86] (FDA)?** - All of the OTC and prescription medicines you can buy have to be "approved" as safe and effective by the FDA. But the FDA defines dietary supplements as a category of food, not as drugs. For this reason, the FDA doesn't require proof of their safety and effectiveness to diagnose, prevent, treat, or cure health conditions. Instead, it's up to the manufacturer to be sure that an herbal health product or supplement is safe before it is sold. The FDA can take herbal health products or supplements off the market if they are found to be unsafe (for example, if they cause serious adverse effects) or are found to contain ingredients that aren't listed on the label (for example, harmful substances).

[86] FDA, Department of Health and Human Services. FDA is the Federal government agency responsible for ensuring that foods and dietary supplements are safe, wholesome and sanitary, and that drugs, medical devices, cosmetics, and food are honestly, accurately and informatively represented to the public. FDA regulates dietary supplements under a different set of regulations than those covering conventional foods and drug products (prescription and over-the-counter). The dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to get FDA approval before producing or selling dietary supplements

- **Is it safe to take herbal health products and supplements if I have health problems?** - Herbal health products and supplements may not be safe if you have certain health problems, are pregnant, or are breastfeeding. Children and older adults also may be at increased risk of adverse effects from these products because their bodies process the ingredients differently.
  If you are going to have surgery, tell your doctor about any herbal health products and supplements you use. These products can cause problems with surgery, including bleeding problems with anesthesia. You should stop using herbal health products or supplements at least two weeks before surgery, or sooner if your doctor recommends it.
  Whether you have a health problem or not, it is always best to talk to your family doctor before taking any herbal health product or supplement.
- **Can herbal health products or supplements change the way OTC or prescription medicines work?** - Yes. Herbal health products or supplements can affect the way the body processes drugs. When this happens, your medicine may not work the way it should. For example, St. John's wort reduces the amount of certain drugs absorbed by the body. When this happens, the drugs may not be absorbed at high enough levels to help the health conditions for which they are prescribed. This can cause serious problems.
  If you take any OTC or prescription medicines, talk to your doctor before taking any type of herbal health product or supplement.
- **How can I find out what is in herbal health products and supplements?** - By law, manufacturers of herbal health products and supplements are responsible for making sure their labels are accurate and truthful. The FDA requires the following information on labels:
  - Name of the product or supplement,
  - Name of the address of the manufacturer or distributor,
  - Complete list of ingredients,
  - Amount of product or supplement in the container or package.

  Avoid any herbal health product or supplement that does not list this information.
  The National Institutes of Health maintains the Dietary Supplement Label Database. It is an online database that gives label information for thousands of dietary supplements. You can look up supplements by brand name, active ingredient, or manufacturer.

- **How can I use herbal health products or supplements safely?** - Don't take any herbal health products or supplements without talking to your family doctor first. If you do use an herbal health product or supplement, read the directions on the label to learn how much to take and how often to take it. You should never take more than the recommended amount. If you have any questions about how much to take, ask your doctor.
  The National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements are good sources of information about herbal health products and supplements.
- **How can I safely store herbal health products and supplements?** - Store all herbal health products and supplements up and away, out of reach and sight of young children. Do not store them in a place that is hot and humid (for example, a bathroom or bathroom cabinet). Keeping these products in a cool, dry place will help keep them from becoming less effective before their expiration date (familydoctor.org, 2015).

# Phytoestrogens

Phytoestrogens are plant substances with oestrogenic properties[87] (Tidy, 2015).

They first came to light about 50 years ago when it was observed that some plants could have an adverse effect on fertility in livestock. Phytoestrogens tend to have weaker effects than most oestrogens, are not stored in the body, and are readily metabolised and eliminated (Tidy, 2015).

## Sources of phytoestrogens

There are more than 20 compounds that can be found in more than 300 plants, such as herbs, grains, and fruits. The three main classes of dietary phytoestrogens are isoflavones, lignans, and coumestans -

- **Isoflavones** - genistein, daidzein, glycitein, and equol - are primarily found in soy beans and soy products, chickpeas and other legumes.
- **Lignans** - enterolactone and enterodiol - are found in oilseeds (primarily flaxseed), cereal bran, legumes, and alcohol (beer and bourbon).
- **Coumestans** - coumestrol - can be found in alfalfa and clover.

[87] have weak female hormone-like (oestrogenic) properties

Most food sources containing these compounds include more than one class of phytoestrogens (Tidy, 2015).

## Effects of phytoestrogens

Much of the evidence about phytoestrogens in bone metabolism is based on animal studies. Soybean protein, soy isoflavones, genistein, daidzein and coumestrol have all been shown to have a protective effect on bone in animals after oophorectomy (Tidy, 2015).

In humans the evidence is conflicting -

- Phytoestrogens have been associated with a decreased risk of osteoporosis, but results from intervention and observational studies have been inconsistent (Kuhnle, H. A. Ward, and Vogiatzoglou, 2011).
- Soy isoflavone supplements have been shown to significantly increase bone mineral density and decrease bone resorption (P. Wei, M. Liu, and Y. Chen, 2012).
- A Cochrane review concluded there was no evidence of any effect on postmenopausal vasomotor symptoms (A. Lethaby, Marjoribanks, and Kronenberg, 2013).
- There is some evidence of soya protein and/or isoflavones having beneficial effect on both blood lipid profile and bone density in postmenopausal women (Cassidy and Hooper, 2006).
- A systematic review[88] of randomised controlled trials[89] was unable to give unequivocal support for the benefit of phytoestrogens for the prevention of osteoporosis (A. M. Whelan, Jurgens, and Bowles, 2006). There is some evidence of adverse effects on laboratory animals, but studies to assess the problem in humans are not yet forthcoming (Reinwald and Weaver, 2006). There is also suggestion that phytoestrogens may enhance osteogenesis at low concentration and inhibit it at higher concentrations (Dang and Lowik, 2005), (Tidy, 2015).

## Conclusion

There is a great deal of evidence about phytoestrogens, but there is also much confusion -

- Much of the evidence relates to animals and in-vitro studies and there are questions as to how readily it should be extrapolated to humans.

[88] collects and looks at multiple studies

[89] studies in which people are allocated at random (by chance alone) to receive one of several clinical interventions

- Oestrogens and similar substances are highly complex and variable. Some may have an agonistic effect on bone, an antagonistic effect on breast tissue and a neutral effect on the endometrium as we have seen with selective oestrogen receptor modulators (SERMs). There may be considerable variation with regard to the effect of plant chemicals too.
- When a substance is not given as a drug in a predetermined dose but is part of the diet, the amount ingested may be highly variable and there may also be problems such as an agonist effect at low dose and an antagonist effect at higher doses.
- Some of the results, such as those related to cognition, are contradictory. This may be due to agonists and antagonists working in different directions.
- Epidemiological studies about multifactorial diseases must be interpreted with care. When comparing different populations we cannot be sure that only one parameter is changed.
- There is very little good, long-term evidence about the effects of phytoestrogens in human populations. Many questions remain to be answered. If a diet high in phytoestrogens does protect women against breast cancer, osteoporosis and heart disease, does it also impair fertility? If it protects men against prostatic cancer, does it also impair spermatogenesis?
- The evidence to suggest that phytoestrogens are protective against osteoporosis is at best poor. Long-term safety is not established.
- There have been many studies on the efficacy and safety of mammalian HRT, including the enormous 'Million Women Study' (Beral, Bull, and Reeves, 2005). The Million Women Study was basically very reassuring but it did outline some causes for concern. The assumption that plant oestrogens are as effective but safer is a very unsafe premise (Tidy, 2015).

# Preparations

Common preparations include teas, decoction[90]s, tincture[91]s, and extracts -

[90] decoction is a method of extraction by boiling of dissolved chemicals from herbal or plant material, which may include stems, roots, bark and rhizomes

[91] an alcohol or water-alcohol solution, usually referring to a preparation from herbal materials

- **A tea, also known as an infusion**[92] - is made by adding boiling water to fresh or dried botanicals and steeping them. The tea may be drunk either hot or cold.
- **More forceful treatment is needed** - for some roots, bark, and berries to extract their desired ingredients. They are simmered in boiling water for longer periods than teas, making a decoction, which also may be drunk hot or cold.
- **A tincture** - is made by soaking a botanical in a solution of alcohol and water. Tinctures are sold as liquids and are used for concentrating and preserving a botanical. They are made in different strengths that are expressed as botanical-to-extract ratios (i.e., ratios of the weight of the dried botanical to the volume or weight of the finished product).
- **An extract** - is made by soaking the botanical in a liquid that removes specific types of chemicals. The liquid can be used as is or evaporated to make a dry extract for use in capsules or tablets (ODS, 2011).

They can also be found in many forms - as fresh or dried products - as liquid or solid extracts - tablets, capsules, or powders, tea bags even, and other forms (ODS, 2011).

[92] the process of extracting chemical compounds or flavours from plant material in a solvent such as water, oil or alcohol, by allowing the material to remain suspended in the solvent over time. An infusion is also the name for the resultant liquid

Chapter 4

# A's

## Alfalfa

### Common Names

Feuille de Luzerne, Grand Trèfle, Herbe aux Bisons, Herbe à Vaches, Lucerne, Luzerne, Medicago, Phyoestrogen, Phytostrogène, Purple Medick, Sanfoin, Blue lucerne, Chilean clover, buffalo grass, father of all foods, buffalo herb, Spanish clover, California clover, holy hay, trefoil, Arabic = alfalfa, Arabic = Alfasafat, Chinese = Zi mu su, French = Luzerne commune, French = fuelle de luzerna, German = Saat-Luzerne, Hindi = Lasunghas, Hindi = Wilayti-gawuth, Italian = Erba medica, Italian = Erba Spagna, Persian = Aspasti, Russian = Ljucerna posevnaja, Spanish = Mielga.

### Latin name

*Medicago Sativa*

**Common cultivars** [93] - include Weevelchek, Saranac, Team, Arc, Classic, and Buffalo.

### What is it?

Alfalfa is an herb. People use the leaves, sprouts, and seeds to make medicine.

[93] a variety of plant that originated and persisted under cultivation

Alfalfa is used for kidney conditions, bladder and prostate conditions, and to increase urine flow. It is also used for high cholesterol, asthma, osteoarthritis, rheumatoid arthritis, diabetes, upset stomach, and a bleeding disorder called thrombocytopenic purpura. People also take alfalfa as a source of vitamins A, C, E, and K4; and minerals calcium, potassium, phosphorous, and iron.

There is no evidence supporting the use of various parts of the alfalfa plant for diuretic, anti-inflammatory, anti-diabetic[94], or anti-ulcer[95] purposes. Results from 1 small human study showed that the plant might reduce cholesterol levels (drugs.com, 2009a).

The hormonal activity of alfalfa was first observed in Veterinary Medicine. Animals observed grazing on alfalfa developed traits similar to animals treated with synthetic oestrogens. Alfalfa contains three major plant oestrogens: coumestrol, genistein, and formonetin (as well as the lesser diadzein and biochanin A). Coumestrol is the most active with a relative activity of 5% that of a natural oestradiol oestrogen. Genistein's activity is about 1%, and formonetin is .01% or less. The amount of "active" phytoestrogens varies with the growing season. It is highest during the full blooming and seeding stages. Also, keep in mind that these are the active percentages for *extracted* phytoestrogens as compared to an equal amount of true oestrogen - the amounts consumed in plant form will vary widely and will likely be in much smaller concentrations. From the Journal of Naturapathic Medicine [1984], Volume 1, Number 1:

> "The practical importance of the phytoestrogens lies with their ability to alter the biological response to endogenous[96] oestrogen. Estradiol receptors will bind to a diverse group of chemical compounds, including other steroids, isoflavones and phytoestrogens. When phytoestrogens bind to oestrogen receptors on cells, they translocate to the nucleus and stimulate cell growth in a manner similar to oestradiol. Despite the apparently weak relative binding capacity of the phytoestrogens, they can have significant hormonal effects. This is due to their lower affinity for the serum oestrogen binding proteins, this resulting in a net effect of enhancing the concentration of available phytoestrogen at the target tissue sites.

[94] something that stabilises and controls blood glucose levels amongst people with diabetes

[95] used to treat ulcers in the stomach and the upper part of the small intestine

> The relative weakness of their oestrogenic action means that these compounds will have an "alterative" or "balancing" effect. Thus, phytoestrogens may be used therapeutically in both hypoestrogenism[97] and hyperoesterogenism[98] states. It is precisely this quality that makes them so useful therapeutically, especially in a naturopathic setting.
>
> In conditions of hypoestrogenism the plant oestrogens will bind directly to oestrogen receptors and provide a mild oestrogenic effect. This is enhanced by the tendency of the phytoestrogens to concentrate in reproductive tissues, in preference to the serum proteins.
>
> When we use these plants medicinally as an alternative to synthetic drugs, it is essential to remember that we are utilizing the specific plant components in order to produce pharmacological actions. Thus, we would be well advised to utilize the most concentrated sources available. In the case of Medicago the preferred forms are solid extracts, fluid extracts and concentrated tinctures. Teas and tablets may not deliver enough active ingredient to be effective."

It should also be noted that alfalfa contains a seperate and distinct "anti-oestrogen" compound that is reported to be about 12% as strong as the phytoestrogens, so there is some "attrition" of effectiveness when this compound is also present (unknown, 2014f).

Alfalfa, like other leguminous crops, is a known source of phytoestrogens, including spinasterol, coumestrol, and coumestan. Because of this, grazing on alfalfa has caused reduced fertility in sheep and in dairy cattle (unknown, 2014a). Alfalfa might also cause some people's skin to become extra sensitive to the sun, so you should use some form of sunblock outside, especially if you are light-skinned. Large amounts of alfalfa might have some of the same effects as oestrogen. But even large amount of alfalfa aren't as strong as oestrogen pills. Taking alfalfa along with oestrogen pills might decrease the effects of oestrogen pills (MedlinePlus, 2014f).

Alfalfa has a high potassium content. People with chronic kidney insufficiency, hypoaldosteronism, or who are using potassium-altering medications should avoid alfalfa to avoid the risk of potentially life-threatening hyperkalaemia[99] (C. Wong, 2015).

[99] too much potassium in the blood

Medicago sativa is alterative, antipyretic, anti-scorbutic[100], aperient[101], diuretic, oxytocic[102], nutritive[103], stimulant and tonic.

The active components include up to 50% protein, beta carotene, chlorophyll, octacosanol, saponins[104], sterols, flavonoids, coumarins, alkaloids, acids, vitamins (A, B, B6, B12, C, D, E, K, niacin, pantothenic acid, biotin, folic acid), amino acids, sugars, minerals (Ca, K,P, Ma, Fe, Zn, Cu), and trace elements.

Alfalfa is one of the oldest cultivated plants. Its name comes from the Arabic, al-fac-facah, "father of all foods".

It's used as livestock forage, as a highly nutritious food for humans, and as an herbal medicine for at least 1500 years. It's considered to have the highest nutritive value of all fodder plants.

Alfalfa has a long history of use in China as an appetite stimulant, and as an herbal treatment for digestive disorders, especially ulcers.

Ayurvedic medicine used medicago sativa as an herbal treatment for ulcers, to alleviate the pain of arthritis and as a treatment for fluid retention.

Early American herbalists used the herb as a treatment for arthritis, boils, cancer, scurvy, and for diseases of the urinary and digestive systems.

Pioneer women in America used alfalfa as an herbal remedy for menstrual disorders.

Modern herbalists use medicago sativa to help women with disorders related to hormonal imbalance. Due to its alterative qualities with regard to hormone levels, alfalfa is used as a natural treatment for disorders such as hot flashes during menopause, fibrocystic breasts, osteoporosis, polycystic ovaries, fibroids and PMS.

Alfalfa may be used to treat both hypoestrogenism and hyperoestero-genism.

---

[100] preventing or relieving scurvy

[101] having a gentle laxative effect

[102] causing the stimulation of the involuntary muscle of the uterus

[103] of or relating to nutrition

[104] any of a group of glycosides widely distributed in plants, which form a durable foam when their watery solutions are shaken, and which even in high dilutions dissolve erythrocytes

Scientific research confirms the effectiveness of medicago sativa as a natural treatment for high cholesterol. It's known to reduce LDL[105], or bad cholesterol, without reducing HDL[106], or good cholesterol.

Alfalfa is traditionally used as an herbal treatment for debility during convalescence or in cases of anaemia.

Alfalfa was used as a natural treatment for infections from surgical incisions, bed sores and as an external poultice[107] for the treatment of earaches.

Studies have shown that alfalfa may reduce blood sugar levels due to its high manganese content. Clinical studies have shown that medicago sativa with a high level of manganese improved the condition of diabetic patients who do not respond to insulin.

Alfalfa contains a molecule analog to the thyrotropin-releasing hormone (TRH). Thyrotropin-releasing hormone is common in the animal kingdom but unknown in the vegetable kingdom. The TRH hormone analog found in alfalfa is also biologically active in animals, suggesting that medicago sativa may be an effective natural therapy for treating secondary hypothyroidism as well as diseases caused by an excess of prolactin[108], as in polycystic ovaries.

Scientific studies indicate that medicago sativa may have a stimulating effect on the immune system.

Alfalfa has been shown to inhibit the development of certain viruses, including herpes simplex virus.

Some in-vitro studies have shown that L-canaverina present in alfalfa has antitumour[109] actions against certain types of leukemia in mice and a selective toxicity[110] against cancer cells in dogs.

Traditional herbalists use Medicago sativa to dilute the strength of digitalis.

---

[105]Low-density lipoprotein - carries cholesterol to the cells that need it. If theres too much cholesterol for the cells to use, it can build up in the artery walls, leading to disease of the arteries. For this reason, LDL is known as "bad cholesterol"

[106]High-density lipoprotein - carries cholesterol away from the cells and back to the liver, where its either broken down or passed out of the body as a waste product. For this reason, HDL is referred to as "good cholesterol" and higher levels are better

[107]a soft moist mass, often heated and medicated, that is spread on cloth over the skin to treat an aching, inflamed, or painful part of the body

[108]A hormone made by the pituitary gland (an organ located at the base of the brain) and important for making breast milk and in ovulation (the release of an egg from an ovary during the menstrual cycle)

[109]used in the treatment of cancer

[110]of antibiotics means that they must be highly effective against the microbe but have minimal or no toxicity to humans

In Columbia, the mucilaginous[111] fruits are used as an herbal treatment for cough.

Alfalfa is one of the best natural sources of vitamin K. Vitamin K helps bones to knit by working with vitamin D and glutamic acid to activate osteocalcin. The combination of these three nutrients is essential for building bone; the body cannot use calcium without all three.

Alfalfa helps to keep calcium out of the linings of arteries. Atherosclerosis is a result of calcium replacing cholesterol in the lining of the blood vessels. This happens when a microscopically[112] small amount of cholesterol becomes lodged in the arterial wall. These can form a mass that can be replaced by artery-hardening calcium. Alfalfa may help prevent the formation of calcium deposits on the arterial wall (unknown, 2015a).

## History

Alfalfa has played an important role as a livestock forage. Its use probably originated in Southeast Asia. The Arabs fed alfalfa to their horses, claiming it made the animals swift and strong, and named the legume "Al-fal-fa" meaning "father of all foods." The medicinal uses of alfalfa stem from anecdotal reports that the leaves cause diuresis and are useful in the treatment of kidney, bladder, and prostate disorders. Leaf preparations have been touted for their antiarthritic and anti-diabetic activity, for treatment of dyspepsia, and as an antiasthmatic. Alfalfa extracts are used in baked goods, beverages, and prepared foods, and the plant serves as a commercial[113] source of chlorophyll and carotene (J. Duke, 1985).

## Botany

This legume grows throughout the world under widely varying conditions. A perennial herb, it has trifoliate dentate leaves with an underground stem that is often woody. Alfalfa grows to approximately 1 m and its blue-violet flowers bloom from July to September.

---

[111] Resembling mucilage; that is, adhesive, viscid, sticky

[112] Too small to be seen without a microscope

[113] a product such as a drug or dietary supplement made in large quantities to be sold

## Chemistry

Dried alfalfa leaves are ground and sold as tablets or powder for use as nutritional supplements. Leaf tablets are rich in protein, calcium, trace minerals, carotene, vitamins E and K, and numerous water-soluble vitamins (Worthington-Roberts and Breskin, 1983). A steroidal saponin fraction composed of several factors (eg, soyasapogenols, hederagenin, medicagenic acid)(Massiot, 1988), (Oleszek, 1988) is believed to play a role in the hypocholesterolemic and haemolytic activity of the leaves and sprouts (M. R. Malinow, P. McLaughlin, Naito, et al., 1978). Alfalfa seeds contain the toxic amino acid L-canavanine, an analog of arginine. Sprouts of certain cultivars of alfalfa contain up to 13 g/kg canavanine (dry weight). Canavanine levels decrease as the plant matures. The alkaloids stachydrine and l-homo-stachydrine found in the seed possess emmenagogue[114] and lactogenic activity (unknown, 1984). Seeds contain up to 11% of a drying oil used in the preparation of paints and varnishes. The chemistry of alfalfa has been well characterised (J. Duke, 1985).

## Uses and Pharmacology

There is no evidence that alfalfa leaves or sprouts possess effective diuretic, anti-inflammatory, anti-diabetic, or anti-ulcer activity in humans. Alfalfa saponins are haemolytic in-vitro (Small, 1990).

## Cholesterol Reduction

Alfalfa plant saponins and fibre (J. Story, 1982) bind significant quantities of cholesterol in-vitro; sprout saponins interact to a lesser degree. In-vitro bile acid adsorption is greatest for the whole alfalfa plant, and this activity is not reduced by the removal of saponins from the plant material.

### Animal data

Several studies indicate that the ingestion of alfalfa reduces cholesterol absorption and atherosclerotic plaque formation in animals (M. R. Malinow, P. McLaughlin, and Papworth, 1977), (M. R. Malinow, Connor, and P. McLaughlin, 1981), (Wilcox and Galloway, 1961), (B. I. Cohen et al., 1990). In one study, the ability of alfalfa to reduce liver cholesterol accumulation in cholesterol-fed rats was enhanced by the removal of saponins. Therefore, alfalfa plant saponins appear to play an important role in neutral steroid excretion,

[114] An agent that induces or hastens menstrual flow

but are not essential for increasing bile acid excretion (J. A. Story, LePage, and Petro, 1984). In a study with prairie dogs, the lowest incidence of cholesterol gallstones was obtained with the diet of the higher fibre content (85% alfalfa) (B. I. Cohen et al., 1990).

### Clinical data

In a study of 15 patients, alfalfa seeds added to the diet helped normalize serum cholesterol concentrations in patients with type II hyperlipoproteinemia (Molgaard, Schenck, and Olsson, 1987).

Cholestaid, a product available in the US containing 900 A measure of weight. It is a metric unit of mass equal to 0.001 gram (it weighs 28,000 times less than an ounce) (mg) of Esterin patented process alfalfa extract with 100 mg citric acid, is said to neutralise the cholesterol in the stomach before it reaches the liver, thus facilitating the excretion of cholesterol from the body with no side effects or toxicity (S. Levy, 1999), (Dewey, 2001) There is no evidence that canavanine or its metabolites affect cholesterol levels.

## Contraindications

The FDA issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts because of frequent bacterial contamination (Drugs.com, 2009).

## Adverse Reactions

Alfalfa ingestion, especially of the seeds, has been associated with various deleterious[115] effects, and alfalfa seeds and fresh sprouts can be contaminated with bacteria such as Salmonella enterica[116] and Escherichia coli[117] (Van Beneden, Keene, and Strang, 1999), (Mahon, Ponka, and W. N. Hall, 1997), (CDC, 1997), (Christy, 1999). The FDA issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts. Ingestion of dried alfalfa preparations is generally without important side effects in healthy adults (Drugs.com, 2009).

[115] damaging or harmful

[116] can cause diarrhoea, fever, and abdominal cramps

[117] can cause food poisoning symptoms, such as severe abdominal cramps, bloody diarrhoea and vomiting

Most healthy adults exposed to salmonella or Escherichia coli will have symptoms such as **diarrhoea**, **nausea**, **abdominal cramping**, and **fever** that are self-limiting. The E. coli infection can lead to haemolytic uremiac syndrome with kidney failure or death in children or the elderly. In 1995, 4 outbreaks of Salmonella infection occurred in the US because of the consumption of contaminated alfalfa sprouts. In 1995 to 1996, 133 patients in Oregon and British Columbia developed salmonellosis from ingesting alfalfa sprouts contaminated with S. enterica (serotype Newport) (Van Beneden, Keene, and Strang, 1999). Also in 1995, 242 patients in the US and Finland developed salmonellosis from ingesting alfalfa sprouts contaminated with S. enterica (serotype Stanley) (Mahon, Ponka, and W. N. Hall, 1997). In June and July 1997, simultaneous outbreaks of E. coli 0157:H7 infection in Michigan and Virginia were independently associated with eating alfalfa sprouts grown from the same seed lot[118] (CDC, 1997). The FDA issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts (Christy, 1999).

The biggest risk in using alfalfa is eating sprouts grown in contaminated water or sprouts that have gone bad and are decomposing. For most people, alfalfa is safe, but it may interact with certain medications. Those who are taking anti-rejection drugs for transplant[119], should not use any form of alfalfa. People who take Coumadin or other anti-coagulant drugs, should consult with their doctors concerning what amounts of green vegetables (which contain high amounts of vitamin K) are safe to consume.

Eating alfalfa sprouts has been linked to systemic lupus erythematosus (SLE[120]). Those diagnosed with SLE should avoid alfalfa products. Consuming large amounts of the seeds has also caused reversible blood abnormalities. In rare instances of excessive consumption of alfalfa herb or sprouts, abnormal red blood cell counts, enlargement of the spleen or relapses of lupus may occur (unknown, 2015a).

## How effective is it?

*Natural Medicines Comprehensive Database* rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

[118] A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits

[119] The replacement of tissue with tissue from the persons own body or from another person

[120] systemic lupus erythematosus

The effectiveness ratings for **Alfalfa** are as follows:

### Insufficient evidence to rate effectiveness for...

- **High cholesterol** - Taking alfalfa seeds seems to lower total cholesterol and LDL cholesterol in people with high cholesterol levels.
- **Kidney problems**
- **Bladder problems**
- **Prostate problems**
- **Asthma**
- **Arthritis**
- **Diabetes**
- **Upset stomach**
- **Other conditions**

More evidence is needed to rate alfalfa for these uses.

## How does it work?

Alfalfa seems to prevent cholesterol absorption in the gut.

## Are there safety concerns?

Alfalfa leaves are possibly safe for most adults. However, taking alfalfa seeds long-term is likely unsafe. Alfalfa seed products may cause reactions that are similar to the autoimmune disease called lupus erythematosus.

Alfalfa might also cause some people's skin to become extra sensitive to the sun, they have **photosensitivity**. Wear sunblock outside, especially if you are light-skinned.

## Are there interactions with medications?

### Major

Do not take this combination.

- **Warfarin (Coumadin)** - Alfalfa contains large amounts of vitamin K. Vitamin K is used by the body to help blood clot. Warfarin (Coumadin) is used to slow blood clotting. By helping the blood clot, alfalfa might decrease the effectiveness of warfarin (Coumadin). Be sure to have your blood checked regularly. The dose of your warfarin (Coumadin) might need to be changed.

## Moderate

Be cautious with this combination.

- **Birth control pills (Contraceptive drugs)** - Some birth control pills contain oestrogen. Alfalfa might have some of the same effects as oestrogen. However, alfalfa is not as strong as the oestrogen in birth control pills. Taking alfalfa along with birth control pills might decrease the effectiveness of birth control pills. If you take birth control pills along with alfalfa, use an additional form of birth control such as a condom.
  Some birth control pills include ethinylestradiol and levonorgestrel (Triphasil), ethinylestradiol and norethindrone (Ortho-Novum 1/35, Ortho-Novum 7/7/7), and others.
- **Oestrogen's** - Large amounts of alfalfa might have some of the same effects as oestrogen. However even large amounts of alfalfa are not as strong as oestrogen pills. Taking alfalfa along with oestrogen pills might decrease the effects of oestrogen pills.
  Some oestrogen pills include conjugated equine oestrogens (Premarin), ethinylestradiol, estradiol, and others.
- **Medications for diabetes (Antidiabetes drugs)** - Alfalfa might decrease blood sugar. Diabetes medications are also used to lower blood sugar. Taking alfalfa along with diabetes medications might cause your blood sugar to go too low. Monitor your blood sugar closely. The dose of your diabetes medication might need to be changed.
  Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

- **Medications that decrease the immune system (Immunosuppressants)** - Alfalfa might increase the immune system. By increasing the immune system, alfalfa might decrease the effectiveness of medications that decrease the immune system.
  Some medications that decrease the immune system include azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone (Deltasone, Orasone), corticosteroids (glucocorticoids), and others.
- **Medications that increase sensitivity to sunlight (Photosensitizing drugs)** - Some medications can increase sensitivity to sunlight. Large doses of alfalfa might also increase your sensitivity to sunlight. Taking alfalfa along with medication that increase sensitivity to sunlight could make you even

more sensitive to sunlight, increasing the chances of sunburn, blistering or rashes on areas of skin exposed to sunlight. Be sure to wear sunblock and protective clothing when spending time in the sun.
Some medications that cause photosensitivity include amitriptyline (Elavil), Ciprofloxacin (Cipro), norfloxacin (Noroxin), lomefloxacin (Maxaquin), ofloxacin (Floxin), levofloxacin (Levaquin), sparfloxacin (Zagam), gatifloxacin (Tequin), moxifloxacin (Avelox), trimethoprim/sulfamethoxazole (Septra), tetracycline, methoxsalen (8-methoxypsoralen, 8-MOP, Oxsoralen), and Trioxsalen (Trisoralen).

## Are there interactions with herbs and supplements?

- **Herbs and supplements that might lower blood sugar** - Alfalfa might lower blood sugar. Using alfalfa along with other herbs and supplements that might lower blood sugar might lower blood sugar too much. Herbs that might lower blood sugar include devil's claw, fenugreek, guar gum, Panax ginseng, and Siberian ginseng.
- **Iron** - Alfalfa might lower the body's absorption of dietary iron.
- **Vitamin E** - Alfalfa might interfere with the way the body takes in and uses vitamin E.

## Are there interactions with foods?

There are no known interactions with foods.

## Pregnancy/Lactation

Documented adverse effects. May cause uterine stimulation. Avoid use (F. J. Brinker, 1998a), (Hayashino, 2005).

## Interactions

The vitamin K found in alfalfa can antagonize the anti-coagulant effect of warfarin, resulting in decreased anti-coagulant[121] activity and lowered prothrombin time (C. H. Brown, 2002). Based on the potential immunostimulating effect of alfalfa, it has been theorised that alfalfa may interfere with the immunosuppressive action of corticosteroids (eg, prednisone) or cyclosporine (L. G. Miller, 1998).

[121] Reduces the ability of the blood to clot

## Dosing

Alfalfa seeds are used commonly as a supplement to lower cholesterol at doses of 0.75 to 3 g/day; however, clinical trials have not been performed to validate this dosage (drugs.com, 2009a). The following doses have been studied in scientific research -

### By mouth

For high cholesterol: a typical dose is 5–10 grams of the herb, or as a steeped strained tea, three times a day. 5–10 mL of a liquid extract (1:1 in 25% alcohol) three times a day has also been used (MedlinePlus, 2014a).

The usual dose of alfalfa leaves for tea is 1 to 2 teaspoons per cup, steeped for 10 to 20 minutes. Powdered alfalfa may be taken in capsule form according to the manufacturer's recommendations. For cholesterol reduction the recommended dosage is 5 to 10 grams of dried alfalfa leaves, taken three times a day (unknown, 2015a).

## Special precautions & warnings

- **Pregnancy or breast-feeding** - Using alfalfa in amounts larger than what is commonly found in food is possibly unsafe during pregnancy and breast-feeding. There is some evidence that alfalfa may act like oestrogen, and this might affect the pregnancy.
- **"Auto-immune diseases" such as multiple sclerosis (MS), lupus (systemic lupus erythematosus, SLE), rheumatoid arthritis (RA), or other conditions** - Alfalfa might cause the immune system to become more active, and this could increase the symptoms of auto-immune diseases. There are two case reports of SLE patients experiencing disease flare after taking alfalfa seed products long-term. If you have an auto-immune condition, it's best to avoid using alfalfa until more is known.
- **Hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** -Alfalfa might have the same effects as the female hormone oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use alfalfa.
- **Diabetes** - Alfalfa might lower blood sugar levels. If you have diabetes and take alfalfa, monitor your blood sugar levels closely.
- **Kidney transplant** - There is one report of a kidney transplant rejection following the three-month use of a supplement that contained alfalfa and black cohosh. This outcome is more likely due to alfalfa than black cohosh. There is some evidence that alfalfa can boost the immune system and this might make the anti-rejection drug cyclosporine less effective.

## Toxicology

Alfalfa tablets have been associated with the reactivation of SLE in at least 2 patients. Changes in intestinal cellular morphology were noted in rats fed alfalfa (Drugs.com, 2009)

Changes in intestinal cellular morphology were noted in rats fed alfalfa; these effects were more extensive in animals fed whole plant material compared with sprouts. The interaction of saponins with cholesterol in cell membranes may only be partly responsible for these changes (J. A. Story, LePage, and Petro, 1984). The importance of the changes in animal intestinal morphology is not clear; it is known that these changes, when observed concomitantly with changes in steroid excretion, may be related to an increased susceptibility to colon cancer (Sprinz, 1971).

A disease similar to SLE has been observed in monkeys fed alfalfa seeds (M. Malinow, 1982). The disease was characterized by haemolytic anaemia, decreased serum complement levels, immunologic changes, and deposition of immunoglobulins in the kidney and skin. Alfalfa ingestion has resulted in pancytopenia and hypocomplementenemia in healthy subjects (M. R. Malinow, Bardana, and Goodnight, 1981). L-canavanine has been implicated as the possible causative[122] agent. The toxicity of L-canavanine is mainly due to its structural similarity to arginine. Canavanine binds to arginine-dependent enzymes interfering with their action. Arginine reduces the toxic effects of canavanine in-vitro (Natelson, 1985) Further, canavanine may be metabolised to canaline, an analog of ornithine. Canaline may inhibit pyridoxal phosphate and enzymes that require the B [6] cofactor. 14 L-canavanine has also been shown to alter intercellular calcium levels (Morimoto, 1989) and the ability of certain B or T cell populations to regulate antibody synthesis (Prete, 1985), (Morimoto et al., 1990). Alfalfa tablets have been associated with the reactivation of SLE in at least 2 patients (J. L. Roberts and Hayashi, 1983).

A case of reversible asymptomatic pancytopenia with splenomegaly has been reported in a man who ingested up to 160 g of ground alfalfa seeds daily as part of a cholesterol-reducing diet. His plasma cholesterol decreased from 218mg/dL to 130 to 160mg/dL (M. R. Malinow, Bardana, and Goodnight, 1981). Pancytopenia was believed to be due to canavanine.

A popular self-treatment for asthma and hay fever suggests the ingestion of alfalfa tablets. There is no scientific evidence that this treatment is effective (Polk, 1982). Fortunately, the occurrence of cross-sensitization between alfalfa (a legume) and grass pollens

[122] acting as a cause

appears unlikely, assuming the tablets are not contaminated with materials from grasses (Brandenburg, 1983). One patient died of listeriosis following the ingestion of contaminated alfalfa tablets (Farber et al., 1990).

### Commentary

*Alfalfa has small amounts of phytoestrogens as compared to oestrogen tablets, and because you can get varying amounts of the active phytoestrogen its not really worth taking.*

## American Ginseng

### Common names

American Ginseng, Anchi Ginseng, Baie Rouge, Canadian Ginseng, Ginseng, Ginseng à Cinq Folioles, Ginseng Américain, Ginseng Americano, Ginseng d'Amérique, Ginseng DAmérique du Nord, Ginseng Canadien, Ginseng de lOntario, Ginseng du Wisconsin, Ginseng Occidental, Ginseng Root, North American Ginseng, Occidental Ginseng, Ontario Ginseng, Panax Quinquefolia, Panax Quinquefolium, Panax quinquefolius, Racine de Ginseng, Red Berry, Ren Shen, Sang, Shang, Shi Yang Seng, Wisconsin Ginseng, Xi Yang Shen, Guandong ginseng, Chinese = Si ren shen, Chinese = Xi yang shen, Finnish = Amerikan ginsengjuuri, German = Amerikanischer Ginseng.

### Latin name

*Panax quinquefolius*

Ginseng is a family of plants. Dietary supplements are derived from American ginseng (Panax quinquefolius) or Asian ginseng. Ginseng can be taken as fresh or dried roots, extracts, solutions, capsules, tablets, sodas, and teas or used as cosmetics. Active ingredients in American ginseng are panaxosides (saponin glycosides). Active ingredients in Asian ginseng are ginsenosides[123] (triterpenoid glycosides).

Siberian ginseng is a different genus and does not contain the ingredients believed to be active in the 2 forms used in supplements.

[123] the presumed active component in ginseng, from the chemical class of saponins

Ginseng products vary considerably in quality because many contain little or no detectable active ingredient. In very few cases, some ginseng products from Asia have been purposefully mixed with mandrake root, which has been used to induce vomiting, or with the drugs phenylbutazone or aminopyrine. These drugs have been removed from the US market because of significant adverse effects (merck, 2015).

The name "ginseng" is used to refer to both American (Panax quinquefolius), see American Ginseng, and Asian or Korean ginseng (Panax ginseng), see Asian Ginseng, which belong to the genus Panax and have a somewhat similar chemical makeup. Both Asian and American ginseng contain ginsenosides, which are the substances thought to give ginseng its medicinal properties. But they contain different types in different amounts.

Siberian ginseng, or Eleuthero (Eleutherococcus senticosus), is an entirely different plant with different effects. It is distantly related to ginseng, but it does not contain the same active ingredient.

Like Asian ginseng, American ginseng is a light tan, gnarled root that often looks like a human body with stringy shoots for arms and legs. Native Americans used the root as a stimulant and to treat headaches, fever, indigestion, and infertility. Ginseng remains one of the most popular herbs in the United States.

Ginseng is sometimes called an "adaptogen[124]," meaning it is an herb that helps the body deal with various kinds of stress, although there is no scientific evidence to prove the benefit of adaptogens (unknown, 2014b).

## What is it?

American ginseng is an herb. The root is used to make medicine.

American ginseng is used for stress, to boost the immune system, and as a general tonic and stimulant.

American ginseng is often used to fight infections such as colds and flu. There is some evidence that it might help prevent colds and flu and make symptoms milder when infections do occur.

American ginseng is used for other infections including human immunodeficiency virus (HIV)/AIDS, infections of the intestine (dysentery), and particular infections (Pseudomonas infections) that are common in people with cystic fibrosis.

Some people use American ginseng to improve digestion and for loss of appetite, as well as for vomiting, inflammation of the colon (colitis), and inflammation of the lining of the stomach (gastritis).

[124] used to improve the health of your adrenal system

American ginseng is also used for low iron in the blood (anaemia), insomnia, diabetes, nerve pain, erectile dysfunction (ED), fever, hangover symptoms, attention deficit-hyperactivity disorder (ADHD), blood and bleeding disorders, cancer, painful joints, dizziness, headaches, convulsions, fibromyalgia, atherosclerosis, memory loss, and as an anti-aging aid.

You may also see American ginseng listed as an ingredient in some soft drinks. Oils and extracts made from American ginseng are used in soaps and cosmetics.

Don't confuse American ginseng with Siberian ginseng (Eleutherococcus senticosus) or Asian ginseng (Panax ginseng). They have different medicinal effects.

Wild American ginseng is becoming rare because it is so popular and has so many uses. Some states have declared American ginseng a threatened or endangered species because so many people try to harvest it.

## Botany

Ginseng commonly refers to Panax quinquefolius, see American Ginseng, or Panax ginseng, see Asian Ginseng, two members of the family Araliaceae. Several other species are less commonly used in Asia. The ginsengs were classified as members of the genus Aralia in older texts. In the eastern and central United States and Canada, Panax quinquefolius is found in rich, cool woods; a large crop is grown commercially in Wisconsin. The short plant grows 3 to 7 compound leaves that drop in the fall and bears a cluster of Red or yellowish fruits from June to July. The shape of the root can vary depending on the species and has been used to distinguish types of ginseng. Medicinally, the root is considered the most valuable part of the plant in providing the pharmacologically active ginsenosides. Ginsenoside content varies with the age of the root, season of harvest, and method of preservation. While at least 4 ginsenosides are detectable in most young roots, this number more than doubles after 6 years of growth. High-quality ginseng is generally collected in the fall after 5 to 6 years of growth (Team, 2011), (WHO, 1999c).

Panax ginseng should not be confused with Siberian ginseng (Eleutherococcus senticosus), a related species with different chemistry (Team, 2011).

## History

Ginseng is perhaps the most widely recognised plant used in traditional medicine and now plays a major role in the herbal health care market. For more than 2,000 years, various forms have been used medicinally. The name Panax derives from the Greek word for "all healing", and its properties have been so touted. Ginseng root's man-shaped figure (shen-seng means "man-

root") led proponents of the Doctrine of Signatures[125], an ancient European herbalists philosophy, to believe that the root could strengthen any part of the body. Through the ages, the root has been used in the treatment of asthenia, atherosclerosis, blood and bleeding disorders, and colitis, as well as to relieve the effects of aging, cancer, and senility.

Prior to its discovery in the early seventeenth century, American ginseng had been used by American Indians, for purposes quite similar to the use of Asian ginseng by the Chinese. It was among the five most important medicinal plants of the Seneca Indians, and was primarily given to the elderly. According to Crow legend, the wife of Sitting Bull learned in a dream that the leaf or root tea would aid in childbirth without suffering. The Penobscots, who referred to it as "man root," prescribed the root tea to increase female fertility. Ginseng was regarded as a "universal remedy" for children and adults by the Meskwaki (Fox) Indians of Wisconsin. It was combined with other medicinal plants to render them more powerful. The Menominee considered the root to be a tonic and strengthener of mental prowess. American ginseng never became an important medicinal plant in American medicine, though the root was official in the United States Pharmacopeia from 1842–1882. It was regarded as a mild stimulant, and soothing to an upset stomach (S. Foster, 2009).

Evidence of the root's general strengthening effect has been examined for its ability to raise mental and physical capacity, as well as its protectant effect against diabetes, neurosis, radiation sickness, and some cancers. Today, its popularity is widely due to the adaptogenic[126] or stress-protective effect of the saponins (Blumenthal, 1997), (Jia, Y. Zhao, and X. Liang, 2009).

[125]This was an important aspect of folk medicine from the Middle Ages until the early modern period. Often associated with the work of herbalists and wise women, it drew upon the belief that natural objects that looked like a part of the body could cure diseases that would arise there. Folk healers in Christian and Muslim countries claimed that God, or Allah, deliberately made plants resemble the parts of the body they could cure. For example, eyebright, a plant whose flower looks like bright blue eyes, was used to treat eye diseases. The use of eyebright for this purpose was still common in the 1700s. This belief became known as the "doctrine of signatures" after the appearance of a book by the German mystic Jakob Boehme called The Signature of All Things (1621). The Swiss physician Paracelsus, an important advocate of the doctrine of signatures, stated that "Nature marks each growth according to its curative benefit." Similarly, the English botanist William Cole (1626-62) believed that "the mercy of God... maketh Herbes for the use of men, and hath given them particular Signatures, whereby a man may read the use of them." (Museum, 2015)

[126]generating a substance that balances the body, particularly when the body is under stress, by either stimulating or relaxing

## Uses

Ginseng root is widely used for its adaptogenic, immunomodulatory[127], antineoplastic[128], cardiovascular, Central Nervous System (CNS), endocrine, and ergogenic[129] effects, but these uses have not been confirmed by clinical trials.

There is some evidence that Panax ginseng may -

- Help boost the immune system,
- Reduce the risk of cancer,
- Improve mental performance and well being (unknown, 2014b).

## Claims

Ginseng is said to enhance physical (including sexual) and mental performance and to have adaptogenic effects. Other claims include reduction in plasma glucose levels; increases in HDL, Hb, and protein levels; stimulation of the immune system; and anticancer, cardiotonic, endocrine, CNS, and oestrogenic effects. Recent Canadian studies show that a polysaccharide extract of Panax quinquefolius is useful in helping prevent colds (merck, 2015).

## Chemistry

American ginseng products are made from ginseng root and the long, thin offshoots called root hairs. The main chemical ingredients of American ginseng are ginsenosides and polysaccharide glycans (quinquefolans A, B, and C) (unknown, 2014b).

Major compounds in ginseng include triterpene saponins, polyacetylenes, sequiterpenes, polysaccharides, peptidoglycans, nitrogen-containing compounds, and other compounds, including fatty acids, carbohydrates, and phenolic compounds (WHO, 1999c), (Jia, Y. Zhao, and X. Liang, 2009), (L. P. Christensen, 2009). The triterpene saponins are considered the most active compounds, and some estimates report up to 150 different ginsenosides, grouped into either dammarane or oleanane groups (L. P. Christensen, 2009). Many analytical methods have been described and standards published. The European Pharmacopoeia requires a minimum of 0.4% combined Rg1 and Rb1 ginsenosides, while the Chinese Pharmacopoeia requires ginseng radix (dry root) to have not less than 0.3% Rg1 and Re combined ginsenosides and not less than 0.2% Rb1 (Jia, Y. Zhao, and X. Liang, 2009).

[127] capable of modifying or regulating one or more immune functions

[128] inhibiting or preventing development of neoplasms; checking maturation and proliferation of malignant cells

[129] a tendency to increase work output

Most traditional ginseng herbal preparations contain ginsenosides. However, a commercially available product, known as CVT-E002, a patented aqueous extract of approximately 80% to 90% poly-furanosyl-pyranosyl-saccharides from the roots of North American ginseng (Panax quinquefolius), does not contain ginsenosides (Chuang et al., 1995).

Adulterants[130] are commonly found in ginseng preparations due to the high cost of authentic ginseng roots, and the presence of natural methylxanthines[131] may also contribute to some reported physiological[132] effects (L. P. Christensen, 2009), (Chuang et al., 1995), (Blumenthal, Gruenwald, et al., 1997).

Variances in cultivation and processing methods, as well as the individual genetics of each plant source, result in varying chemical compositions among commercial products. This may contribute to the lack of consensus among studies on the pharmacology and efficacy of ginseng and should be considered when conducting and interpreting research (WHO, 1999c), (C. F. Chen, Chiou, and J. T. Zhang, 2008). A second factor that may have produced erratic results is the discovery that ginsenosides are metabolised extensively by the human gut microflora and that some of the metabolites are pharmacologically active. Colonic bacteria can remove the 3 sugars from ginsenoside Rb1 in stepwise fashion[133], and the deglycosylated compounds are then esterified in the liver with the fatty acids stearic, palmitic, and oleic acid. These esters persist in the liver for as long as 24 hours (Hasegawa, 2004). Thus, differences in an individual's gut flora may lead to differing pharmacological responses to ginseng preparations.

## Uses and Pharmacology

Reviews of the effects of ginseng have been published. Most studies have used whole-root preparations, with considerable variations due to uncertain species identification, age of the roots, and curing process used. Variations in saponins between the species also may contribute to the lack of consensus among researchers on ginseng's pharmacology (WHO, 1999c), (L. P. Christensen, 2009), (Kurihara and Kiruchi, 1973).

[130] a substance or chemical which is added to a drug to increase the quantity, reduce manufacturing costs and change the potency of the drug

[131] a chemical group of drugs derived from xanthine (a purine derivative); members of the group include theophylline, caffeine, and theobromine

[132] relating to the action of a drug when given to a healthy person, as distinguished from its therapeutic action

[133] showing a gradual progression as if step by step

## Cancer

### Animal data

Both ginsenosides and polyacetylenes have demonstrated anti-carcinogenic[134] effects in-vitro, including direct cytotoxic[135] and growth inhibitory effects, induction of differentiation, and inhibition of metastasis[136]. High concentrations of M1, an active metabolite of Rb1, Rb2, and Rc, induced cell death of mouse melanoma cells by regulating proteins involved in apoptosis[137]. Ginsenosides Rh2 and Rh3 induced differentiation of promyelocytic[138] leukemia cells into granulocytes; Rg3 inhibited adhesion and invasion of melanoma cells and decreased pulmonary metastasis (L. P. Christensen, 2009), (Qi, C. Z. Wang, and C. S. Yuan, 2010), (Ng, 2006).

### Clinical data

Epidemiological data support a protective effect of ginseng on nonspecific organ cancers (L. P. Christensen, 2009), (T. K. Yun, S. Zheng, and S. Y. Choi, 2010). A long-term study of ginseng 1 g taken weekly for 3 years among adults with long-term atrophic gastritis showed no effect on the overall relative risk of cancer. In the male subgroup analysis, there was a reduction in the risk of non-organ-specific cancers (T. K. Yun, S. Zheng, and S. Y. Choi, 2010).

Trials evaluating the effect of ginseng (both Panax quinquefolius and Panax ginseng) on cancer-related fatigue at doses of 1 to 2 g/day over 8 to 12 weeks have shown effects for some, but not all, aspects of mental and physical functioning (Barton, Soori, and B. A. Bauer, 2010), (J. H. Kim, C. Y. Park, and S. J. Lee, 2006). Ginseng may improve some of the adverse effects of chemotherapy-related transcatheter arterial chemoembolization[139] (Yinglu et al., 2009).

---

[134] pertaining to a substance or device that neutralizes the effects of a cancer-causing substance

[135] relating to, or producing a toxic effect on cells

[136] transmission of pathogenic microorganisms or cancerous cells from an original site to one or more sites elsewhere in the body, usually by way of the blood vessels or lymphatics

[137] A natural process of self-destruction in certain cells that is determined by the genes and can be initiated by a stimulus or by removal of a repressor agent

[138] A cell containing a few granules formed in the transition from myeloblast to myelocyte during the development of a granulocyte; it is the predominant cell type seen in granulocytic leukemia

[139] injection of chemotherapeutic agent(s) and/or inert particles into tumour vessel(s)

## Cardiovascular effects

Ginseng saponins have been reported to act as selective calcium antagonists and enhance the release of nitric oxide from endothelial and neuronal cells. In-vitro studies have shown that total ginseng saponins extracted from Panax notoginseng and Panax quinquefolius inhibited calcium entry through receptor-operated calcium channels without affecting calcium entry through voltage channels or intracellular calcium release (L. P. Christensen, 2009), (C. Y. Kwan, 1995).

### Animal data

In studies involving rabbits and dogs, ginsenosides Ro and Rb from Panax ginseng offered a protective effect in myocardial ischaemia and reperfusion injuries. This effect may be partly mediated by increased release of prostacyclin and by activation of nitric oxide synthase and subsequent release of nitric oxide. An inhibitory effect on platelet aggregation and on the conversion of fibrinogen to fibrin has been demonstrated, and the prevention of atheroma in rabbits fed a high-cholesterol diet has been observed (L. P. Christensen, 2009), (X. Chen, 1996).

### Clinical data

Clinical trials evaluating the effect of ginseng on the cardiovascular system are limited. Hypotensive and hypertensive effects have been postulated. In a short-term study in healthy adults, ginseng 3 g had no effect on blood pressure but lowered the arterial augmentation index (Jovanovski, A. Jenkins, and Dias, 2010), while a 12-week study among hypertensive adults found no effect of ginseng on 24-hour blood pressure or on renal function (P. M. Stavro et al., 2006). Shenfu injection, a mixture of ginseng and monkshood, has been used to prevent reperfusion injury following mitral valve replacement (C. D. Zheng and Min, 2008). Sanchi (Panax notoginseng) is widely used in traditional Chinese medicine in acute ischaemic stroke. The saponins in sanchi are similar to those found in Panax ginseng and are classified as dammarane saponins (Rb1 and Rg1 primarily). A review of clinical trials found limited evidence of effect of sanchi on short-term effects of ischaemic stroke, but noted that the trials were of limited methodological quality (X. Chen, M. Zhou, and Q. Li, 2008).

## CNS effects

Rb1 and Rg1 appear to play a major role in CNS stimulatory and inhibitory effects and may modulate neurotransmitters. Cholinergic[140] activity, implicated in mediating learning and memory processes, is affected by certain ginsenosides. Antioxidant, anti-inflammatory, antiapoptotic[141], and immune stimulatory effects are suggested to contribute to a protective effect in neurodegenerative disorders (Radad et al., 2006).

### Animal data

Animal studies show that Rb1, Rg1, and Re prevent scopolamine-induced memory deficits, and that Rb1 and Rg1 appear to increase central choline uptake and facilitate the release of acetylcholine from hippocampal tissues. Results from a study in aged rats suggest that daily oral administration of Panax ginseng extract 8 g/kg/day for 12 days improved learning performance. In animal tissues, ginseng extract inhibited gamma-aminobutyric acid (GABA), glutamine, dopamine, noradrenalin, and serotonin uptake in a concentration-dependent[142] manner (L. P. Christensen, 2009), (Radad et al., 2006), (Bahrke and W. R. Morgan, 2000), (Attele, J. A. Wu, and C. S. Yuan, 1999).

### Clinical data

Limited high-quality clinical trials have been conducted, and systematic reviews include data from very few studies (Kurihara and Kiruchi, 1973), (M. S. Lee et al., 2009). An anxiolytic[143] effect via GABA modulation was suggested to be responsible for an observed improvement in sleep disorders for fermented ginseng (Kitaoka, Uchida, and Okamoto, 2009). Among healthy adults, short-term effects of Panax ginseng and Panax quinquefolius include increased mental performance, increased calmness, and decreased mental fatigue (Reay, D. O. Kennedy, and A. B. Scholey, 2006a), (A. Scholey, Ossoukhova, and L. Owen, 2010), (Reay, A. B. Scholey, and D. O. Kennedy, 2010). A review of the effect of ginseng on cognitive

[140] this refers to any compound that can increase levels of acetylcholine or choline in the brain

[141] something that prevents apoptosis

[142] A drug that shows optimum response in its effect when its concentration is either equal or greater than 10 times above the MIC (minimum inhibitory concentration) at the site of infection for certain target micro-organism

[143] having the ability to inhibit anxiety

function[144] in Alzheimer disease found an effect in favour of ginseng for the mini-mental status examination and Alzheimer Disease Assessment Scale for the 2 included studies (M. S. Lee et al., 2009), (Heo, S. T. Lee, and Chu, 2008).

## Diabetes

### Animal data

Widespread usage of ginseng and the availability of limited clinical trial data make animal studies largely redundant.

Evidence appears to support the modulation of insulin sensitisation and secretion based on cholinergic, dopaminergic[145], adrenergic, and nitric oxide actions found with ginsenosides. These have been noted to affect glucose metabolism in animal studies (Radad et al., 2006), (Vuksan, Sievenpiper, and Koo, 2000), (Vuksan, M. P. Stavro, and Sievenpiper, 2000).

### Clinical data

Limited quality clinical trials have been conducted among adults with diabetes, with the majority of studies evaluating ginseng in healthy volunteers. Improvements in blood glucose measures and glycaemic control have been reported in some, (Vuksan, Sievenpiper, and Koo, 2000), (Vuksan, M. P. Stavro, and Sievenpiper, 2000), (Sievenpiper, M. K. Sung, and Di Buono, 2006), (Reay, A. B. Scholey, Milne, et al., 2009), (Reay, D. O. Kennedy, and A. B. Scholey, 2006b) but not all, (Reay, A. B. Scholey, and D. O. Kennedy, 2010), (Vuksan, M. K. Sung, and Sievenpiper, 2008), (E. d. Andrade, Mesquita, and Claro Jde, 2007) studies.

## Ergogenic effects

### Animal data

Widespread usage of ginseng and the availability of limited clinical trial data make animal studies largely redundant.

[144] an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering

[145] related to dopamine

## Clinical data

Evidence supporting the efficacy of ginseng in improving physical performance is conflicting. Physical performance in young, active volunteers did not improve in 4 studies; however, other studies reported a decrease in heart rate and an increase in maximal oxygen uptake (Kurihara and Kiruchi, 1973), (Kulaputana, Thanakomsirichot, and Anomasiri, 2007). One comprehensive literature search evaluated Panax ginseng preparations in data from human studies. Properly controlled studies using higher doses (standardised to 2 g/day of dried root) administered for at least 8 weeks and in larger subject numbers more often exhibited improvement in physical or psychomotor performance. Benefit was seen in untrained subjects or in those older than 40 years (Bucci, 2000).

# Immunomodulatory and adaptogenic effects

## Animal data

Animal studies have shown that ginseng extracts can prolong swimming time, prevent stress-induced ulcers, stimulate the proliferation[146] of hepatic ribosomes, increase natural killer-cell activity, and possibly enhance the production of interferons (V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984b). Increased spleen B lymphocyte proliferation and serum immunoglobulin production have been documented in animal models. Increased peritoneal exudate macrophage production of the cytokines IL-1, tumour necrosis factor-alpha, and IL-6, and the production of nitric oxide has also been reported (M. Wang, Guilbert, and L. Ling, 2001), (Haddad et al., 2005).

## Clinical data

Studies in healthy volunteers measuring T-lymphocyte immunomodulation yield equivocal results (Kurihara and Kiruchi, 1973), (Attele, J. A. Wu, and C. S. Yuan, 1999). Studies in healthy sedentary men and healthy physically active men have found no effect of ginseng on immune markers (Kulaputana, Thanakomsirichot, and Anomasiri, 2007), (Biondo et al., 2008). Modulation of CD8+ T cells and interleukin production was reported in sedentary men beginning to exercise (Biondo et al., 2008). A possible effect of ginseng on the CD4+ T cell count in HIV-positive men was reported (unknown, 2009b).

[146] Multiplying or increasing in number. In biology, cell proliferation occurs by a process called cell division

Clinical trials supported by the manufacturers of a patented Panax quinquefolius preparation suggest a lowered incidence of influenza with the use of ginseng as a prophylactic[147], especially among elderly patients (McElhaney, Gravenstein, and Cole, 2004), (Predy, V. Goel, R. Lovlin, Donner, et al., 2005), (Predy, V. Goel, R. Lovlin, Shan, et al., 2005), (Predy, V. Goel, R. E. Lovlin, et al., 2006), (McElhaney, V. Goel, et al., 2006). Dosage studies have taken place to evaluate the effect of ginseng in children with upper respiratory tract infections (Vohra, Johnston, and Laycock, 2008).

## Other effects

Studies in postmenopausal women suggest ginseng 1 g daily (as Korean Red ginseng) may increase sexual arousal possibly via a relaxing effect on the clitoral cavernosal muscle and vaginal smooth muscle (Oh et al., 2010).

In men, an improvement in erectile function has been shown in a meta-analysis[148] of clinical studies (Jang et al., 2008), (T. H. Kim, S. H. Jeon, and Hahn, 2009).

- **Diabetes** - Several human studies show that American ginseng lowered blood sugar levels in people with type 2 diabetes. The effect was seen both on fasting blood sugar and on postprandial[149] glucose levels. One study found that people with type 2 diabetes who took American ginseng before or together with a high sugar drink experienced less of an increase in blood glucose levels. Other studies suggest that North American ginseng prevents diabetes-related complications including retinal and cardiac functional changes by reducing stress. More research is needed (unknown, 2014b).
  One study in mice found that the American ginseng berry was more effective at lowering blood sugar levels than the root.
- **Cancer** - American ginseng has been shown to inhibit tumour growth. In one laboratory study on colorectal cancer cells, researchers found that American ginseng possessed powerful anti-cancer properties (unknown, 2014b).
- **Colds and flu** - In two studies, people who took a specific product called Cold FX for 4 months got fewer colds than people who took a placebo. And those who got colds found their symptoms did not last as long compared to those who took a placebo (unknown, 2014b).
- **Attention deficit hyperactivity disorder (ADHD)** - One preliminary study suggests that American ginseng, in combination with ginkgo (Ginkgo biloba), may help treat ADHD. More research is needed (unknown, 2014b).

[147] a preventative measure

[148] a statistical technique for combining the findings from independent studies

[149] after eating

- **Immune system enhancement** - Some scientists believe American ginseng enhances the immune system. In theory, this improvement in immune function could help the body fight off infection and disease. Several clinical studies have shown that American ginseng does boost the performance of cells that play a role in immunity (unknown, 2014b).
- **Cognition** - One preliminary study found that daily consumption of American ginseng enhanced cognitive function in mice. More research is needed (unknown, 2014b).

## Contraindications

Contraindications have not been established aside from known hypersensitivity.

## Adverse effects

Nervousness and excitability may occur but decrease after the first few days. Ability to concentrate may decrease, and plasma glucose may become abnormally low (causing hypoglycaemia). Because ginseng has an oestrogen–like effect, women who are pregnant or breastfeeding should not take it, nor should children. Occasionally, there are reports of more serious effects, such as asthma attacks, increased blood pressure, palpitations, and, in postmenopausal women, uterine bleeding. To many people, ginseng tastes unpleasant.

Ginseng can interact with antihyperglycaemic drugs, aspirin, other NSAIDs, corticosteroids, digoxin, oestrogens, monoamine oxidase inhibitors, and warfarin (merck, 2015).

## Side-effects

Side effects are rare, but may include -

- High blood pressure,
- Insomnia,
- Restlessness,
- Anxiety,
- Euphoria,
- Diarrhoea,
- Vomiting,
- Headache,
- Nosebleed,
- Breast pain,
- Vaginal bleeding (unknown, 2014b).

It is estimated that more than 6 million people regularly ingest ginseng in the United States. There have been few reports of severe reactions, and a very low incidence of adverse events has been reported in clinical trials (Seely et al., 2008). Hypersensitivity and anaphylaxis[150] have been reported (B. Barrett and D. J. Brown, 2007).

Inappropriate use of Panax ginseng has been described and caused symptoms such as **hypertension**, **diarrhoea**, **insomnia**, **breast pain**, **vaginal bleeding**, **rash**, **confusion**, and **depression**. A ginseng abuse syndrome was described based on an uncontrolled study[151] in which participants used up to 15 g ginseng daily. When the dosage was reduced to 1.7 g/day, adverse reactions resolved (WHO, 1999c), (Seely et al., 2008).

Oestrogenic effects have been reported in both pre- and postmenopausal women. However, studies with standardised extracts have shown no effect on oestrogenic receptors (rats) or progesterone receptors (humans) (WHO, 1999c), (Seely et al., 2008).

## Pregnancy/Lactation

Use during pregnancy and lactation should be avoided due to insufficient evidence of safety (WHO, 1999c), (Seely et al., 2008). An association of ginseng with androgenization in a case report is considered doubtful and more likely due to adulterants in the preparation (Seely et al., 2008), (Ernst, 2002b). Evidence from a cohort study[152] and a review of clinical trials conducted in Singapore found no association of adverse events among pregnant women consuming ginseng products, and ginseng is widely used in Asian countries in pregnant women (Seely et al., 2008). Concerns regarding oestrogenic effects of ginseng are unestablished, while in-vitro teratogenic[153]ity in rats has been reported at artificially high doses of ginsenosides (WHO, 1999c), (Seely et al., 2008).

[150] a serious allergic reaction that is rapid in onset and may cause death

[151] A clinical study that lacks a comparison (i.e., a control) group

[152] a cohort is any group of people who are linked in some way and followed over time. Researchers observe what happens to one group that's been exposed to a particular variable for example, the effect of company downsizing on the health of office workers. This group is then compared to a similar group that hasn't been exposed to the variable

[153] able to disturb the growth and development of an embryo or foetus

## Interactions

Limited evidence exists for any established interactions, with most data derived from laboratory studies and healthy volunteers. Very fewcase reports exist; however, caution should be exercised when using the following medicines with ginseng: anti-diabetic drugs insulin, anti-psychotic drugs, caffeine and other stimulants, furosemide, and MAOIs (WHO, 1999c), (Seely et al., 2008).

A 26-year-old man taking imatinib 400mg daily for 7 years was diagnosed with imatinib-induced hepatotoxicity 3 months after he started drinking energy drinks containing Panax ginseng. After treatment, he was able to restart imatinib without recurrence of elevations in his liver enzymes (Bilgi et al., 2010).

In a study in healthy volunteers, administration of a single dose of nifedipine after subjects ingested ginseng for 18 days increased nifedipine plasma concentrations 53% when measured 0.5 hours after nifedipine administration (M. Smith, K. M. Lin, and Y. P. Zheng, 2001).

Reports of an interaction between warfarin and ginseng are conflicting. There are case reports that ginseng may decrease the anti-coagulant effect of warfarin. However, open-label studies[154] found no effects of Panax ginseng on international normalized ratio or prothrombin times after 2 weeks of coadministration[155] (Rosado, 2003), (X. Jiang, K. M. Williams, and Liauw, 2004), (S. H. Lee et al., 2008).

Likewise, in studies conducted among healthy volunteers, ginseng exerted no influence on the pharmacokinetics[156] of zidovudine (Panax ginseng) (L. S. Lee et al., 2008) or indinavir (Panax quiquefolius) (A. S. Andrade, Hendrix, and T. L. Parsons, 2008).

If you are being treated with any of the following medications, you should not use ginseng without talking to your doctor -

- **Medications for diabetes** - American ginseng may lower blood sugar levels, so it could interfere with the effectiveness of prescription drugs for diabetes. Talk to your doctor before taking American ginseng if you are taking medicines for diabetes, including insulin and oral hypoglycaemic agents, such as metformin (Glucophage) (unknown, 2014b).

[154] when both the researcher and the participant know the treatment the participant is receiving

[155] administered along with something else

[156] involves the relationship between the dose of the drug and the concentration (amount) of the drug in the body. Pharmacokinetics observes how drug move around the body. The four key steps involved are - absorption, distribution, metabolism and elimination

- **Blood-thinning medications (anticoagulants)** - One small study suggested that American ginseng might decrease the effectiveness of warfarin (Coumadin), a blood-thinning medication. If you take any blood-thinning medications, talk to your doctor before taking ginseng (unknown, 2014b).
- **MAOIs (monoamine oxidase inhibitors)** - Ginseng may increase the risk of side effects when taken with MAOIs, a type of antidepressant. There have been reports of interaction between ginseng and phenelzine (Nardil) causing headaches, tremors, and mania. MAOIs include -
  - Isocarboxazid (Marplan),
  - Phenelzine (Nardil),
  - Tranylcypromine (Parnate) (unknown, 2014b).
- **Antipsychotic medications** - American ginseng may increase the effects of medications used to treat psychiatric disorders such as schizophrenia and bipolar disorder. So they should not be taken together (unknown, 2014b).
- **Stimulants** - Ginseng may increase the stimulant effect and side effects of some medications taken for attention deficit hyperactivity disorder (ADHD), including amphetamine and dextroamphetamine (Adderall) and methylphenidate (Concerta, Ritalin) (unknown, 2014b).

## Available Forms

American ginseng (dried) is available in water, water and alcohol, alcohol liquid extracts, and in powders, capsules, and tablets. American ginseng is available with other herbs in several combination formulas.

Be sure to read the label carefully so that you are purchasing the type of ginseng that you want. If you are looking for Asian ginseng, make sure you buy Korean, Red, or Panax ginseng. If you are looking for American ginseng, you should buy Panax quinquefolius (unknown, 2014b).

## Dosage

Ginseng root is standardised according to ginsenosides content, and can be chewed or taken as a powder, liquid extract, decoction, or infusion.

According to the Complete German Commission E Monographs, crude preparations of dried root powder 1 to 2 g can be taken daily for up to 3 months (Blumenthal, Gruenwald, et al., 1997). In numerous clinical trials, the dosage of crude root has ranged from 0.5 to 3 g/day and the dose of extracts has generally ranged from 100 to 400 glsmg (WHO, 1999c), (Kurihara and Kiruchi, 1973), (Ng, 2006). Other trials have used higher dosages (Vuksan, M. K. Sung, and Sievenpiper, 2008). The following doses have been studied in scientific research -

## By mouth

- **For reducing blood sugar after a meal in people with type 2 diabetes** - 3 grams up to 2 hours before a meal. American ginseng should be taken within 2 hours of a meal. If it is taken too long before eating, the blood sugar might become too low.
- **For preventing upper respiratory tract infections such as the common cold or flu** - a specific American ginseng extract called CVT-E002 (Cold-fX, Afexa Life Sciences, Canada) 200 mg twice daily for 3–4 months has been used (MedlinePlus, 2014b).

## Paediatric

American ginseng is not recommended for use in children except under a doctor's supervision (unknown, 2014b).

## Adult

Available forms include -

- Standardised extract,
- Fresh root,
- Dried root,
- Tincture (1:5),
- Fluid extract (1:1) (unknown, 2014b).

# Before using ginseng

Some medical conditions may interact with ginseng. Tell your doctor or pharmacist if you have any medical conditions, especially if any of the following apply to you -

- if you are pregnant, planning to become pregnant, or are breast-feeding,
- if you are taking any prescription or nonprescription medicine, herbal preparation, or dietary supplement,
- if you have allergies to medicines, foods, or other substances,
- if you have a fever, a history of high or low blood pressure, oestrogen-dependent cancer, diabetes, or heart problems,
- if you are taking "water pills" (diuretics such as bumetanide or furosemide).

Some medicines may interact with ginseng. However, no specific interactions with ginseng are known at this time.

This may not be a complete list of all interactions that may occur. Ask your health care provider if ginseng may interact with other medicines that you take. Check with your health care provider before you start, stop, or change the dose of any medicine.

Do not use ginseng if -

- you are allergic to any ingredient in ginseng,
- you are undergoing surgery, or you have any bleeding or blood clots.

Contact your doctor or health care provider right away if any of these apply to you.

## How to use ginseng

Use ginseng as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Take ginseng with a meal.
- There are different types of ginseng, which vary widely in quality. Read product labeling carefully.
- Ginseng may cause trouble sleeping. Do not take it in the early evening or at bedtime.
- If you miss taking a dose of ginseng for 1 or more days, there is no cause for concern. If your doctor recommended that you take it, try to remember to take your dose every day.

Ask your health care provider any questions you may have about how to use ginseng.

Ginseng is used for -

- Endurance and stamina. It is claimed to strengthen the body to resist disease and fight fatigue and stress, resulting in an improvement in physical and mental performance.

Ginseng is a dietary supplement. It is unknown exactly how ginseng works.

## Important safety information

- It is best to avoid taking ginseng for long periods of time (several months or more).
- **Diabetes patients** - Ginseng may affect your blood sugar. Check blood sugar levels closely and ask your doctor before adjusting the dose of your diabetes medicine.
- Ginseng is not recommended for use in children. Safety and effectiveness have not been confirmed.
- **Pregnancy and breast-feeding** - If you become pregnant while taking ginseng, discuss with your doctor the benefits and risks of using ginseng during pregnancy. It is unknown if ginseng is excreted in breast milk. If you are or will be breast-feeding while you are using ginseng, check with your doctor or pharmacist to discuss the risks to your baby.

## Possible side effects

All medicines may cause side effects, but many people have no, or minor, side effects. Check with your doctor if any of these most common side effects persist or become bothersome -

**Agitation, diarrhoea,** **headache, nervousness, trouble sleeping**.

Seek medical attention right away if any of these severe side effects occur -

Severe allergic reactions - **rash**, **hives**[157] **tightness in the chest**, **swelling of the mouth, face, lips, or tongue**, **vaginal bleeding**

This is not a complete list of all side effects that may occur. If you have questions about side effects, contact your health care provider. Call your doctor for medical advice about side effects.

### If overdose is suspected

Symptoms may include **trouble sleeping** or **swelling of ankles, feet, face, or hands**.

## How effective is it?

*Natural Medicines Comprehensive Database* rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

The effectiveness ratings for **American ginseng** are as follows -

### Possibly effective for...

- **Diabetes** - Taking 3 grams of American ginseng by mouth, up to two hours before a meal, can lower blood sugar after a meal in patients with type 2 diabetes. However, larger doses do not seem to lower blood sugar more. Different American ginseng products may have different effects. Researchers think that is because they contain different amounts of the active chemicals called ginsenosides.
- **Respiratory tract infections** - Some evidence suggests that taking a specific American ginseng extract called CVT-E002 (Cold-FX, Afexa Life Sciences, Canada), 200 mg twice daily over a 3–4 month period during flu season, might prevent cold or flu symptoms in adults between the ages of 18 and 65. People older than 65 seem to need a

[157] an allergic skin reaction causing localised Redness, swelling, and itching, itching, difficulty breathing,

flu shot at month 2 along with this treatment in order to decrease their risk of getting the flu or colds. This extract also seems to help make symptoms milder and last a shorter length of time when infections do occur. Some evidence suggests that the extract might not reduce the chance of getting the first cold of a season, but it seems to reduce the risk of getting repeat colds in a season.

## Possibly ineffective for...

- **Athletic performance** - Taking 1600 mg of American ginseng by mouth for 4 weeks does not seem to improve athletic performance; however, laboratory tests[158] show that it might decrease muscle damage during exercise.
- **High blood pressure** - Research suggests that taking 3 grams of American ginseng daily for up to 12 weeks does not affect blood pressure in people with high blood pressure.

## Insufficient evidence to rate effectiveness for...

- **Attention deficit-hyperactivity disorder (ADHD)** - There is early evidence that a specific product (AD-fX, Afexa Life Sciences, Canada), containing American ginseng extract in combination with ginkgo leaf extract, might help improve ADHD symptoms such as anxiety, hyperactivity, and impulsiveness in children aged 3–17 years.
- **Breast cancer** - Some studies conducted in China suggest that breast cancer patients treated with any form of ginseng (American or Panax) do better and feel better. However, this may not be a result of taking the ginseng, because the patients in the study were also more likely to be treated with the prescription cancer drug tamoxifen. It is difficult to know how much of the benefit to attribute to ginseng.
- **Cancer-related fatigue** - Early research suggests that taking 700–2000 mg of American ginseng daily for 8 weeks does not reduce fatigue in people with cancer.
- **Mental performance** - Some evidence suggests that taking one 100–400 mg dose of American ginseng improves short-term memory and reaction time before a mental test.
- **Menopausal symptoms** - Early evidence suggests that taking a product containing American ginseng, black cohosh, dong quai, milk thistle, red clover, and chasteberry tree (Phyto-Female Complex) twice daily for 3 months reduces menopausal symptoms, including hot flashes, night sweats, and sleep quality.
- **Stress**
- **Anaemia**

[158] A medical procedure that involves testing a sample of blood, urine, tissue, or other substance collected from the body. Tests can help determine a diagnosis, plan treatment, check to see whether treatment is working, or monitor a disease over time

- Insomnia
- **Gastritis**
- **Impotence**
- **Fever**
- **HIV/AIDS**
- **Fibromyalgia**
- **Other conditions**

More evidence is needed to rate the effectiveness of American ginseng for these uses.

## How does it work?

American ginseng contains chemicals called ginsenosides that seem to affect insulin levels in the body and lower blood sugar. Other chemicals, called polysaccharides, might affect the immune system.

## Are there safety concerns?

American ginseng is **possibly safe** in adults and children when used short-term. It can cause some side effects including **diarrhoea**, **itching**, **insomnia**, **headache**, and **nervousness**. In some people, American ginseng might also cause rapid heartbeat, increased blood pressure or decreased blood pressure, breast tenderness, vaginal bleeding in women, and other side effects. Uncommon side effects that have been reported include a **severe rash** called **Stevens-Johnson syndrome**, **liver damage**, and **severe allergic reaction**.

## Proper storage of ginseng

Store ginseng at room temperature, between 59 and 86 degrees F (15 and 30 degrees C), in a cool, dry place. Store away from heat, moisture, and light. Do not store in the bathroom. Most herbal products are not in childproof containers. Keep ginseng out of the reach of children and away from pets.

## General information

- If you have any questions about ginseng, please talk to your doctor, pharmacist, or other health care provider.
- Ginseng is to be used only by the patient for whom it is prescribed. Do not share it with other people.
- If your symptoms do not improve or if they become worse, check with your doctor.
- Check with your pharmacist about how to dispose of unused medicine (CDI, 2015).

## Special precautions & warnings

- **Pregnancy and breast-feeding** - American ginseng is **possibly unsafe** in pregnancy. One of the chemicals in Panax ginseng, a plant related to American ginseng, has been linked to possible birth defects. Do not take American ginseng if you are pregnant.
  Not enough is known about the safety of American ginseng during breast-feeding. Stay on the safe side and avoid use.
- **Diabetes** - American ginseng might lower blood sugar. In people with diabetes who are taking medications to lower blood sugar, adding American ginseng might lower it too much. Monitor your blood sugar closely if you have diabetes and use American ginseng.
- **Hormone-sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** - American ginseng preparations that contain chemicals called ginsenosides might act like oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use American ginseng that contains ginsenosides. However, some American ginseng extracts have had the ginsenosides removed (Cold-fX, Afexa Life Sciences, Canada). American ginseng extracts such as these that contain no ginsenosides or contain only a low concentration of ginsenosides do not appear to act like oestrogen.
- **Trouble sleeping (insomnia)** - High doses of American ginseng have been linked with insomnia. If you have trouble sleeping, use American ginseng with caution.
- **Schizophrenia (a mental disorder)** - High doses of American ginseng have been linked with sleep problems and agitation in people with schizophrenia. Be careful when using American ginseng if you have schizophrenia.
- **Surgery** - American ginseng might affect blood sugar levels and might interfere with blood sugar control during and after surgery. Stop taking American ginseng at least 2 weeks before a scheduled surgery.

## Are there interactions with medications?

### Major

**Do not take this combination**

- **Warfarin (Coumadin)** - Warfarin (Coumadin) is used to slow blood clotting. American ginseng has been reported to decrease the effectiveness of warfarin (Coumadin). Decreasing the effectiveness of warfarin (Coumadin) might increase the risk of clotting. It is unclear why this interaction might occur. To avoid this interaction, do not take American ginseng if you take warfarin (Coumadin).

## Moderate

**Be cautious with this combination**

- **Medications for depression (MAOIs)** - American ginseng might stimulate the body. Some medications used for depression can also stimulate the body. Taking American ginseng along with these medications used for depression might cause side effects such as anxiousness, headache, restlessness, and insomnia.
  Some of these medications used for depression include phenelzine (Nardil), tranylcypromine (Parnate), and others.
- **Medications for diabetes (Antidiabetes drugs)** - American ginseng might decrease blood sugar. Diabetes medications are also used to lower blood sugar. Taking American ginseng along with diabetes medications might cause your blood sugar to go too low. Monitor your blood sugar closely. The dose of your diabetes medication might need to be changed.
  Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia) , chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others.

- **Medications that decrease the immune system (Immunosuppressants)** - American ginseng can increase the immune system. Taking American ginseng along with some medications that decrease the immune system might decrease the effectiveness of these medications. Some medications that decrease the immune system include azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), pRednisone (Deltasone, Orasone), and other corticosteroids (glucocorticoids).

# Are there interactions with herbs and supplements?

## Herbs and supplements that can lower blood sugar

American ginseng might lower blood sugar. If it is taken along with other herbs and supplements that might lower blood sugar, blood sugar might get too low in some people. Some herbs and supplements that might lower blood sugar include devil's claw, fenugreek, ginger, guar gum, Panax ginseng, and Siberian ginseng.

# Are there interactions with foods?

There are no known interactions with foods.

## Surgery

Stop taking American ginseng at least 7 days prior to surgery. American ginseng can lower blood glucose levels and could create problems for patients fasting before surgery. In addition, American ginseng may act as a blood thinner, increasing the risk of bleeding during or after the procedure (unknown, 2014b).

## Toxicology

Embryotoxicity due to ginsenosides Rb1, Rc, Re, and Rg1 has been demonstrated in rat embryos (Seely et al., 2008). In-vitro studies found no carcinogenicity, mutagenic[159]ity, or teratogenicity for Radix ginseng (WHO, 1999c).

A doping-control urinalysis was conducted under International Olympic Committee (IOC) doping control guidelines for CVT-E002 200 and found no IOC-banned substances that might induce a positive doping-control urinalysis (D. P. Goel et al., 2004).

## Commentary

*As the quality is so variable, and also the total content of usable American Ginseng, it is expensive and therefore not worth the risk of being taken.*

## Definition

Radix Ginseng is the dried root of Panax ginseng, otherwise known as "American Ginseng".

## Common Names

Chosen ninjin, Ginsengwurzel, hakusan, hakushan, higeninjin, hongshen, hungseng, hungshen, hunseng, jenseng, jenshen, jinpi, kao-li-seng, minjin, nhan sam, ninjin, ninzin, niuhuan, otane ninjin, renshen, san-pi, shanshen, sheng-sai-seng, shenshaishanshen, shengshaishen, t'ang-seng, tyosenninzin, yakuyo ninjin, yakuyo ninzin, yehshan-seng, yuan-seng, yuanshen

## Latin name

*Panax schinseng*

[159]a mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level

## Geographical distribution

Mountain regions of China (Manchuria), the Democratic People's Republic of Korea, Japan, the Republic of Korea, and the Russian Federation (eastern Siberia) (Bruneton, 1995c), (WHO, 1989). It is commercially produced mainly by cultivation (Shibata, 1985).

## Major chemical constituents

The major chemical constituents[160] are triterpene saponins. More than 30 are based on the dammarane structure, and one (ginsenoside Ro) is derived from oleanolic acid (Shibata, 1985), (Bruneton, 1995c), (J. F. Cui, 1995), (Sprecher, 1987). The dammarane saponins are derivatives of either protopanaxadiol or protopanaxatriol. Members of the former group include ginsenosides Ra1-3, Rb1-3, Rc, Rc2, Rd, Rd2, and Rh2; (20S)-ginsenoside Rg3; and malonyl ginsenosides Rb1, Rb2, Rc, and Rd. Examples of protopanaxatriol saponins are ginsenosides Re2, Re3, Rf, Rg1, Rg2, and Rh1; 20- gluco-ginsenoside Rf; and (20R)-ginsenosides Rg2 and Rh1. Those considered most important are ginsenosides Rb1, Rb2, Rc, Rd, Rf, Rg1, and Rg2; Rb1, Rb2, and Rg1 are the most abundant.

## Pharmacology

### Experimental pharmacology

The suggested mode of action of Radix Ginseng is twofold. First, the drug has an adaptogenic effect (Wagner, Norr, and Winterhoff, 1994), which produces a non-specific increase in the body's own defences against exogenous[161] stress factors and noxious chemicals (Sonnenborn and Proppert, 1991). Secondly, the drug promotes an overall improvement in physical and mental performance (Wagner, Norr, and Winterhoff, 1994), (Sonnenborn and Proppert, 1991), (R. T. Owen, 1981a), (Phillipson and L. A. Anderson, 1984).

Treatment of cultured mammalian cells, isolated organs, and animal models (primarily mice and rats) with Radix Ginseng before or during exposure to physical, chemical, or psychological stress increased the ability of the respective model systems to resist the damaging effects of various stressors (Sonnenborn and Proppert, 1991). These results were demonstrated in cases of radiation poisoning (Takeda, Yonezawa, and Katoh, 1981), (Yonezawa, Katoh, and Takeda, 1985), (J. S. Zhang, 1987), viral infection and tumour

[160] A component, part, or ingredient of a larger whole. For example, valerenic acid and valepotriate are constituents of the dietary supplement valerian

[161] outside the body

load[162] (Qian, 1987), (T. K. Yun, Y. S. Yun, and I. W. Han, 1980), alcohol or carbon tetrachloride poisoning (C. W. Choi, S. I. Lee, and Huk, 1984), (Hikino, 1985a), (Nakagawa, 1985), oxygen deprivation and hypobaric pressure (X. Chen, 1987), (G. Lu, X. J. Cheng, and W. X. Yuan, 1988b), light or temperature stress, emotional stress, and electrical shock or restricted movement (Banerjee and Izquierdo, 1982), (X. J. Cheng, 1987), (Saito, 1974). The mechanism by which the drug exerts its activity is most likely through the hypothalamuspituitaryadrenal axis (Filaretov, 1986), (G. Lu, X. J. Cheng, and W. X. Yuan, 1988a), (Ng, W. W. Li, and Yeung, 1987) and through its immunostimulant effect (Sonnenborn, 1989a).

Intraperitoneal administration to rats of ginseng saponin fractions or the ginsenosides Rb1, Rb2, Rc, Rd, and Re elevated serum levels of adrenocorticotropic hormone (ACTH) and corticosterone (Hiai, 1979), (Hiai, Sasaki, and Oura, 1979). Pretreatment with dexamethasone, which blocks hypothalamus and pituitary functions, prevented ginseng saponin-mediated release of ACTH and corticosterone, and thereby demonstrated that the increase in serum corticosterone by ginseng occurs indirectly through release of ACTH from the pituitary (Hiai, 1979), (Hiai, Sasaki, and Oura, 1979).

The immunomodulatory[163] activity of ginseng appears to be at least partly responsible for its adaptogenic effect (Sonnenborn, 1989a), (V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984a), (Sonnenborn, 1987). Alcohol extracts of Radix Ginseng stimulated phagocytosis in-vitro, were mitogenic[164] in cultured human lymphocytes, stimulated the production of interferon, and enhanced the activity of natural killer cells (Fulder, 1977), (S. Gupta, 1980). Intraperitoneal administration of an extract of the drug to mice stimulated cell-mediated immunity[165] against Semliki Forest virus, elevated antibody levels against sheep red blood cells and natural killer cells (V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984c), and stimulated the production of interferon (Jie, Cammisuli, and Baggiolini, 1984).

Improvement in physical and mental performance has been observed in mice and rats after oral or intraperitoneal administration of the drug (Avakian, 1984), (Brekhman and Dardymov, 1969), (Hassan Samira, 1985), (V. Petkov, 1978), (Bombardelli, Cristoni, and Lietti, 1980). Oral administration of ginseng saponin fractions to mice increased endurance and prolonged swimming time in swimming tests (Bombardelli, Cristoni, and Lietti, 1980). However, two studies concluded that ginseng had no positive effects on the physical performance in mice and rats (W. H. Lewis, Zenger, and R. G. Lynch, 1983), (Martinez and Staba, 1984). The

[162] Refers to the number of cancer cells, the size of a tumour, or the amount of cancer in the body

[163] capable of modifying or regulating one or more immune functions

[164] stimulating cell division, which division is known as "mitosis"

[165] an immune response that does not involve antibodies, but rather involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen

adaptogenic effects of Radix Ginseng are generally attributed to the ginsenosides (C. X. Liu and P. G. Xiao, 1992), (Z. W. Yang, 1986). The ginsenosides have been shown to alter mechanisms of fuel homeostasis[166] during prolonged exercise, by increasing the capacity of skeletal muscle to oxidize free fatty acids in preference to glucose for cellular energy production (Avakian, 1984). Other constituents of Radix Ginseng, such as vanillic and salicylic acid, have also been reported to have "antifatigue" activity in rats (B. H. Han, Y. N. Han, and M. H. Park, 1985). Furthermore, the antioxidant activity of ginseng was associated with both the ginsenosides and the flavonoid constituents (Sonnenborn and Proppert, 1991), (H. Kim, 1992). The ginsenosides protected pulmonary vascular endothelium against freeradical- induced injury (H. Kim, 1992).

Mice given ginseng extract or ginsenosides Rb1 and Rg2 orally during passive avoidance response tests showed an improvement in learning ability which was negatively influenced by stress (Wagner, Norr, and Winterhoff, 1994), and rats showed improved retention of learned behaviour (V. D. Petkov, 1993). Ginsenosides Rg1 and Rb1 are the active nootropic constituents of the drug (C. X. Liu and P. G. Xiao, 1992), and improve memory and learning in normal as well as cognition-impaired animals. The mode of action involves an increase in the synthesis and release of acetylcholine, and a decrease of brain serotonin levels (C. X. Liu and P. G. Xiao, 1992). In cerebral and coronary blood vessels, extracts of Radix Ginseng produced vasodilatation, which improved brain and coronary blood flow (K. C. Huang, 1993). The vasodilator[167]y activity of the ginsenosides appears to be primarily due to relaxation of vascular smooth muscles. The ginsenosides block the constricting effects of norepinephrine in isolated aorta strips, and inhibit the uptake of 45Ca2+ in the membrane and sarcolemma of rabbit heart tissue. Inhibition of Ca2+ uptake in the muscle membrane contributes to the mechanism of vasodilatation (K. C. Huang, 1993).

A number of polypeptides and glycans isolated from Radix Ginseng, named GP and panaxans AE, respectively, have demonstrated hypoglycaemic activity when given intraperitoneally to mice (Marles and Farnsworth, 1995), (B. X. Wang, 1989). Two of the glycans, panaxans A and B, have been shown to stimulate hepatic glucose utilisation by increasing the activity of glucose-6-phosphate 1-dehydrogenase, phosphorylase a, and phosphofructokinase (Marles and Farnsworth, 1995). Panaxan A did not affect plasma insulin levels or insulin sensitivity, but panaxan B elevated the plasma insulin level by stimulating insulin secretion from pancreatic islets, and further enhanced insulin sensitivity by increasing insulin binding to receptors (Marles and Farnsworth, 1995). The panaxans are not active after oral administration. Administration of GP (intravenously or subcutaneously) to mice or rats decreased blood

[166] a self-regulating process by which biological systems in the human body tend to maintain stability while adjusting to conditions that are optimal for survival

[167] causing dilation of blood vessels

glucose and liver glycogen levels (B. X. Wang, 1989). Radix Ginseng also contains a number of other constituents with hypoglycaemic activity (Marles and Farnsworth, 1995), (Davydov, Molokovsky, and Limarenko, 1990). Adenosine, isolated from a water extract of Radix Ginseng, enhanced lipogenesis and cyclic AMP accumulation of adipocytes, and some of the ginsenosides inhibited ACTH-induced lipolysis, suppressed insulin-stimulated lipogenesis, and stimulated the release of insulin from cultured islets (Marles and Farnsworth, 1995).

Subcutaneous administration of a ginseng extract enhanced the mating behaviour of male rats (C. Kim, 1976). The drug further stimulated spermatogenesis in rat (M. Yamamoto, 1977), and rabbit testes, and increased the motility and survival of rabbit sperm outside the body (C. Kim, 1976).

Intragastric or intradermal administration of an ethanol[168] extract of the drug to rats decreased histamine-, pentagastrin-, carbachol- and vagal stimulation induced gastric[169] secretion, and inhibited gastric ulcers induced by stress or by pyloric ligation (Y. Suzuki, 1991b), (Y. Suzuki, 1991a), (Matsuda and Kubo, 1984).

Liver-protectant activity of ginseng has been demonstrated in-vitro and in-vivo[170] (Hikino, 1985b), (J. H. Lin, 1995). Intraperitoneal administration of Radix Ginseng extracts to normal and dexamethasone-treated rats did not influence the blood chemistry of normal rats, but it decreased aspartate aminotransferase and alanine aminotransferase levels in dexamethasone-treated animals, thereby demonstrating a liver-protectant effect (J. H. Lin, 1995). However, another study demonstrated that an intraperitoneal injection of a methanol extract of Radix Ginseng had no protective activity against carbon tetrachloride-induced hepatotoxicity in rats (Kumazawa, 1990).

## Clinical pharmacology

### Antifatigue activity

The results of clinical studies measuring increased performance and anti-fatigue effects of ginseng extracts are conflicting and, in general, most studies suffer from poor methodology, lack of proper controls, and no standardisation of the ginseng extracts used.

The influence of chronic Radix Ginseng administration (2 g/day orally for 4 weeks) on substrate utilisation, hormone production, endurance, metabolism, and perception of effort during consecutive days of exhaustive exercise in 11 naval cadets was reported. No significant differences

[168] A type of alcohol. Also called ethyl alcohol or grain alcohol

[169] having to do with the stomach

[170] within the living organism

were observed between the control group and the group receiving the ginseng supplementation (Knapik, J. E. Wright, and Welch, 1983). Another clinical trial with eight participants reported no significant difference between placebo and ginseng administration during exhaustive exercise after 7 days of treatment (Morris, I. Jacobs, and Kligerman, 1994). A randomised, double-blind, cross-over study[171] sought the effects of ginseng on circulatory, respiratory, and metabolic functions during maximal exercise in 50 men (21–47 years old) (Pieralisi, Ripari, and Vecchiet, 1991). Total tolerated workload and maximal oxygen uptake were significantly higher following ginseng administration than with placebo. At the same workload, oxygen consumption, plasma lactate levels, ventilation, carbon dioxide production, and heart rate during exercise were all lower in the ginseng treatment group. The results indicated that the ginseng preparations effectively increased the work capacity of the participants by improving oxygen utilisation (Pieralisi, Ripari, and Vecchiet, 1991). A placebo-controlled, cross-over study determined the effects of ginseng on the physical fitness of 43 male triathletes (Van Schepdael, 1993). The participants received 200mg of a ginseng preparation twice daily for two consecutive training periods of 10 weeks. No significant changes were observed during the first 10-week period, but ginseng appeared to prevent the loss of physical fitness (as measured by oxygen uptake and oxygen pulse) during the second 10-week period (Van Schepdael, 1993). Two further studies with athletes given 100 mg of a standardised ginseng extract twice daily for 9 weeks reported significant improvement in aerobic capacity and reduction in blood lactate and heart rates (Forgo and Kirchdorfer, 1982), (Forgo and Kirchdorfer, 1981), but placebos or controls were not used in either of the two studies. Further extension of these studies using placebo-controlled, double-blind trials demonstrated significant improvement in the ginseng group as compared with the placebo group[172] (Forgo, 1983). Similar results were reported in another study on athletes, and the differences between the ginseng and placebo groups lasted for approximately 3 weeks after the last ginseng dose (Forgo and Schimert, 1985). The effects of 1200mg of Radix Ginseng in a placebo-controlled, double-blind cross-over study in fatigued night nurses were assessed and the results were compared with placebo and with effects on nurses engaged in daytime work (Hallstrom, Fulder, and Carruthers, 1982). Ginseng restored ratings on tests of mood, competence, and general performance, and the study concluded that ginseng had anti-fatigue activity (Hallstrom, Fulder, and Carruthers, 1982).

Aqueous and standardised ginseng extracts were tested in a placebo-controlled, double-blind study for immunomodulatory actions (Scaglione, 1990). Sixty healthy volunteers were divided into three groups of 20 each and were given either a placebo or 100 mg of aqueous ginseng extract or 100 mg of standardised ginseng extract, every 12 hours for 8 weeks. Blood

[171] a type of clinical trial in which the study participants receive each treatment in a random order

[172] a group that is given a placebo in a research study

samples drawn from the volunteers revealed an increase in chemotaxis[173] of polymorphonuclear leukocytes, the phagocytic[174] index, and the total number of T3 and T4 lymphocytes after 4 and 8 weeks of ginseng therapy, as compared with the placebo group. The group receiving the standardised extract also increased their T4: T8 ratio and the activity of natural killer cells. The conclusion of this study was that ginseng extract stimulated the immune system in humans, and that the standardised extract was more effective than the aqueous extract (Scaglione, 1990).

## Psychomotor activity

A double-blind, placebo-controlled clinical study assessed the effect of standardised ginseng extract (100 mg twice daily for 12 weeks) on psychomotor performance in 16 healthy individuals (D'Angelo, 1986). Various tests of pyschomotor performance found a favourable effect on attention, processing, integrated sensory-motor function, and auditory reaction time. The study concluded that the drug was superior to the placebo in improving certain psychomotor functions in healthy subjects (D'Angelo, 1986).

## Antidiabetic activity

Radix Ginseng has been shown in clinical studies to have beneficial effects in both insulin-dependent and non-insulin-dependent diabetic patients (H. J. Kwan and Wan, 1994), (Sotaniemi, Haapakoski, and Rautio, 1995). Oral administration of ginseng tablets (200 mg daily for 8 weeks) to 36 noninsulin- dependent patients elevated mood, improved physical performance, reduced fasting blood glucose and serum aminoterminal propeptide of type III procollagen concentrations, and lowered glycated haemoglobin (Sotaniemi, Haapakoski, and Rautio, 1995).

## Impotence

Ginseng extracts improved sperm production in men and may have some usefulness in treating impotence (R. T. Owen, 1981b). The ginsenosides, which appear to be the active components, are thought to depress blood prolactin levels, thereby increasing libido (R. T. Owen, 1981b). In one clinical study, 90 patients with erectile dysfunction were treated with ginseng saponins (600 mg orally per day). Treatment improved rigidity, tumescence, and libido, but not the frequency of coitus (H. K. Choi and Seong, 1995).

[173] movement of an organism in response to a chemical stimulus

[174] causing waste material to be engulfed and absorbed, also harmful microorganisms, or other foreign bodies in the bloodstream and tissues to be absorbed

## Medicinal uses

- **Uses supported by clinical data** - Radix Ginseng is used as a prophylactic and restorative[175] agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness, and loss of concentration, and during convalescence ("Ginseng radix" 1991), (Hallstrom, Fulder, and Carruthers, 1982), (D'Angelo, 1986), (Pieralisi, Ripari, and Vecchiet, 1991), (Van Schepdael, 1993), (Forgo and Kirchdorfer, 1982), (Forgo and Kirchdorfer, 1981), (Forgo, 1983), (Forgo and Schimert, 1985).
- **Uses described in pharmacopoeias and in traditional systems of medicine** - Radix Ginseng has been used clinically in the treatment of diabetes (unknown, 1992), but further clinical studies are needed. The drug is also used in the treatment of impotence, prevention of hepatotoxicity, and gastrointestinal disorders such as gastritis and ulcers (unknown, 1992), (Bruneton, 1995c).
- **Uses described in folk medicine, not supported by experimental or clinical data** - Treatment of liver disease, coughs, fever, tuberculosis, rheumatism, morning sickness, hypothermia, dyspnoea[176], and nervous disorders (Bruneton, 1995c).

## Contraindications

None ("Ginseng radix" 1991), (Sonnenborn, 1989b), (Bradley, 1992), (Sonnenborn and Hänsel, 1992).

## Adverse reactions

Various researchers who studied Radix Ginseng extracts using conventional toxicological methods in five different animal models reported no acute or chronic toxicity of the extract (Bradley, 1992), (Sonnenborn and Hänsel, 1992), (Soldati, 1984).

On the basis of Radix Ginseng's long use, and the relative infrequency of significant demonstrable side-effects, it has been concluded that the use of Radix Ginseng is not associated with serious adverse effects if taken at the recommended dose (Sonnenborn and Hänsel, 1992), (Soldati, 1984). However, in Siegel's open study[177] of 133 patients ingesting large quantities, ginseng was reported to result in hypertension, nervousness, irritability, diarrhoea, skin eruptions, and insomnia, which were collectively called ginseng abuse syndrome (GAS) (Siegel, 1979). Critical analysis of this report has shown that there were no controls or analyses to determine the type of ginseng being ingested or the constituents of the preparation taken,

[175] Tending or having the power to restore

[176] shortness of breath

[177] a study with no exclusion criteria

and that some of the amounts ingested were clearly excessive (as much as 15 g per day, where the recommended daily dose is 0.5–2g) (Sonnenborn, 1989b), (Sonnenborn and Hänsel, 1992), (V. Tyler, 1994). When the dose was decreased to 1.7 g/day the symptoms of the "syndrome" were rare. Thus the only conclusion that can be validly extracted from the Siegel study is that the excessive and uncontrolled intake of ginseng products should be avoided (Sonnenborn and Hänsel, 1992).

One case of ginseng-associated cerebral arteritis has been reported in a patient consuming a high dose of an ethanol extract of ginseng root (approximately 6g in one dose) (Ryu and Y. Y. Chien, 1995). However, again the type and quantity of ginseng extract were not reported. Two cases of mydriasis and disturbance in accommodation, as well as dizziness have been reported after ingestion of large doses (3–9g) of an unspecified type of ginseng preparation (Lou, 1989).

Oestrogenic-like side-effects have been reported in both premenopausal and postmenopausal women following the use of ginseng. Seven cases of mastalgia[178] (Palmer, Montgomery, and Monteiro, 1978), (Koriech, 1978), (Punnonen and Lukola, 1980) and one case of vaginal bleeding in a postmenopausal woman (101) were reported after ingestion of unspecified ginseng products. An increased libido in premenopausal women has also been reported (Punnonen and Lukola, 1980). Specific studies on the possible hormonal side-effects of ginseng have been carried out with a standardised ginseng extract (Buchi and Jenny, 1984), (Forgo, Kayasseh, and Staub, 1981), (Reinhold, 1990). Under physiological conditions, there is no interaction of the ginseng extract with either cytosolic oestrogen receptors isolated from mature rat uterus or progesterone receptors from human myometrium (Buchi and Jenny, 1984). Furthermore, clinical studies have demonstrated that a standardised ginseng extract does not cause a change in male and female hormonal status (Forgo, Kayasseh, and Staub, 1981), (Reinhold, 1990).

The "ginseng abuse syndrome" has been reported as having elevated blood pressure, nervousness, insomnia, skin eruptions, and diarrhoea (Siegel, 1979). A German review article of the worldwide scientific literature concludes that no report of side effects for ginseng offered complete or controllable data (Sonnenborn and Proppert, 1990). The article concludes that the symptoms only seem to appear in countries where herbs are not controlled as to content and dosage, and that with appropriate informed use, ginseng is a safe medicine.

## Warnings

No information available.

[178] breast pain

## Precautions

### General

Diabetic patients should consult a doctor prior to taking Radix Ginseng, as ginseng intake may slightly reduce blood glucose levels (H. J. Kwan and Wan, 1994), (Sotaniemi, Haapakoski, and Rautio, 1995).

## Drug interactions

There are two reports of an interaction between Radix Ginseng and phenelzine, a monoamine oxidase inhibitor (B. D. Jones and Runikis, 1987), (Shader and Greenblatt, 1985). The clinical significance of this interaction has not been evaluated.

## Drug and laboratory test interactions

None reported.

## Carcinogenesis, mutagenesis, impairment of fertility

Radix Ginseng is not carcinogenic or mutagenic in-vitro, and does not have any effect on fertility (Sonnenborn and Hänsel, 1992).

## Pregnancy: teratogenic effects

Radix Ginseng is not teratogenic in-vivo (Sonnenborn and Hänsel, 1992).

## Pregnancy: non-teratogenic effects

The safety of Radix Ginseng for use in pregnancy has not been established.

## Nursing mothers

Excretion of Radix Ginseng compounds into breast milk and its effects on the newborn have not been established.

## Paediatric use

The safety and efficacy of Radix Ginseng use in children have not been established.

### Dosage forms

Crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks, wines, and lozenges. Store in a cool, dry place in well-sealed containers (BHP, 1990).

### Dosage

Unless otherwise prescribed, daily dose (taken in the morning): dried root 0.5–2g by decoction; doses of other preparations should be calculated accordingly ("Ginseng radix" 1991), (D'Angelo, 1986), (Bradley, 1992), (WHO, 1999b).

### Commentary

*As the quality is so variable, and also the total content of usable American/Radix Ginseng, it is expensive and therefore not worth the risk of being taken.*

## Angelica

### Common names

European angelica, wild parsnip, garden angelica, garden archangel, holy ghost, masterwort, wild celery,Swedish = fjällkvanne, Chinese = chien-tu, French = angélique, German = Echt engelwurz, French = archangelique, German = Angelika, German = Brustwurz, German = Engelwurz, Russian = djagil' aptenyj, Swedish = kvanne.

### Latin name

*Angelica archangelica*

### Botany

European angelica is a biennial or perennial herb native to northern and eastern Europe (Leung and S. Foster, 1996) and parts of Asia (Budavari, 1996), (Wichtl and N. Bisset, 1994). Its natural habitat includes Iceland, Scotland, Holland, and Lapland (Grieve, 1979), (Leung and S. Foster, 1996). In Germany, it is cultivated in the states of Bavaria and Thüringen (Lange and Schippmann, 1997). The material of commerce is obtained

from northern Europe, including the United Kingdom (BHP, 1996), almost entirely from plants cultivated in the Netherlands, Poland, and Germany, and to a lesser extent from Belgium, Italy, and the Czech Republic (Wichtl and N. Bisset, 1994).

Angelica is a widely cultivated, aromatic[179] biennial, northern European herb with fleshy, spindle-shaped roots, an erect stalk, and many greenish-yellow flowers arranged in an umbel. The seeds are oblong and off-white. It is similar to and sometimes confused with the extremely toxic water hemlock, Cicuta maculata.

Angelica grows wild in Scandinavia, Greenland, Iceland, central Europe and some parts in North Asia. It will only grow in damp soil (unknown, 2015b).

There are several recognised varieties of *angelica archangelica*, wild and cultivated. In the US, *angelica atropurpurea* is often cultivated in place of the European species (drugs.com, 2009b).

## History

Angelica has been cultivated as a medicinal and flavouring plant in Scandinavian countries since the 12th century and in England since the 16th century. The roots and seeds are used to distill about 1% of a volatile oil used in perfumery and as a flavouring for gin and other alcoholic beverages. The candied leaves and stems are used to decorate cakes. The oil has been used medicinally to stimulate gastric secretion, treat flatulence, and topically treat rheumatic and skin disorders (drugs.com, 2009b).

Angelica has for centuries been an important medicinal plant and food source, especially to the Sami or Lapps in northern Finland, Norway and Sweden and the Inuits in Greenland.

The plant was well know among the Vikings and according to the Icelandic sagas the plant was protected by law from over harvesting until the year 1000's. In Norway the plant was cultivated in special gardens and it was probably the first medicinal plant that was exported from the Nordic countries to the rest of Europe.

In the 14th century angelica had become well know as a medicinal herb throughout Europe. During the Middle Ages the root of the plant was believed to be effective as a treatment for the plague and in the 17th and 18th century the herb was widely used against intestinal infections such as dysentery and cholera (unknown, 2015b).

During the 16 and 17th centuries angelica was combined with other herbs to make "Carmelite water", a medieval drink thought to cure headache, promote relaxation, and long life, and protect against poisons and witches' spells.

[179] Having an agreeable, somewhat pungent, spicy odour

After the bacterial theory[180] was proven in relation to the bubonic plaque of 1665 it was realised that Angelica had antibacterial[181] properties (Maeder, 2015).

Angelica archangelica (Linn.) (Apiaceae/Umbelliferae) is also known as Angelica officinalis and is differentiated from other popular species in use as the European Angelica. The other two most commonly used species are called Angelica atropurpurea (American) and Angelica sinensis (Chinese), known as Dong Quai, see Dong Quai for further information. In English it is simply called "Angelica". In China and Asia use of angelica species are second only to ginseng.

Its name was derived from a monks dream in which St. Michael the Archangel appeared telling the monk what herb to use to help victims of the bubonic plague that was decimating Europe in 1665 (Grieve, 1971). When it was discovered that this herb was helpful in protecting and healing those that had the plague the country-side was very nearly stripped of the plant by peasants and nobility alike. Old chronicles report that anyone who kept a piece of angelica root in their mouth all through the day would be preserved from the plague. This herb blooms about May 8th, (old calendar) St. Michael's feast day and is so named in his honour. Even though this herb is named in honour of a Christian angel many angelica festivals are held in Livonia, East Prussia and Pomerania and celebrated in the pagan manner with dance and chanting of ancient ditties in languages no longer understood. European angelica has been viewed as a magical herb for more than 1000 years. Peasants made angelica leaf necklaces to protect their children from illness and witchcraft. Witches were reported never to use angelica and if it was in woman's garden or home it was her defense against witchcraft charges (Maeder, 2015).

## Action

Anti-spasmodic, cholagogue, stimulates the secretion of gastric juices.

## Composition of Drug

Angelica root consists of the dried root and rhizome of Angelica archangelica, as well as their preparations in effective dosage.

The drug contains essential oil, coumarin, and coumarin derivatives (herbalgram, 1990a).

[180] a fundamental tenet of medicine that states that microorganisms, which are too small to be seen without the aid of a microscope, can invade the body and cause certain diseases

[181] having the ability to destroy bacteria or suppress their growth or their ability to reproduce

## Chemistry and Pharmacology

Angelica root contains 0.35–1.9% volatile oil, of which 80–90% are monoterpene hydrocarbons such as b-phellandrene (1328%), a-phellandrene (214%) and a-pinene (1431%); sesquiterpenes (Wichtl and N. Bisset, 1994); 0.3% angelic acid (Budavari, 1996), (Weiss, 1988); 6% resin; sterols (e.g., sitosterol); phenolic acids such as chlorogenic and caffeic acids (Weiss, 1988), fatty acids (e.g., palmitic, oleic, and linoleic acids); coumarins (approximately 0.2% osthol) and furanocoumarins (e.g., angelicin, bergapten); sugars; and tannins (Bruneton, 1995a), (Leung and S. Foster, 1996), (Wichtl and N. Bisset, 1994).

Includes - Alpha-pinene, Aluminium, Arachidonic acid, Ascorbid acid, Ash, Bergapten, Beta-carotene, Beta-sitosterol, Beta-sitosterol-glocoside, Biotin, Cadinene, Calcium, Carbohydrates, Carvacrol, Choline, Chromium, Cobalt, Copper, EO, Falcarindiol, Farcarinol, Falcarinone, Ferulic acid, Folacin, Folinic acid, Fructose, Glucose, Iron, Isosafrole, Ligustilde, Linoleic acid, Magnesium, Manganese, Myristic acid, N-butylidenphthalide, N-butylphthalide, N-dodecanol, N-valero-phenone-o-carbonic-acid, Nicotinamide, Nicotinic acid, Oleic acid, P-cymene, Palmitic acid, Pantothenic acid, Phosphorus, Phthalides, Potassium, Protein, Riboflavin, Safrole, Scopoletin, Sedanoic acid, Selenium, sesquiterpene, Silicon, Sodium, Stearic acid, Thiamin, Tin Umbelliferone, Vanilic acid, Vitamin B12, Vitamin E, Zinc. Other chemical constituents are Psoralens, Coumarins and coumarin derivatives, volatile oil, valeric acid, angelic acid, angelicin resin, terebangelene and other terepenes; bitter iridoids, tannins, Linalool, Borneol, acetylenic compounds, chalcones, polysaccharides, phytosterols, flavonoids, Vitamin A and B.

The oil of the seeds contain methyl-ethylacetic acid and hydroxymyristic acid as well as essentials oils known to contain d–phelladrene, -pinen, osthenole, osthole, angelicin, thujene, camphene, and numerous other compounds (Maeder, 2015).

Note: Under proper storage conditions, angelica root still loses approximately 0.05–0.10% volatile oil content each year. Therefore, product shelf life should be determined based on this known rate of volatilisation, calculating the difference between the volatile oil content on the date of packaging against the minimum amount required in the drug codex or pharmacopeial monograph (Braun, 1997). Shelf life for the cut or sliced root is maximum 18 months and for the powdered root only 24 hours (DAB-DDR, 1983), (Meyer-Buchtela, 1999).

The German Commission E reported anti-spasmodic and cholagogue[182] actions, and that it stimulates the secretion of gastric juices (herbwisdom, 2015g).

[182] agent that stimulates bile flow from the gallbladder into the duodenum

The British Herbal Pharmacopoeia reported aromatic bitter and spasmolytic[183] actions (BHP, 1996). The Merck Index reported its therapeutic category as carminative, diaphoretic[184], and diuretic (Budavari, 1996). In addition, animal studies using the root oil have documented antibacterial activity against Mycobacterium avium and anti-fungal[185] activity against 14 types of fungi (Opdyke, 1975). In-vitro, angelica root extracts of various species have demonstrated calcium-antagonist-like effects, which may be relevant for treatment of cardiovascular disease (Leung and S. Foster, 1996).

Some of its early uses are at least partially supported by in-vitro studies of angelica's active coumarin and furanocoumarin constituents. One of these, angelicin, relaxes smooth muscles in-vitro, including those in the gastrointestinal and respiratory tracts. Angelica also relaxes tracheal (S. P. Zhao and Y. Z. Zhang, 1985) and vascular smooth muscles in-vitro. This latter effect is likened to calcium-antagonist mechanisms (Härmälä et al., 1992). European angelica may also increase uterine contractions, similar to the effects shown by Chinese angelica, Angelica sinensis (dong quai) in anaesthetized rabbits (M. Harada, M. Suzuki, and Y., 1984), (ABC, 2000), (ABC, 2000).

The volatile oil contains many monoterpenes; $\beta$-phellandrene is the principal component of var. angelica , while sabinene is the most abundant monoterpene of var. sativa (Kerrola, 1994a). Sesquiterpenes also are numerous in the oil; $\alpha$-copaene and other tricyclic sesquiterpenes are characteristic constituents (M. Jacobson, 1987). Supercritical fluid extraction has been studied as an alternative method of extracting angelica volatiles (Kerrola, 1994b). The shelf life of the root is limited because of the loss of the volatile oil while in storage.

The small organic acid, angelic acid, was the first compound purified from the root in 1842 (Buchner, 1842). 15-pentadecanolide (Exaltolide) is a fatty acid lactone constituent of the root with a musk-like odour, used as a fixative in perfumes (Stanchev, 1993).

As with most of the many species of angelica, A. archangelica contains a wide variety of coumarins and their glycosides. The angular furanocoumarins, archangelicin (B. Nielsen, 1964) and angelicin, (Corcilius, 1956) and congeners (Härmälä, 1992) are present in the roots, and many glycosides and esters of linear furanocoumarins also have been reported.

A trisaccharide, umbelliferose, originally was isolated from angelica roots (Wikström, 1956), (drugs.com, 2009b).

[183] having the ability to relieve spasms or convulsions

[184] able to increase perspiration

[185] effective against fungal infections

## Uses

Angelica has been used medicinally to stimulate gastric secretion, treat flatulence, and topically treat rheumatic and skin disorders.

Angelica root oil was preferentially relaxant on tracheal smooth muscle preparations compared with ileal muscle (S. P. Zhao and Y. Z. Zhang, 1985). The oil had no effect on skeletal muscle in a second study (Lis-Balchin, 1997). The calcium-blocking activity of angelica root has been examined relative to solvent used in extraction, and furanocoumarins were identified as the likely active species (Härmälä et al., 1992). The root oil has been found to have anti-fungal and antibacterial activity (Opdyke, 1975), (drugs.com, 2009b).

Other medicinal qualities are - carminative, anti-spasmodic, topical anti-inflammatory, diuretic, expectorant, digestive tonic, anti-rheumatic[186], uterine stimulant[187], cholagogue, stomatic[188], and diaphoretic. This herb helps relieve anaemia, abdominal bloating, chronic bronchitis, dyspepsia, flatulence, gastrointestinal spasms, loss of appetite, peptic discomforts, arthritis and joint pain, typhoid, ulcers. It has been used as a blood purifier, to promote blood circulation and in both sexes. It relieves peripheral circulation problems and reduces high blood pressure by acting to stabilise blood vessels (Maeder, 2015).

The upper part of the root is considered a great blood builder. The tail of the root is used in emergencies as a blood clot dissolver after serious accidents or for expelling retained afterbirth (placenta). The coumarins are a valuable medication for reducing high protein oedemas such as lymphoedema[189]. It has also been used to treat psoriasis accompanying arthritis (International Cyber Business Services, 2000). It is also hepatoprotective[190], nephroprotective[191], and analgesic[192].

Angelica roots and leaves are used for medicinal purposes although the stems were used in olden times when the Doctrine of Signatures was a popular way to choosing herbal remedies. Because the stems are hollow it was thought that they aided in healing respiratory ailments. Latter day German researchers have discovered that angelica relaxes the windpipe, suggesting that it has some validity in treatment of colds, flu, bronchitis

[186] counteracting rheumatism and rheumatoid disease

[187] having the ability to cause, or increase the frequency and intensity of, uterine contractions

[188] relating to the mouth

[189] swelling of the lymph nodes

[190] has the ability to prevent damage to the liver

[191] has the ability to prevent damage to the kidneys

[192] an agent that relieves pain without causing loss of consciousness

and asthma. Additional research has also validated its use in digestive complaints[193] as it is found to relax the intestines. Japanese researchers have reported anti-inflammatory effects confirming the use of angelica to treat arthritic problems (Maeder, 2015).

The stems of angelica are edible. They are very rich in nutrients and can be eaten in the same manner as celery. The outer layer of the stems is usually removed and only the green and juicy inner part is eaten. They have a strong taste, but if cooked the flavour becomes milder.

The plant has been used as a flavour agent in liqueurs for centuries and is still the main flavour ingredient in the French liqueurs Bénédictine and Chartreuse (unknown, 2015b).

Loss of appetite, peptic discomforts such as mild spasms of the gastrointestinal tract, feeling of fullness, flatulence (herbalgram, 1990a).

## Sedation

Angelic acid was formerly used as a sedative. The angular furanocoumarin angelicin also has been reported to have sedative properties, although recent experimental evidence of this is limited. The carminative action of the volatile oil is because of an unremarkable monoterpene content (drugs.com, 2009b).

### Animal data

Research reveals no animal data regarding the use of angelica for sedation (drugs.com, 2009b).

### Clinical data

Research reveals no clinical data regarding the use of angelica for sedation.

Often used as a flavouring or scent, angelica has been used medicinally to stimulate gastric secretion, treat flatulence, and topically treat rheumatic and skin disorders; however, there is little documentation to support these uses (drugs.com, 2009b).

The German Commission E approved angelica for loss of appetite, peptic discomforts such as mild spasms of the gastrointestinal tract, feeling of fullness, and flatulence (ABC, 2000).

[193] In medicine, a disorder, disease, or symptom

The German Standard License indicates the use of angelica root tea for treatment of complaints such as feeling of fullness, flatulence, and mild cramp-like gastrointestinal disturbances, as well as stomach conditions such as insufficient formation of gastric juice (Braun, 1997). In India, it is used to treat anorexia nervosa and flatulent dyspepsia (Karnick, 1994), (ABC, 2000).

## Contraindications

The leaf and seed of angelica are unapproved. None known (herbalgram, 1990a).

Pregnant women should not use it as it is a strong emmenagogue.

Do not use if experiencing heavy menstrual bleeding. Do not use during menstruation.

If given for delayed onset of menstruation be sure the patient is not pregnant.

Do not give to children under two years of age.

Older children and adults over 65 years use low strength dosage and increase if necessary.

It should not be used by diabetics, due to its ability to cause weakness.

Psoralens in angelica cause sun sensitivity in fair skinned people.

"Psoralens also promote tumour growth, leading the authors of a report in the journal Science to advise against taking angelica internally. On the other hand, a recent animal study showed another angelica constituent - alpha-angelica lactone - has an anti-cancer effect" (Castleman, 1991).

Do not use if experiencing loose stools or diarrhoea.

Do not use with Warfarin as it is considered a natural anti-coagulant.

Do not give to constitutionally weak people; those with chronic, low-grade infections (Maeder, 2015).

## Side Effects

The furanocoumarins present in angelica root sensitize the skin to sunlight. Subsequent exposure to UV radiation can lead to inflammation of the skin. During treatment with the drug or its preparations, prolonged sun-bathing and exposure to intense UV radiation should be avoided (ABC, 2000). **Sensitive to sunlight** and **sensitive to UV radiation** (ABC, 2000).

The linear furanocoumarins are well-known dermal photosensitizers, while the angular furanocoumarins are less toxic (Ceska, 1986). The presence of linear furanocoumarins in the root indicates that the plant parts should be used with caution if exposure to sunlight is expected. The coumarins are not important constituents of the oil, which, therefore, gives the oil a greater margin of safety in that respect (drugs.com, 2009b).

## Use During Pregnancy and Lactation

Documented adverse effects. Emmenagogue effects. Avoid use (drugs.com, 2009b).

Not recommended during pregnancy (McGuffin et al., 1997). No restrictions known during lactation.

## Interactions with Other Drugs

Avoid using angelica root concurrently with warfarin.

Theoretically, there is a possible increased risk of bleeding when using angelica root concurrently with warfarin. The additive or synergistic[194] effects of coumarin or coumarin derivatives possibly may be present in angelica root (L. Miller, 1998), (A. Heck, 2000). Because warfarin has a narrow therapeutic index, it would be prudent[195] to avoid concurrent use.

## Dosage and Administration

Angelica root typically is given at doses of 3 to 6 g/day of the crude root (drugs.com, 2009b).

### Daily dosage of the root

- 4.5 g of drug,
- 1.5–3 g fluidextract[196] (1:1),
- 1.5 g tincture (1:5),
- equivalent preparations;
- 10–20 drops of essential oil (herbalgram, 1990a).

Unless otherwise prescribed - 4.5 g per day of cut dried root and other oral galenical preparations[197].

[194] enhancing the effect of another force or agent

[195] wise, using good judgement

[196] a liquid preparation of a vegetable drug, containing alcohol as a solvent or preservative, or both, of such strength that each milliliter contains the therapeutic constituents of 1 g of the standard drug it represents

[197] preparations of botanical drugs

## Dried root and rhizome

1–2 g, three times daily (BHP, 1983), (Karnick, 1994), (C. A. Newall, L. A. Anderson, and Phillipson, 1996b).

Dried whole root - 4.5 grams per day, equivalent to 1.5 to 3.0 grams per day of the 1:1 fluidextract or 1.5 grams of the 1:5 tincture (Maeder, 2015).

## Decoction

Place 1.5 g fine-cut root in 150–250 ml cold water, bring to a boil and simmer for approximately 10 minutes in a covered vessel (Meyer-Buchtela, 1999), (Wichtl and N. Bisset, 1994).

Or: Simmer 2–4 g in 150 ml boiling water for approximately 10 minutes. Drink warm, several times daily one half-hour before meal times (Braun, 1997), (Meyer-Buchtela, 1999).

Decoction - 1 teaspoon powdered roots per cup of water. Bring to boil and simmer 2 minutes. Remove from heat and let stand 15 minutes. Drink up to 3 cups a day (Maeder, 2015).

Please note - angelica decoctions are bitter tasting (Maeder, 2015).

## Infusion

Steep 2–4 g in 150 ml boiled water for approximately 10 minutes. Drink warm, several times daily one half-hour before meal times (Braun, 1997), (Meyer-Buchtela, 1999).

[Note: According to the Austrian Pharmacopeia, the average single dose for angelica root tea infusion is 1.5 g per cup (Meyer-Buchtela, 1999), (OAB, 1991).]

As a tea - 1 teaspoon of the dried and finely chopped root in one cup of boiling water and then letting it steep for a few minutes before the tea is strained (unknown, 2015b).

Infusion - 1 teaspoon powdered seeds or leaves per cup of boiling water. Steep 10–15 minutes, let cool and drink up to 3 cups a day (Maeder, 2015).

## Fluidextract

Fluidextract - 1:1 (g/ml): 1.5–3 ml (Blumenthal, Busse, et al., 1998); 0.5–2.0 ml, three times daily (BHP, 1983), (Karnick, 1994), (C. A. Newall, L. A. Anderson, and Phillipson, 1996b).

### Tincture

1:5 (g/ml): 1.5 ml (Blumenthal, Busse, et al., 1998); 0.5–2.0 ml, three times daily (BHP, 1983), (C. A. Newall, L. A. Anderson, and Phillipson, 1996b).

As a tincture - the recommended dosage is usually 20–40 drops taken three times daily (unknown, 2015b).

Tincture - $\frac{1}{2}$ to 1 teaspoon or 10 to 40 drops up to three times a day (Maeder, 2015).

### Essential oil - Oleum Angelicae

10–20 drops (Blumenthal, Busse, et al., 1998).

If essential oil is being used, the recommended dose is 10–20 drops of oil per day (Maeder, 2015).

### Commercial preparations

If using commercial extracts follow package directions.

"Dilute up to 10 drops of angelica oil with 25 ml of almond, sunflower, or olive oil, and use for massage oil on arthritic and rheumatic joints." (Ody, 1993)

"Soak a compress in hot diluted tincture or decoction and apply to painful arthritic or rheumatic joints." (Ody, 1993).

## Toxicology

Poisoning has been recorded with high doses of angelica oils (drugs.com, 2009b).

## Commentary

*Due to its short shelf life, and it not having any oestrogenic effect, its not worth taking.*

# Anise

## Common Names

Anise, aniseed, sweet cumin, anason, anasur, anisu, star anise, Chinese anise, Chinese = ou hui xiang, French = anis vert, German = Anis, Hindi = saunf, Italian = anice vero, Japanese = seri nisii, Russian = anis obyknovennyj, Sanskrit = shetapusapa

## Latin Name

*Pimpinella anisum*

## Overview

> The seed wasteth and consumeth winde, and is good against belchings and upbraidings of the stomacke, alaieth gripings of the belly, provoketh urine gently, maketh abundance of milke, and stirreth up bodily lust: it staieth the laske (diarrhoea), and also the white flux in women (Gerard, 1597).

As John Gerard says anise is good for wind and flatulence. And anise has been used to treat menstrual cramps, but you may develop sensitivity after repeated use (Felter, 1922).

Anise, like fennel, contains anethole, a phytoestrogen (Tabacchi, 1974).

The anise seeds have been used since ancient times for their content of aromatic essential oil in traditional medicine, for cosmetics, alcoholic beverages like anisette, arrack, ouzo and raki, and in cooking.

The ripe seeds of anise contain about 2.5% of fragrant oil that is responsible for most of the beneficial effect associated with them. The oil consists mostly of antheole and its derivatives, like diantheole and photoantheole. Methylchavicol and para-methoxyphenylacetone, flavonoids like quercetin, and cumarins are also present.

Anise oil which is produced from crushed anise seed by steam distillation is valuable in perfumes and soaps, and has also been used in toothpaste, mouthwashes and skin creams.

When taken internally the anise seeds have been used to relieve indigestion, colic, gas, halitosis, bloating, abdominal cramps and to remove nausea. The seeds have mild diuretic and diaphoretic properties and they have also been used for their antiseptic effects.

Anise oil works as an expectorant, which helps in the coughing up of mucus in conditions like asthma, bronchitis, the common cold, and the whooping cough. It is therefore being used as an ingredient in cough syrup[198]s and lozenges.

Anise seeds also have mild oestrogenic effects most likely due to the presence of diantheole and photoantheole in the oil. This is why the seeds have been used traditionally to promote lactation in nursing mothers, increase libido and to relief symptoms of PMS.

Ointments and soap containing anise oil can help as a natural remedy for oily skin and to treat impurities like mild acne.

[198] a concentrated sugar solution that contains medication

Since anise oil is poisonous for many insects, ointments containing anise oil has also be used as a natural treatment for scabies and lice infestations (unknown, 2015c).

## Botany

In some texts, anise is referred to as Anisum vulgare Gartner or A. officinarum Moench. Do not confuse with the "Chinese star anise" ( Illicium verum Hook. filius. Family: Magnoliaceae). Anise is an annual herb that grows 0.3 to 0.6 m and is cultivated widely throughout the world (Leung and S. Foster, 1996). The flowers are yellow, growing in compound umbels. Its leaves are feather-shaped. The 2 mm long, greenish-brown, ridged seeds are used as food or herb and are harvested when ripe in autumn (Chevallier, 1996). Aniseed has an anethole-like odour and a sweet, aromatic taste (Wichtl and N. Bisset, 1994), described as "liquorice-like", which has led to traditional use of anise oils in liquorice candy (Leung and S. Foster, 1996).

## History

Anise has a history of use as a spice and a fragrance. It has been cultivated in Egypt for at least 4,000 years. Records of its use as a diuretic and treatment of digestive problems and toothache are seen in medical texts from this era. In ancient Greek history, writings explain how anise helps breathing, relieves pain, stimulates urination, and eases thirst (Chevallier, 1996). The essential oil has been used commercially since the 1800s. The fragrance is used in food, soap, creams, and perfumes. Anise often is added to liquorice candy or used as a "liquorice" flavour substitute; it is also a fragrant component of anisette liqueur.

## Chemistry

Examination of the mycoflora of anise seed resulted in the isolation of 15 fungal genera, 78 species and six varieties, including Aspergillus, Penicillium, and Rhizopus (Moharram, Abdel-Mallek, and Abdel-Hafez, 1989). Naturally occurring mycotoxins also were present in thin-layer chromatography analysis of anise spice extract (El-Kady, El-Maraghy, and Eman Mostafa, 1995). Gamma irradiation has inhibited mould growth on anise in humid conditions (Mahmoud, 1992).

Anise oil (1% to 4%) is obtained by steam distillation of the dried fruits of the herb. The highest quality oils result from anise seeds of ripe umbels in the centre of the plant (Tsvetkov, 1970). A major component of the oil is trans-anethole (75% to 90%), responsible for the characteristic taste and smell, as well as for its medicinal properties (Wichtl and N. Bisset, 1994), (Chandler

and Hawkes, 1984b), (Tabacchi, 1974). The cis-isomer is 15 to 38 times more toxic than the trans-isomer (D. M. Penetar et al., 2006). Spectrophotometric determination of anethole in anise oil has been performed (Mohamed et al., 1976).

The volatile oil also has related compounds that include estragole (methyl chavicol, 1% to 2%), anise ketone (p-methoxyphenylacetone), and beta caryophyllene. In smaller amounts are anisaldehyde, anisic acid, limonene, alpha-pinene, acetaldehyde, p-cresol, cresol, and myristicin (the psychomimetic compound previously isolated from nutmeg) (Wichtl and N. Bisset, 1994), (Harborne, Heywood, and C. A. Williams, 1969), (unknown, 1973), (C. Newall, 1996). Oil of Feronia limonia has some similarity to anise oil and may be used as a substitute (Shah et al., 1985).

Constituents of the whole seed include coumarins, such as umbelliferone, umbelliprenine, bergapten, and scopoletin. Lipids (16%) include fatty acids, beta-amyrin, stigmasterol, and its salts (Leung and S. Foster, 1996), (C. Newall, 1996). Flavonoids in aniseed include rutin, isoorientin, and isovitexin (C. Newall, 1996).Protein (18%) and carbohydrate (50%) are also present. Terpene hydrocarbons in the plant also have been described (Burkhardt et al., 1986).

## Mechanism of action

Pharmacological effects of anise are caused mainly by anethole, which has structural similarities to catecholamines (eg, epinephrine, norepinephrine, dopamine) (C. Newall, 1996). Sympathomimetic-type[199] effects have been attributed to anethole in at least 1 report (Albert-Puleo, 1980a).

## Expectorant

Anise is well known as a carminative and an expectorant. It is used to decrease bloating and settle the digestive tract. In higher doses, anise is used as an anti-spasmodic and an antiseptic for the treatment of cough, asthma, and bronchitis (Chevallier, 1996), (Wichtl and N. Bisset, 1994), (Chandler and Hawkes, 1984b), (C. Newall, 1996).

### Animal data

Research reveals no animal data regarding the use of anise as an expectorant.

[199] mimicking stimulation of the sympathetic nervous system

## Clinical data

Research reveals no clinical data regarding the use of anise as an expectorant.

## Antimicrobial

Anise has been evaluated for its antimicrobial[200] action against gram-negative and gram-positive organisms (Narasimha and Nigam, 1970). Constituent anethole also inhibits growth of mycotoxin-producing Aspergillus in culture (Leung and S. Foster, 1996). Anise is used in dentifrices as an antiseptic and in lozenges and cough preparations for its weak antibacterial effects (Leung and S. Foster, 1996), (D. M. Penetar et al., 2006). One report testing aromatic waters (including anise) on the growth and survival of Pseudomonas aeruginosa has been published (Y. K. Ibrahim and Ogunmodede, 1991).

## Animal data

Research reveals no animal data regarding the use of anise as an antimicrobial.

## Clinical data

Research reveals no clinical data regarding the use of anise as an antimicrobial.

## Uses

Anise has been used as a flavouring in alcohols, liqueurs, dairy products, gelatins, puddings, meats, and candies, and as a scent in perfumes, soaps, and sachets. The oil has been used to treat lice, scabies, and psoriasis. Anise frequently is used as a carminative and expectorant. Anise also is used to decrease bloating and settle the digestive tract in children. In high doses, it is used as an anti-spasmodic and an antiseptic and for the treatment of cough, asthma, and bronchitis. However, research reveals no clinical data regarding the use of anise for any of these applications.

The seeds and the oil they produce contain thymol, terpineol and anethole, which can be used to treat pectoral affections and coughs. When used as a lozenge, aniseed is an effective expectorant. Bronchial irritation can be soothed by drinking a tea made from the seeds, and people that suffer from

[200] tending to destroy microbes, prevent their develop- ment, or inhibit their pathogenic action

spasmodic asthma may also find relief from the seeds. Drops of aniseed oil may be used in a vaporiser to clear congestion and soothe coughing. Gargling with a tea made of the seeds can also provide relief for sore throat, laryngitis or pharyngitis.

The seeds have also been used to reduce flatulence, cure sleeplessness, aid nursing mothers with the production of milk and to stimulate appetite. Aniseed can also improve digestion, alleviate cramps and reduce nausea.

A paste made from the seeds may be applied to the forehead, neck or temples to relieve headaches and migraines. A similar paste can be used to treat lice and scabies.

Some components of aniseed are known to have calming effects that can relieve anxiety and nervousness. These components include thymol, stigmaterol, linalol, terpineol, alpha-pineno and eugenol.

Anise has aphrodisiac properties that can increase libido. Drinking one glass of water infused with the crushed seeds each night can increase one's sex drive.

The seed's healing properties can also be yielded through external means like vaporisation and pastes (unknown, 2015c).

## Other uses

Anise has promoted iron absorption in rats, suggesting possible use as a preventative agent in iron deficiency anaemia (el-Shobaki, Z. A. Saleh, and N. Saleh, 1990). The oil, when mixed with sassafras oil, is used as an insecticide (Chandler and Hawkes, 1984b). Applied externally, the oil has been used to treat lice and scabies (Chevallier, 1996). As a skin penetration enhancer, anise oil has little activity compared with eucalyptus and other oils (A. Williams and Barry, 1989), but topical application of the constituent bergapten, in combination with ultraviolet light, has been used in psoriasis treatment (C. Newall, 1996).

## Adverse Reactions

The German commission E monograph lists side effects of anise as "occasional allergic reactions of the skin, respiratory tract, and gastrointestinal tract" (Wichtl and N. Bisset, 1994). When applied to human skin in a 2% concentration in petrolatum base, anise oil produced no dermatological reactions. The oil is not considered to be a primary irritant. However, anethole has been associated with sensitisation and skin irritation and may

cause erythema, scaling, and vesiculation[201] (unknown, 1973). Anise oil in toothpaste has been reported to cause contact sensitivity, cheilitis[202], and stomatitis (D. M. Penetar et al., 2006). The constituent bergapten may cause photosensitivity (C. Newall, 1996).

Anise is safe to use in small doses, but ingesting large amounts of the seed can cause **convulsions**, **narcosis**, **circulatory problems** and **coma**. Improper use may also cause **seizures**, **paralysis**, **lack of clarity** and other **mental problems**. Users should only take the seed as directed and avoid consuming high doses (unknown, 2015c).

Anise oil is not without side effects, as large quantities used internally can cause nausea and vomiting, seizures and even pulmonary oedema. This is why pure anise oil should not be used internally as pulmonary oedema has occurred after ingestion of such a small quantity as 1–5ml pure anise oil (Resource, 2015a).

Using seeds internally is safe as they do not contain more than 2.5% oil. Used externally, pure anise oil can cause skin irritations, therefore the oil is formulated with other emollient[203]s to form an ointment in which the oil is sufficiently diluted to be safe.

**Skin rashes**, **swelling of skin or tongue**, **breathing difficulties**, and/or **tightness in the chest** could indicate an allergic reaction in which case a doctor should be consulted immediately.

Anise should not be used during pregnancy and a health care provider should be consulted before the use by nursing mothers (Resource, 2015a).

## Pregnancy/Lactation

Generally recognized as safe for use as food (GRAS). Avoid dosages above those found in food because safety and efficacy have not been established (USA, 2004). Aniseed is a reputed abortifacient[204]. Excessive use is not recommended in pregnancy (Chevallier, 1996), (C. Newall, 1996).

## Interactions

None well documented.

[201] blistering

[202] an abnormal condition of the lips characterized by inflammation and cracking of the skin

[203] a moisturising treatment applied directly to the skin

[204] causing abortion

## Dosage

There are no recent clinical studies to guide use of anise; however, a typical dose in dyspepsia is 0.5 to 3 g of seed or 0.1 to 0.3 mL of the essential oil.

### Infusion

First one or two teaspoons of anise seeds should be crushed to release the volatile oils then the crushed seeds should stand for five to ten minutes in one cup of boiling water. Many herbalists recommend one cup three times daily (unknown, 2015c).

### Oil

A popular choice is one drop of the anise seed taken internally mixed with half a teaspoonful of honey (unknown, 2015c).

## Toxicology

Anise oil has GRAS status and is approved for food use. The acute oral oral lethal dose, 50% (LD-50) of the oil in rats is 2.25 g/kg. No percutaneous absorption of the oil occurred through mouse skin within 2 hours (F. Meyer and E. Meyer, 1959). The oral LD-50 of anethole is 2,090 mg/kg in rats; rats fed a diet containing 0.25% anethole for 1 year showed no ill effects, while those receiving 1% anethole for 15 weeks had microscopic changes in hepatocytes (D. M. Penetar et al., 2006).

The cis-isomer of anethole is 15 to 38 times more toxic to animals than the trans-isomer, the relative content being dependent on plant species (Leung and S. Foster, 1996), (D. M. Penetar et al., 2006). Ingestion of the oil in doses as small as 1 ml may result in **pulmonary oedema**, **vomiting**, and **seizures** (Spoerke, 1980). The oestrogenic activity of anethole and its dimers may alter hormone therapy (eg, contraceptive pills).

While the seed has many benefits, high doses of the essential oil are toxic due to its narcotic properties (unknown, 2015c).

## Commentary

*Although it is reputed to be a phytoestrogen, there are no oestrogenic effects observed.*

## Definition

Aetheroleum Anisi consists of the essential oil obtained by steam distillation from the dry ripe fruits of Pimpinella anisum (unknown, 1972), (unknown, 1986), (unknown, 1987), (unknown, 1995), (unknown, 1996b).

## Common names

Anacio, Anes, Aneis, anice, anice verde, Anis, anisbibernelle, anis verde, anis vert, anisoon, anisum, Anizs, anizsolaj, annsella, badian, badian rumi, boucage, boucage anis, Gruner Anis, habbat hlawa, jintan manis, jinten manis, petit anis, pimpinelle, razianag, razianaj, roomy, saunf, yansoon, (unknown, 1972), (Scientific and Commission, 1985), (Hänsel, 1994), (C. C. d. Guzman and Siemonsma, 1999), (Halmai and Novak, 1963), (Farnsworth, 2001).

## Geographical distribution

Indigenous to the eastern Mediterranean region, western Asia and Europe. Cultivated in southern Europe and northern Africa, and in Argentina, Bulgaria, Chile, China, India, Islamic Republic of Iran, Japan, Mexico, Romania, Russian Federation and Turkey (C. C. d. Guzman and Siemonsma, 1999).

## Description

An aromatic annual herb, up to 60 cm high with an erect, cylindrical, striated, smooth stem. Leaves alternate below, opposite above, the lower being long-petioled, ovate-orbicular, dentate, the upper with short dilated petioles, pinnatifid or ternately pinnate with long, entire or cut cuneate segments. Inflorescence long-stalked, compound umbel with 8–14 rays; flowers small, white, each on a long hairy pedicel. Fruit comprises a mouse-shaped cremocarp with a small stylopod and two minutely pubescent mericarps that do not readily separate from the carpophore (Scientific and Commission, 1985), (Youngken, 1950).

## Major chemical constituents

The major constituents are trans-anethole (84–93%), cis-anethole ($< 0.5\%$), methylchavicol (estragole, isoanethole; 0.5–6.0%), linalool (0.1–1.5%) and p-anisaldehyde (0.1–3.5%) (unknown, 1996b).

## Pharmacology

## Clinical pharmacology

The absorption of anethole from the gastrointestinal tract was assessed in healthy volunteers. The drug was rapidly absorbed from the gastrointestinal tract and rapidly eliminated in the urine (54–69%) and through the lungs (13–17%). The principal metabolite was 4-methoxyhippuric acid (approximately 56%); other metabolites were 4-methoxybenzoic acid and three other unidentified compounds (Sangster, Caldwell, and Hutt, 1987), (Caldwell and J. D. Sutton, 1988). Increases in drug dose did not alter the pattern of metabolite distribution in humans, contrary to findings in animal models (Sangster, Caldwell, and R. L. Smith, 1984).

## Experimental pharmacology

### Antimicrobial activity

Aetheroleum Anisi, 500 mg/l, inhibited the growth of Alternaria alternata, Alternaria tenuissima, Aspergillus spp., Botryodiplodia spp., Cladosporium herbarum, Cladosporium werneckii, Colletotrichum capsici, Curvularia lunata, Curvularia pallescens, Fusarium moniliforme, F. oxysporum, Mucor spinescens, Penicillium chrysogenum, P. citrinum and Rhizopus nigricans (Shukla and Tripathi, 1987). The oil (concentration not specified) inhibited the growth of Aspergillus flavus, A. niger, Fusarium oxysporum and Penicillium spp. In-vitro (S. K. Gangrade, 1991). The oil, 1.0 ml/plate, inhibited the growth of Rhizoctonia solani and Sclerotinia sclerotiorum, but was inactive against Fusarium moniliforme and Phytophthora capsici in-vitro (Müller-Riebau, B. Berger, and Yegen, 1995). The oil (concentration not specified) did not inhibit the growth of Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa or Staphylococcus aureus but did inhibit that of Aspergillus aegyptiacus, Penicillium cyclopium and Trichoderma viride in-vitro (El-Keltawi, Megalla, and Ross, 1980). The oil (concentration not specified) was active against Bacillus subtilis, Escherichia coli, Lentinus lepideus, Pseudomonas aeruginosa and Staphylococcus aureus (Janssen, 1986). The oil inhibited the growth of Candida albicans, Candida krusei, Candida parapsilosis, Candida tropicalis, Microsporum gypseum, Rhodotorula rubra and Saccharomyces cerevisiae, minimum inhibitory concentration (MIC[205]) 0.097%, and Geotrichum spp., MIC 1.562% (Pepeljnjak, 2000).

[205] the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation

## Anticonvulsant activity

Intraperitoneal administration of 1.0 ml/kg body weight (bw) of the oil to mice suppressed tonic convulsions induced by pentylenetetrazole or maximal electroshock (Pourgholami, 1999). Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents provided protection against convulsions induced by pentylene tetrazole, picrotoxin and electroshock (Elisabetsky, 1995), (Elisabetsky, Silva Brum, and Souza, 1999). Intraperitoneal administration of 2.5 g/kg bw of linalool to mice interfered with glutamate function and delayed convulsions induced by N-methyl-d-aspartate (Silva Brum, Elisabetsky, and Souza, 2001). Linalool acts as a competitive antagonist of [ 3 H]-glutamate binding and as a non-competitive antagonist of [ 3 H]-dizocilpine binding in mouse cortical membranes. The effects of linalool were investigated on [ 3 H]-glutamate uptake and release in mouse cortical synaptosomes. Linalool, 1.0 mmol/l, Reduced potassium-stimulated glutamate release (Silva Brum, 2001). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

## Anti-inflammatory activity

Anethole is a potent inhibitor of tumour necrosis factor tumour necrosis factor (TNF)-induced nuclear factor nuclear factor (NF)-$\beta$ activation, inhibitor-$\beta alpha$ phosphorylation and degradation, and NF-$\beta$ reporter gene expression in-vitro, demonstrating that anethole suppresses inflammation by inhibiting TNF-induced cellular responses (Chainy, 2000).

## Antispasmodic activity

The oil inhibited the phasic contractions of ileal myenteric plexus-longitudinal muscle preparations isolated from guinea-pigs in-vitro, median effective dose 60 mg/l (Reiter and Brandt, 1985a). The oil, 1:20 000, decreased the rate and extent of contractions in intestinal smooth muscle isolated from rats, cats or rabbits in-vitro, and antagonised the stimulant activity of acetylcholine, barium chloride, pilocarpine and physostigmine (J. W. C. Gunn, 1920). Anethole, 0.05–1.00 mg/ ml, blocked twitching induced by acetylcholine and caffeine in toad rectus abdominis and sartorius muscles, but had no effect on skeletal muscle twitching induced by nerve stimulation in isolated rat diaphragm (Albuquerque, Sorenson, and Leal-Cardoso, 1995).

## Bronchodilatory activity

The oil, 1.0 mmol/l, had relaxant effects in precontracted, isolated guinea-pig tracheal chains indicating a bronchodilatory effect. It also induced a parallel rightwards shift in the methacholine-response curve (methacholine is a muscarinic receptor antagonist), indicating that the broncho-dilatory activity may be due to an inhibitory effect of the oil on the muscarinic receptors (Boskabady and Ramazani-Assari, 2001).

## Oestrogenic activity

Subcutaneous administration of 0.1 ml of the oil to ovariectomized[206] rats had an oestrogenic effect equivalent to that of 0.1 µg of estradiol (Sharaf and Goma, 1965). Intra-peritoneal administration of 0.1 ml of the oil had a uterine relaxation effect in female rats (Sharaf and Goma, 1965). Anethole is thought to be the oestrogenic component of the oil; polymers of this compound, such as dianethole and photoanethole, have also been suggested (Albert-Puleo, 1980b).

## Expectorant activity

Intragastric administration of 10.0–50.0 mg/kg bw of the oil to guinea-pigs increased bronchial secretions, demonstrating an expectorant effect (Boyd and Pearson, 1946). Intragastric administration of two drops of the oil as an emulsion with gummi arabicum to cats induced hypersecretion of the respiratory tract (Van Dongen and Leusink, 1953). However, other researchers have demonstrated that administration of the oil to cats by steam inhalation had no effect on respiratory tract fluid except when given in toxic doses, which increased the output (Boyd and Sheppard, 1968). Administration of the oil by inhalation to anaesthetized rabbits did not appreciably affect respiratory tract fluids until doses of 720.0 mg/kg bw and over were used in a vaporiser (Boyd and Sheppard, 1968), (Boyd, 1970). At this dose, 20% of the animals died and there was local irritation of the lining of the respiratory tract, which appeared as congestion at 6 hours and progressed to leukocytic infiltration and destruction of the ciliated mucosa at 24 hours (Boyd and Sheppard, 1968). Inhalation of 1 ml/kg bw of anisaldehyde in anaesthetized rabbits significantly increased ($P < 0.05$) the volume of respiratory fluid collected for 4–6 hours after treatment and decreased the specific gravity of the fluid in treated animals compared with untreated controls (Boyd and Sheppard, 1970).

[206] To remove one or both ovaries (the female reproduc- tive organs in which eggs are made and stored)

### Liver effects

Subcutaneous administration of 100.0 mg/kg bw of the oil per day for 7 days stimulated liver regeneration in partially hepatectomized rats (Gershbein, 1977a).

## Medicinal uses

- **Uses supported by clinical data** - None.
- **Uses described in pharmacopoeias and well established documents** - Treatment of dyspepsia and mild inflammation of the respiratory tract (BHP, 1996), (Blumenthal, Busse, et al., 1998).
- **Uses described in traditional medicine** - As an aphrodisiac, carminative, emmenagogue, galactogogue[207] and insecticide. Treatment of chronic bronchitis (C. C. d. Guzman and Siemonsma, 1999), (Farnsworth, 2001).

## Contraindications

Aetheroleum Anisi is contraindicated in cases of known allergy to aniseed and anethole (Fraj, 1996). Owing to the traditional use of the oil as an emmenagogue and to induce labour, its experimental oestrogenic and potential mutagenic effects, and reports of anethole toxicity in infants (Hänsel, 1994), (Gorelick, 1995), use of the oil in pregnancy and nursing, and in children under the age of 12 years is contraindicated.

## Adverse reactions

Contact dermatitis[208] was reported in a cake factory worker after external exposure to a 5% concentration of Aetheroleum Anisi (Garcia-Bravo, 1997). Occasional allergic reactions to the oil affecting the skin, respiratory tract and gastrointestinal tract are reported (Blumenthal, Busse, et al., 1998). Inhalation of powdered Fructus Anisi induced an allergic effect in one subject with asthma. Skin-prick tests showed a positive reaction to the fruits and the patient had high specific anti-aniseed immunoglobulin E antibodies in his blood (Fraj, 1996). Anethole toxicity in infants has been reported, and presents clinically with symptoms of hypertonia[209], continued crying, atypical ocular movements, twitching, cyanosis, vomiting and lack of appetite (Hänsel, 1994), (Gorelick, 1995). Ingestion of 1.0–5.0 ml of the oil can result in **nausea**, **vomiting**, **seizures** and **pulmonary oedema** (Chandler and Hawkes, 1984a).

[207] a substance that produces lactation

[208] any skin inflammation that occurs when the skin's surface comes in contact with a substance originating outside the body

[209] reduced ability of muscles to stretch due to increased muscle tension

In cases of overdose (> 50 mg/kg), the ingestion of milk and alcohol is contraindicated owing to increased resorption.

## Warnings

Applications of Aetheroleum Anisi should be limited to inhalation therapy (N. G. Bisset, 1994).

## Precautions

- **Carcinogenesis, mutagenesis, impairment of fertility** - Inconsistent results have been reported concerning the mutagenicity of trans-anethole in the Salmonella/microsome assay. One group showed that anethole was mutagenic (Sekizawa and Shibamoto, 1982a), another that it was very weakly mutagenic in S. typhimurium strains TA1535, TA100 and TA98 (Swanson, 1979). In a further study, trans-anethole (concentrations not specified) did not increase the mutant frequency in the Salmonella/microsome assay, but did increase mutant frequency in the L5178Y mouse-lymphoma TK+/- assay in a dose-dependent[210] manner, with metabolic activation (Gorelick, 1995). Trans-anethole did not induce chromosome aberrations in-vitro in the Chinese hamster ovary cell assay (Gorelick, 1995). Trans-anethole was weakly hepatocarcinogenic[211] in female rats when administered at a dose of 1% in the diet for 121 weeks; however, this effect is not mediated by a genotoxic event (Marshall and Caldwell, 1996). Trans-anethole was investigated for its anti-fertility activity in rats, after intragastric administration of doses of 50.0 mg/kg bw, 70.0 mg/kg bw and 80.0 mg/kg bw (Dhar, 1995). Anti-implantation activity of 100% was observed in animals treated with the highest dose. The compound has been reported to show oestrogenic, antiprogestational[212], androgenic[213] and anti-androgenic[214] activities (Dhar, 1995).
- **Pregnancy: non-teratogenic effects** - See Contraindications.
- **Nursing mothers** - See Contraindications.
- **Paediatric use** - See Contraindications.
- **Other precautions** - No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; and teratogenic effects in pregnancy.

[210] effects change when the dose of the treatment is changed

[211] producing or tending to produce cancer of the liver

[212] an abortifacient

[213] pertaining to the development of male characteristics, including body hair, the genital organs and muscle mass

[214] having the ability to block the male hormone testosterone from binding to androgen receptors

## Dosage forms

Essential oil. Preparations containing 5–10% essential oil for inhalation are also available. Store in a well-filled, tightly sealed container, protected from light and heat (unknown, 1996b).

## Dosage

Average daily dose for internal use: essential oil 0.3 g; equivalent for other preparations (Blumenthal, Busse, et al., 1998).

## Toxicology

The LD-50 of anisaldehyde in rats was 1.51 g/kg bw, with death occurring within 4–18 hours following depression of the central nervous system (Jenner, 1964). The LD-50 in guinea-pigs was 1.26 g/kg bw, death occurring after 1–3 days (Jenner, 1964).

The safety and metabolism of trans-anethole were evaluated in rats as a model for assessing the potential for hepatotoxicity in humans exposed to the compound as a flavouring agent. In chronic dietary studies in rats, hepatotoxicity was observed when the estimated daily hepatic production of anethole epoxide exceeded 30 mg/kg bw. Chronic hepatotoxicity and a low incidence of liver tumours were observed at a dietary intake of trans-anethole of 550.0 mg/kg bw per day (Newberne, 1999). The effects of trans-anethole on drug metabolizing enzymes were assessed in rats; intragastric administration of 125.0 mg/kg or 250.0 mg/kg bw per day for 10 days had no effect on total cyctochrome P450 content in liver microsomes (Rompelberg, Verhagen, and Van Bladeren, 1993). In a chronic feeding study, trans-anethole was administered to rats in the diet at concentrations of 0, 0.25%, 0.5% and 1.0% for 117–121 weeks, giving an average dose of 105–550.0 mg/kg bw per day. No abnormalities related to treatment were observed with the exception of a very low incidence of hepatocarcinomas in female animals treated with the 1.0% dose (Truhaut, 1989). The acute LD-50 of anethole in rats was 2090.0 mg/kg bw; repeated doses of 695.0 mg/kg bw caused mild liver lesions consisting of slight discolouration, mottling and blunting of the lobe edges (Albert-Puleo, 1980b).

## Commentary

*Slight oestrogenic affect, but it may be competing for your oestrogen receptors.*

# Asian Ginseng

## Common names

Asian ginseng, ginseng, Chinese ginseng, Korean ginseng, Asiatic ginseng, Asian Ginseng, Chinese Ginseng, Guigai, Jiln Ginseng, Korean Ginseng, Ninjin, Oriental Ginseng, Panax schinseng, Red Ginseng, Ren Shen, Seng, Shen Lu, Shen Ts'Ao, Tane-Ninzin

## Latin name

*Panax ginseng*

Asian ginseng is native to China and Korea and has been used in various systems of medicine for many centuries. Asian ginseng is one of several types of true ginseng (another is American ginseng, Panax quinquefolius). The herb called Siberian ginseng or eleuthero (Eleutherococcus senticosus) is not a true ginseng.

## Overview

Asian Ginseng is one of the most highly regarded of herbal medicines in the Orient, where it has gained an almost magical reputation for being able to promote health, general body vigour, to prolong life and treat many ailments including depression, diabetes, fatigue, ageing, inflammations, internal degeneration, nausea, tumours, pulmonary problems, dyspepsia, vomiting, nervousness, stress, and ulcers.

Asian Ginseng has a history of herbal use going back over 5,000 years. It is one of the most highly regarded of herbal medicines in the Orient, where it has gained an almost magical reputation for being able to promote health, general body vigour and also to prolong life. The genus name Panax is derived from the Greek word meaning "panacea" or "all-healing"; the species ginseng is said to mean "wonder of the world". Both terms refer to the medicinal virtues of the plant. In the last decade it has gained popularity in the West and there is extensive literature on the beneficial effects of ginseng and its constituents.

Panax Ginseng is thought to be even more beneficial when taken with Ginkgo Biloba.

Ginseng has been listed by some as useful in the treatment of anaemia, cancer, depression, diabetes, fatigue, hypertension, insomnia, shock, effects of radiation, effects of morphine and cocaine use, environmental, physical and mental stress, and chronic illness. It has been said to act as a stimulant, promote endurance, increase life expectancy, relax the nervous system, improve mental awareness, encourage proper hormonal functions,

improve lipid levels, lower cholesterol, improve nerve growth, and increase resistance to disease. It has been used to increase the appetite and bodily energy, regulate menses, ease childbirth, increase fertility of women, and treat periodontal disease

Research has shown that Ginseng may have the ability to act as an "adaptogen", prolonging life by combating viral infections and Pseudomonas aeruginosa. Research continues to support ginseng's protective role against anti-cancer treatments and drugs, perhaps even countering the side effects of chemotherapy.

There is some thought that Ginseng may be useful for the prevention of abuse and dependence of opioids and psychostimulants.

Ginseng has been used to both stimulate and relax the nervous system. It increases capillary circulation in the brain and decreases the effects of stress. Though there are many kinds of ginsengs in the world but they cannot rival Asian Ginseng in ingredients and medicinal effects. It contains as many as 29 different ginsenosides while the others contains 8–9.

Asian Ginseng contains anti-ageing substances such as antioxidants and insulin-like substances which are not found in any other type of ginseng.

Ginsenosides are a diverse group of steroidal saponins, which demonstrate the ability to target a myriad of tissues, producing an array of pharmacological responses. However, many mechanisms of ginsenoside activity still remain unknown. Since ginsenosides and other constituents of ginseng produce effects that are different from one another, and a single ginsenoside initiates multiple actions in the same tissue, the overall pharmacology of ginseng is remains remarkably complex and esoteric.

In western herbal medicine, Panax ginseng's regulating effects on the immune system have been studied for potential effectiveness in preventing colds, flu, and some forms of cancer. In clinical studies, Panax ginseng has been shown to lower blood levels of both sugar and cholesterol, therefore it may help treat type 2 diabetes and high cholesterol. Its other potential uses are not as well defined, however. In separate studies of laboratory animals and humans, Panax ginseng had a relaxing effect on muscles in the lungs. The resulting airway expansion may help relieve asthma symptoms and other lung conditions that result from constricted airways.

In other studies, a combination of Panax ginseng and gingko is believed to boost memory and thinking processes. Early results from laboratory study may show that chemicals in Panax ginseng promote the growth of blood vessels, which could be valuable in treating extensive injuries.

Recent reports on the pharmacology of ginseng indicate a wide range of effects, including influence on the central nervous system, endocrine and adrenocortical systems, internal, organs, metabolism, blood pressure and sugar, gonadotropic activity, cellular ageing, tumours, and stress. Ginseng appears to relieve stress, increase sexual activity, and facilitate mating in laboratory animals. The herb has been reported to be effective in prolonging

survival time during cardiac arrest. It is reported to show hypoglycaemic activity. Asian Ginseng has also been identified to protect the testis against 2,3,7,8-tetrachloro-di-benzo-di-p-DIOXIN inducing testicular damage. This particular dioxin is the most dangerous of perhaps the most toxic chemical group known to science. Dioxins are known to cause cancer in humans.

Other data shows it works not only in preventing adult diseases including cancer, diabetes, hypertension, and impotence but can also aid in treatment.

German Commission E monograph and WHO support the use of ginseng as a prophylactic and restorative agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness, and loss of concentration, and during convalescence. In general, ginseng is used as a tonic, stimulant, aphrodisiac, immune booster, blood pressure modulator (lowers and raises, depending on needs), and a modulator of blood sugar level (lowers or raise, depending on needs).

## History

Ginseng is perhaps the most widely recognised plant used in traditional medicine and now plays a major role in the herbal health care market. For more than 2,000 years, various forms have been used medicinally. The name Panax derives from the Greek word for "all healing", and its properties have been so touted. Ginseng root's man-shaped figure (shen-seng means "man-root") led proponents of the Doctrine of Signatures, an ancient European herbalists philosophy, to believe that the root could strengthen any part of the body. Through the ages, the root has been used in the treatment of asthenia, atherosclerosis, blood and bleeding disorders, and colitis, as well as to relieve the effects of aging, cancer, and senility.

Prior to its discovery in the early seventeenth century, American ginseng had been used by American Indians, for purposes quite similar to the use of Asian ginseng by the Chinese. It was among the five most important medicinal plants of the Seneca Indians, and was primarily given to the elderly. According to Crow legend, the wife of Sitting Bull learned in a dream that the leaf or root tea would aid in childbirth without suffering. The Penobscots, who referred to it as "man root," prescribed the root tea to increase female fertility. Ginseng was regarded as a "universal remedy" for children and adults by the Meskwaki (Fox) Indians of Wisconsin. It was combined with other medicinal plants to render them more powerful. The Menominee considered the root to be a tonic and strengthener of mental prowess. American ginseng never became an important medicinal plant in American medicine, though the root was official in the United States Pharmacopeia from 1842–1882. It was regarded as a mild stimulant, and soothing to an upset stomach (S. Foster, 2009).

Evidence of the root's general strengthening effect has been examined for its ability to raise mental and physical capacity, as well as its protectant effect against diabetes, neurosis, radiation sickness, and some cancers. Today, its popularity is widely due to the adaptogenic or stress-protective effect of the saponins (Blumenthal, 1997), (Jia, Y. Zhao, and X. Liang, 2009).

Ginseng has been used in Chinese medicine for thousands of years. The name "ginseng" refers to both American (Panax quinquefolius) and Asian or Korean ginseng (Panax ginseng), which are made up of similar chemicals. Siberian ginseng, or Eleuthero (Eleutherococcus senticosus), is a completely different plant and does not have the same active ingredients. Both Asian and American ginseng contain substances called ginsenosides, which researchers think are the active ingredients.

Like American ginseng, Asian ginseng is a gnarled root that looks like a human body with stringy shoots for arms and legs. Long ago, herbalists thought that because of the way ginseng looks it could treat many problems, from fatigue and stress to asthma and cancer. In traditional Chinese medicine (TCM), ginseng is often combined with other herbs.

Today, ginseng is sometimes called an adaptogen, which is a substance that is supposed to help the body better cope with mental or physical stress. Scientists have not found any evidence that adaptogens exist. But ginseng has been studied for several conditions, and it is one of the most popular herbs in the United States (unknown, 2014c).

Treatment claims for Asian ginseng are numerous and include the use of the herb to support overall health and boost the immune system. Traditional and folk uses of ginseng include improving the health of people recovering from illness; increasing a sense of well-being and stamina; improving both mental and physical performance; treating erectile dysfunction, hepatitis C, and symptoms related to menopause; and lowering blood glucose and controlling blood pressure.

## Botany

Ginseng commonly refers to Panax quinquefolius see American Ginseng, or Panax ginseng, see Asian Ginseng, 2 members of the family Araliaceae. Several other species are less commonly used in Asia. The ginsengs were classified as members of the genus Aralia in older texts. In the eastern and central United States and Canada, Panax quinquefolius is found in rich, cool woods; a large crop is grown commercially in Wisconsin. The Asian species Panax ginseng is cultivated in Korea and China. The short plant grows 3 to 7 compound leaves that drop in the autumn and bears a cluster of red or yellowish fruits from June to July. The shape of the root can vary depending on the species and has been used to distinguish types of ginseng. Medicinally, the root is considered the most valuable part of the plant in providing the pharmacologically active ginsenosides. Ginsenoside content varies with the age of the root, season of harvest, and method of

preservation. While at least 4 ginsenosides are detectable in most young roots, this number more than doubles after 6 years of growth. High-quality ginseng is generally collected in the fall after 5 to 6 years of growth (Team, 2011), (WHO, 1999c).

Panax ginseng should not be confused with Siberian ginseng (Eleutherococcus senticosus), a related species with different chemistry (Team, 2011).

## Properties

Adaptogen, alterative, anti-complement[215], auto-immune stimulant[216], antioxidant, antitumour, antiviral[217], aphrodisiac, carminative, demulcent[218], emetic, expectorant, nervine[219], phagocytic, psychotropic[220], somnogenic[221], stimulant, stomachic, tonic.

## Chemistry

Major compounds in ginseng include triterpene saponins, polyacetylenes, sequiterpenes, polysaccharides, peptidoglycans, nitrogen-containing compounds, and other compounds, including fatty acids, carbohydrates, and phenolic compounds (WHO, 1999c), (Jia, Y. Zhao, and X. Liang, 2009), (L. P. Christensen, 2009). The triterpene saponins are considered the most active compounds, and some estimates report up to 150 different ginsenosides, grouped into either dammarane or oleanane groups (L. P. Christensen, 2009). Many analytical methods have been described and standards published. The European Pharmacopoeia requires a minimum of 0.4% combined Rg1 and Rb1 ginsenosides, while the Chinese Pharmacopoeia requires ginseng radix (dry root) to have not less than 0.3% Rg1 and Re combined ginsenosides and not less than 0.2% Rb1 (Jia, Y. Zhao, and X. Liang, 2009).

Most traditional ginseng herbal preparations contain ginsenosides. However, a commercially available product, known as CVT-E002, a patented aqueous extract of approximately 80% to 90% poly-furanosyl-pyranosyl-saccharides from the roots of North American ginseng (Panax quinquefolius), does not contain ginsenosides (Chuang et al., 1995). Adulterants

[215] a substance that counteracts the action of a complement

[216] stimulates the auto-immune system

[217] destroying or inhibiting the growth and reproduction of viruses

[218] any of several oily substances used for soothing and reducing irritation of surfaces that have been abraded or irritated, especially mucosal surfaces

[219] a plant remedy that has a beneficial effect upon the nervous system

[220] affecting mental activity, behavior, or perception

[221] promoting sleep

are commonly found in ginseng preparations due to the high cost of authentic ginseng roots, and the presence of natural methylxanthines may also contribute to some reported physiological effects (L. P. Christensen, 2009), (Chuang et al., 1995), (Blumenthal, Gruenwald, et al., 1997).

Variances in cultivation and processing methods, as well as the individual genetics of each plant source, result in varying chemical compositions among commercial products. This may contribute to the lack of consensus among studies on the pharmacology and efficacy of ginseng and should be considered when conducting and interpreting research (WHO, 1999c), (C. F. Chen, Chiou, and J. T. Zhang, 2008). A second factor that may have produced erratic results is the discovery that ginsenosides are metabolised extensively by the human gut microflora and that some of the metabolites are pharmacologically active. Colonic bacteria can remove the 3 sugars from ginsenoside Rb1 in stepwise fashion, and the deglycosylated compounds are then esterified in the liver with the fatty acids stearic, palmitic, and oleic acid. These esters persist in the liver for as long as 24 hours (Hasegawa, 2004). Thus, differences in an individual's gut flora may lead to differing pharmacological responses to ginseng preparations.

Asian ginseng supplements are made from the ginseng root, and the long, thin offshoots, called root hairs. Both Asian or Korean and American ginseng have ginsenosides, saponins that are ginseng's active ingredients. Asian ginseng also contains glycans (panaxans), polysaccharide fraction DPG-3-2, peptides, maltol, B vitamins, flavonoids, and volatile oil (unknown, 2014c).

## Uses and Pharmacology

Reviews of the effects of ginseng have been published. Most studies have used whole-root preparations, with considerable variations due to uncertain species identification, age of the roots, and curing process used. Variations in saponins between the species also may contribute to the lack of consensus among researchers on ginseng's pharmacology (WHO, 1999c), (L. P. Christensen, 2009), (Kurihara and Kiruchi, 1973).

## Cancer

### Animal data

Both ginsenosides and polyacetylenes have demonstrated anti-carcinogenic effects in-vitro, including direct cytotoxic and growth inhibitory effects, induction of differentiation, and inhibition of metastasis. High concentrations of M1, an active metabolite of Rb1, Rb2, and Rc, induced cell death of mouse melanoma cells by regulating proteins involved in apoptosis. Ginsenosides

Rh2 and Rh3 induced differentiation of promyelocytic leukaemia cells into granulocytes; Rg3 inhibited adhesion and invasion of melanoma cells and decreased pulmonary metastasis (L. P. Christensen, 2009), (Qi, C. Z. Wang, and C. S. Yuan, 2010), (Ng, 2006).

### Clinical data

Epidemiological data support a protective effect of ginseng on nonspecific organ cancers (L. P. Christensen, 2009), (T. K. Yun, S. Zheng, and S. Y. Choi, 2010). A long-term study of ginseng 1 g taken weekly for 3 years among adults with long-term atrophic gastritis showed no effect on the overall relative risk of cancer. In the male subgroup analysis, there was a reduction in the risk of non-organ-specific cancers (T. K. Yun, S. Zheng, and S. Y. Choi, 2010).

Trials evaluating the effect of ginseng (both Panax quinquefolius and Panax ginseng) on cancer-related fatigue at doses of 1 to 2 g/day over 8 to 12 weeks have shown effects for some, but not all, aspects of mental and physical functioning (Barton, Soori, and B. A. Bauer, 2010), (J. H. Kim, C. Y. Park, and S. J. Lee, 2006). Ginseng may improve some of the adverse effects of chemotherapy-related transcatheter arterial chemoembolization (Yinglu et al., 2009).

## Cardiovascular effects

Ginseng saponins have been reported to act as selective calcium antagonists and enhance the release of nitric oxide from endothelial and neuronal cells. In-vitro studies have shown that total ginseng saponins extracted from Panax notoginseng and Panax quinquefolius inhibited calcium entry through receptor-operated calcium channels without affecting calcium entry through voltage channels or intracellular calcium release (L. P. Christensen, 2009), (C. Y. Kwan, 1995).

### Animal data

In studies involving rabbits and dogs, ginsenosides Ro and Rb from Panax ginseng offered a protective effect in myocardial ischaemia and reperfusion injuries. This effect may be partly mediated by increased release of prostacyclin and by activation of nitric oxide synthase and subsequent release of nitric oxide. An inhibitory effect on platelet aggregation and on the conversion of fibrinogen to fibrin has been demonstrated, and the prevention of atheroma in rabbits fed a high-cholesterol diet has been observed (L. P. Christensen, 2009), (X. Chen, 1996).

## Clinical data

Clinical trials evaluating the effect of ginseng on the cardiovascular system are limited. Hypotensive and hypertensive effects have been postulated. In a short-term study in healthy adults, ginseng 3 g had no effect on blood pressure but lowered the arterial augmentation index (Jovanovski, A. Jenkins, and Dias, 2010), while a 12-week study among hypertensive adults found no effect of ginseng on 24-hour blood pressure or on renal function (P. M. Stavro et al., 2006). Shenfu injection, a mixture of ginseng and monkshood, has been used to prevent reperfusion injury following mitral valve replacement (C. D. Zheng and Min, 2008). Sanchi (Panax notoginseng) is widely used in traditional Chinese medicine in acute ischaemic stroke. The saponins in sanchi are similar to those found in Panax ginseng and are classified as dammarane saponins (Rb1 and Rg1 primarily). A review of clinical trials found limited evidence of effect of sanchi on short-term effects of ischaemic stroke, but noted that the trials were of limited methodological quality (X. Chen, M. Zhou, and Q. Li, 2008).

## CNS effects

Rb1 and Rg1 appear to play a major role in CNS stimulatory and inhibitory effects and may modulate neurotransmitters. Cholinergic[222] activity, implicated in mediating learning and memory processes, is affected by certain ginsenosides. Antioxidant, anti-inflammatory, antiapoptotic, and immune stimulatory effects are suggested to contribute to a protective effect in neurodegenerative disorders (Radad et al., 2006).

## Animal data

Animal studies show that Rb1, Rg1, and Re prevent scopolamine-induced memory deficits, and that Rb1 and Rg1 appear to increase central choline uptake and facilitate the release of acetylcholine from hippocampal tissues. Results from a study in aged rats suggest that daily oral administration of Panax ginseng extract 8 g/kg/day for 12 days improved learning performance. In animal tissues, ginseng extract inhibited gamma-aminobutyric acid (gamma-aminobutyric acid (GABA)), glutamine, dopamine, noradrenalin, and serotonin uptake in a concentration-dependent manner (L. P. Christensen, 2009), (Radad et al., 2006), (Bahrke and W. R. Morgan, 2000), (Attele, J. A. Wu, and C. S. Yuan, 1999).

[222] this refers to any compound that can increase levels of acetylcholine or choline in the brain

### Clinical data

Limited high-quality clinical trials have been conducted, and systematic reviews include data from very few studies (Kurihara and Kiruchi, 1973), (M. S. Lee et al., 2009). An anxiolytic effect via GABA modulation was suggested to be responsible for an observed improvement in sleep disorders for fermented ginseng (Kitaoka, Uchida, and Okamoto, 2009). Among healthy adults, short-term effects of Panax ginseng and Panax quinquefolius include increased mental performance, increased calmness, and decreased mental fatigue (Reay, D. O. Kennedy, and A. B. Scholey, 2006a), (A. Scholey, Ossoukhova, and L. Owen, 2010), (Reay, A. B. Scholey, and D. O. Kennedy, 2010). A review of the effect of ginseng on cognitive function in Alzheimer disease found an effect in favour of ginseng for the mini-mental status examination and Alzheimer Disease Assessment Scale for the 2 included studies (M. S. Lee et al., 2009), (Heo, S. T. Lee, and Chu, 2008).

## Diabetes

### Animal data

Widespread usage of ginseng and the availability of limited clinical trial data make animal studies largely redundant.

Evidence appears to support the modulation of insulin sensitisation and secretion based on cholinergic, dopaminergic, adrenergic, and nitric oxide actions found with ginsenosides. These have been noted to affect glucose metabolism in animal studies (Radad et al., 2006), (Vuksan, Sievenpiper, and Koo, 2000), (Vuksan, M. P. Stavro, and Sievenpiper, 2000).

### Clinical data

Limited quality clinical trials have been conducted among adults with diabetes, with the majority of studies evaluating ginseng in healthy volunteers. Improvements in blood glucose measures and glycaemic control have been reported in some, (Vuksan, Sievenpiper, and Koo, 2000), (Vuksan, M. P. Stavro, and Sievenpiper, 2000), (Sievenpiper, M. K. Sung, and Di Buono, 2006), (Reay, A. B. Scholey, Milne, et al., 2009), (Reay, D. O. Kennedy, and A. B. Scholey, 2006b) but not all, (Reay, A. B. Scholey, and D. O. Kennedy, 2010), (Vuksan, M. K. Sung, and Sievenpiper, 2008), (E. d. Andrade, Mesquita, and Claro Jde, 2007) studies.

## Ergogenic effects

### Animal data

Widespread usage of ginseng and the availability of limited clinical trial data make animal studies largely redundant.

## Clinical data

Evidence supporting the efficacy of ginseng in improving physical performance is conflicting. Physical performance in young, active volunteers did not improve in 4 studies; however, other studies reported a decrease in heart rate and an increase in maximal oxygen uptake (Kurihara and Kiruchi, 1973), (Kulaputana, Thanakomsirichot, and Anomasiri, 2007). One comprehensive literature search evaluated Panax ginseng preparations in data from human studies. Properly controlled studies using higher doses (standardised to 2 g/day of dried root) administered for at least 8 weeks and in larger subject numbers more often exhibited improvement in physical or psychomotor performance. Benefit was seen in untrained subjects or in those older than 40 years (Bucci, 2000).

# Immunomodulatory and adaptogenic effects

## Animal data

Animal studies have shown that ginseng extracts can prolong swimming time, prevent stress-induced ulcers, stimulate the proliferation of hepatic ribosomes, increase natural killer-cell activity, and possibly enhance the production of interferons (V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984b). Increased spleen B lymphocyte proliferation and serum immunoglobulin production have been documented in animal models. Increased peritoneal exudate macrophage production of the cytokines IL-1, tumour necrosis factor-alpha, and IL-6, and the production of nitric oxide has also been reported (M. Wang, Guilbert, and L. Ling, 2001), (Haddad et al., 2005).

## Clinical data

Studies in healthy volunteers measuring T-lymphocyte immunomodulation yield equivocal results (Kurihara and Kiruchi, 1973), (Attele, J. A. Wu, and C. S. Yuan, 1999). Studies in healthy sedentary men and healthy physically active men have found no effect of ginseng on immune markers (Kulaputana, Thanakomsirichot, and Anomasiri, 2007), (Biondo et al., 2008). Modulation of CD8+ T cells and interleukin production was reported in sedentary men beginning to exercise (Biondo et al., 2008). A possible effect of ginseng on the CD4+ T cell count in HIV-positive men was reported (unknown, 2009b).

Clinical trials supported by the manufacturers of a patented Panax quinquefolius preparation suggest a lowered incidence of influenza with the use of ginseng as a prophylactic, especially among elderly patients (McElhaney, Gravenstein, and Cole, 2004), (Predy, V. Goel, R. Lovlin,

Donner, et al., 2005), (Predy, V. Goel, R. Lovlin, Shan, et al., 2005), (Predy, V. Goel, R. E. Lovlin, et al., 2006), (McElhaney, V. Goel, et al., 2006). Dosage studies have taken place to evaluate the effect of ginseng in children with upper respiratory tract infections (Vohra, Johnston, and Laycock, 2008).

- **Other effects** - Studies in postmenopausal women suggest ginseng 1 g daily (as Korean Red ginseng) may increase sexual arousal possibly via a relaxing effect on the clitoral cavernosal muscle and vaginal smooth muscle (Oh et al., 2010).
  In men, an improvement in erectile function has been shown in a meta-analysis of clinical studies (Jang et al., 2008), (T. H. Kim, S. H. Jeon, and Hahn, 2009).

## Research

Many studies of Asian or Korean ginseng have used combinations of herbs. So it is not always possible to say whether ginseng by itself produced the results. Research on Asian ginseng has included the following conditions -

- **Colds and flu** - It has been said that Asian ginseng boosts the immune system, which might help the body fight off infection and disease. The best evidence is that it may help reduce your risk of getting a cold or flu. Studies have found that ginseng seems to increase the number of immune cells in the blood and improve the immune system's response to a flu vaccine. In one study, 227 people got either ginseng or placebo for 12 weeks, and got a flu vaccine after 4 weeks. The number of colds and flu were two-thirds lower in the group that took ginseng.
  Two studies found that ginseng lowered the chance of getting a cold. In one double-blind, placebo-controlled study of 323 people, those who took 400 mg of ginseng daily for 4 months had fewer colds. When they did get a cold, it was less severe and shorter than the colds of people who took placebo (unknown, 2014c).
- **Heart health** - Asian ginseng seems to be an antioxidant. Antioxidants help rid the body of free radicals[223] , which are substances that can damage DNA and contribute to heart disease, diabetes, and other conditions. Preliminary studies suggest Asian ginseng may improve the symptoms of heart disease in people. It also may decrease LDL (bad) cholesterol levels and raise HDL (good) cholesterol.
  Asian ginseng's effect on blood pressure is more complicated. Some studies suggest it lowers blood pressure while others found that it causes blood pressure to rise. This has led researchers to question if ginseng increases blood pressure at usual doses, but lowers it when doses are higher. Until researchers know for sure, you should not take ginseng if you have high blood pressure unless your doctor tells you it is OK (unknown, 2014c).

[223] see Free radicals and antioxidants

- **Type 2 diabetes** - Although American ginseng has been studied more for diabetes, both types of Panax ginsengs may lower blood sugar levels in people with type 2 diabetes. However, in a few studies it looked like Asian or Korean ginseng raised blood sugar levels. Some people think that the ginsenosides in American ginseng might lower blood sugar while different ginsenosides in Asian ginseng could raise blood sugar levels. Until researchers know more, you should not take ginseng if you have diabetes without your doctor's supervision and monitoring (unknown, 2014c).
- **Mental performance** - People who take ginseng often say they feel more alert. Several studies report that Asian ginseng may slightly improve thinking or learning. Early research shows that Asian ginseng may improve performance on such things as mental arithmetic, concentration, memory, and other measures. Some studies have also found a positive effect with the combination of Asian ginseng and Ginkgo biloba.
  Most of the studies have found that ginseng does improve mental performance. But they have measured different kinds of mental function. That makes it hard to know exactly what the effects of ginseng are. For example, one study found that people who took ginseng increased their ability for abstract thought. But it did not create any changes in their reaction time or concentration levels (unknown, 2014c).
- **Physical endurance** - There have been a number of studies using Asian ginseng for athletic performance in people and laboratory animals. Results have been mixed, with some studies showing better strength and endurance, others showing improved agility or reaction time, and others showing no effect at all. Even so, athletes often take Asian ginseng to boost both endurance and strength. Asian ginseng was also found to reduce fatigue in a study of 332 people (unknown, 2014c).
- **Stress and well-being** - Asian ginseng is sometimes credited with helping the body deal with physical or mental stress. While these properties can be difficult to study, there is some evidence that ginseng (both Asian and American) can improve quality of life, although quality of life can be hard to measure, too.
  A study of 501 men and women living in Mexico City found better quality of life measures (energy, sleep, sex life, personal satisfaction, and well-being) in those taking Asian ginseng. Another well-designed study found that people who took a nutritional supplement with ginseng said they had better quality of life than those taking the same supplement without ginseng (unknown, 2014c).
- **Fertility/erectile dysfunction** - Asian ginseng is widely believed to boost sexual performance. But there are not many studies to back this up. In animal studies, Asian ginseng has increased sperm production, sexual activity, and sexual performance. A study of 46 men has also shown an increase in sperm count as well as motility. Another study

in 60 men found that Asian ginseng increased sex drive and decreased erection problems. Also, in one study of 45 men, those who took 900 mg of Korean ginseng 3 times per day for 8 weeks had less trouble getting an erection than those who took placebo (unknown, 2014c).

- **Cancer** - Several studies suggest that Asian ginseng may reduce the risk of some types of cancers. In one observational study[224], researchers followed 4,634 people for 5 years. They found that those who took ginseng had lower risks of lung, liver, pancreatic, ovarian, and stomach cancers. But the study could not be sure that other things, including healthy eating habits, were responsible for the lower risk of cancer. The study also found that taking ginseng only 3 times a year led to a big reduction in cancer risk.
  Several studies suggest that Asian ginseng slows down or stops the growth of tumours, although researchers are not yet sure how it might work in humans. More research is needed (unknown, 2014c).
- **Menopausal symptoms** - There have been only a few studies of ginseng for menopausal symptoms. Two well-designed studies evaluating Red Korean (Asian) ginseng suggest it may relieve some of the symptoms of menopause, improving sense of well-being and mood, particularly feelings of depression. People took ginseng along with a vitamin and mineral supplement. Other studies show no effect (unknown, 2014c).

## Pregnancy/Lactation

Use during pregnancy and lactation should be avoided due to insufficient evidence of safety (WHO, 1999c), (Seely et al., 2008). An association of ginseng with androgenization in a case report is considered doubtful and more likely due to an adulterant in the preparation (Seely et al., 2008), (Ernst, 2002b). Evidence from a cohort study and a review of clinical trials conducted in Singapore found no association of adverse events among pregnant women consuming ginseng products, and ginseng is widely used in Asian countries in pregnant women (Seely et al., 2008). Concerns regarding oestrogenic effects of ginseng are unestablished, while in-vitro teratogenicity in rats has been reported at artificially high doses of ginsenosides (WHO, 1999c), (Seely et al., 2008).

## Interactions

Limited evidence exists for any established interactions, with most data derived from laboratory studies and healthy volunteers. Very few case reports exist; however, caution should be exercised when using the following medicines with ginseng: antidiabetic drugs insulin, antipsychotic drugs, caffeine and other stimulants, furosemide, and MAOIs (WHO, 1999c), (Seely et al., 2008).

[224] it draws a conclusion by comparing subjects against a control group

A 26-year-old man taking imatinib 400 mg daily for 7 years was diagnosed with imatinib-induced hepatotoxicity 3 months after he started drinking energy drinks containing Panax ginseng. After treatment, he was able to restart imatinib without recurrence of elevations in his liver enzymes (Bilgi et al., 2010).

In a study in healthy volunteers, administration of a single dose of nifedipine after subjects ingested ginseng for 18 days increased nifedipine plasma concentrations 53% when measuRed 0.5 hours after nifedipine administration (M. Smith, K. M. Lin, and Y. P. Zheng, 2001).

Reports of an interaction between warfarin and ginseng are conflicting. There are case reports that ginseng may decrease the anticoagulant effect of warfarin. However, open-label studies found no effects of Panax ginseng on international normalized ratio or prothrombin times after 2 weeks of coadministration (Rosado, 2003), (X. Jiang, K. M. Williams, and Liauw, 2004), (S. H. Lee et al., 2008).

Likewise, in studies conducted among healthy volunteers, ginseng exerted no influence on the pharmacokinetics of zidovudine (Panax ginseng) (L. S. Lee et al., 2008) or indinavir (Panax quiquefolius) (A. S. Andrade, Hendrix, and T. L. Parsons, 2008).

If you are currently being treated with any of the following medications, you should not use Asian ginseng without first talking to your health care provider -

- **angiotensin converting enzyme (ACE) inhibitors (blood pressure medications)** - Asian ginseng may interact with angiotensin-converting enzyme (ACE) inhibitors used to lower high blood pressure. These medications include -
  - Captopril (Capoten),
  - Benazepril (Lotensin),
  - Enalapril (Vasotec),
  - Lisinopril (Prinivil, Zestril),
  - Fosinopril (Monopril),
  - Ramipril (Altace),
  - Perindopril (Aceon),
  - Quinapril (Accupril),
  - Moexipril (Univasc),
  - Trandolapril (Mavik).
- **Calcium channel blockers (heart and blood pressure medications)** - Asian ginseng may make certain heart medications, including calcium channel blockers, work differently than intended. These medications include -
  - Amlodipine (Norvasc),
  - Diltiazem (Cardizem),
  - Nifedipine (Procardia).

- **Blood-thinners (anticoagulants and antiplatelets)** - Asian ginseng may increase the risk of bleeding, especially if you already take blood thinners, such as aspirin, warfarin (Coumadin), or clopidogrel (Plavix).
- **Caffeine** - Ginseng may make the effect of caffeine stronger, possibly causing nervousness, sweating, insomnia, or irregular heartbeat.
- **Diabetes medications, including insulin** - Ginseng may lower blood sugar levels, increasing the risk of hypoglycaemia or low blood sugar.
- **Drugs that suppress the immune system** - Asian ginseng may boost the immune system and may interact with drugs taken to treat an autoimmune disease or drugs taken after organ transplant.
- **Stimulants** - Ginseng may increase the stimulant effect and side effects of some medications taken for attention deficit hyperactivity disorder (ADHD), including amphetamine and dextroamphetamine (Adderall) and methylphenidate (Concerta, Ritalin).
- **MAOIs (monoamine oxidase inhibitors)** - Ginseng may increase the risk of mania when taken with MAOIs, a kind of antidepressant. There have been reports of interaction between ginseng and phenelzine (Nardil) causing headaches, tremors, and mania. MAOIs include -
  - Isocarboxazid (Marplan),
  - Phenelzine (Nardil),
  - Tranylcypromine (Parnate).
- **Morphine** - Asian ginseng may block the painkilling effects of morphine.
- **Psychiatric medications** - Asian ginseng may exaggerate the effects of this anti-psychotic medication, so these should not be taken together. There have been reports of a possible interaction between Asian ginseng and the antidepressant medication, phenelzine (which belongs to a class known as monoamine oxidase inhibitors), resulting in symptoms ranging from manic-like episodes to headache and tremulousness.
- **Furosemide (Lasix)** - Some researchers think Asian ginseng may interfere with Lasix, a diuretic that helps the body get rid of excess fluid (unknown, 2014c).

## Surgery

Stop taking Asian ginseng at least 7 days prior to surgery. Asian ginseng may act as a blood thinner, increasing the risk of bleeding during or after a procedure (unknown, 2014c).

Ginseng is used for -

- **Endurance and stamina** - It is claimed to strengthen the body to resist disease and fight fatigue and stress, resulting in an improvement in physical and mental performance. Siberian ginseng, from a different species of ginseng, is claimed to boost the immune system, increasing resistance to colds and mild infections. Check with your pharmacist for more details regarding the particular brand you use.

Ginseng is a dietary supplement. It is unknown exactly how ginseng works.

Do NOT use ginseng if -

- you are allergic to any ingredient in ginseng,
- you are undergoing surgery, or you have any bleeding or blood clots.

Contact your doctor or health care provider right away if any of these apply to you.

## Before using ginseng

Some medical conditions may interact with ginseng. Tell your doctor or pharmacist if you have any medical conditions, especially if any of the following apply to you -

- if you are pregnant, planning to become pregnant, or are breast-feeding,
- if you are taking any prescription or nonprescription medicine, herbal preparation, or dietary supplement,
- if you have allergies to medicines, foods, or other substances,
- if you have a fever, a history of high or low blood pressure, oestrogen-dependent cancer, diabetes, or heart problems,
- if you are taking "water pills" (diuretics such as bumetanide or furosemide).

Some medicines may interact with ginseng. However, no specific interactions with ginseng are known at this time.

This may not be a complete list of all interactions that may occur. Ask your health care provider if ginseng may interact with other medicines that you take. Check with your health care provider before you start, stop, or change the dose of any medicine.

## How to use ginseng

Use ginseng as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Take ginseng with a meal.
- There are different types of ginseng, which vary widely in quality. Read product labeling carefully.
- Ginseng may cause trouble sleeping. Do not take it in the early evening or at bedtime.

- If you miss taking a dose of ginseng for 1 or more days, there is no cause for concern. If your doctor recommended that you take it, try to remember to take your dose every day.

Ask your health care provider any questions you may have about how to use ginseng.

## Important safety information

- It is best to avoid taking ginseng for long periods of time (several months or more).
- **Diabetes patients** - Ginseng may affect your blood sugar. Check blood sugar levels closely and ask your doctor before adjusting the dose of your diabetes medicine.
- Ginseng is not recommended for use in children. Safety and effectiveness have not been confirmed.
- **Pregnancy and breast-feeding** - If you become pregnant while taking ginseng, discuss with your doctor the benefits and risks of using ginseng during pregnancy. It is unknown if ginseng is excreted in breast milk. If you are or will be breast-feeding while you are using ginseng, check with your doctor or pharmacist to discuss the risks to your baby.

The root of Asian ginseng contains active chemical components called ginsenosides (or panaxosides) that are thought to be responsible for the herbs claimed medicinal properties. The root is dried and used to make tablets or capsules, extracts, and teas, as well as creams or other preparations for external use.

In 1999, sixteen medical trials were reviewed, and it was concluded that the efficacy of ginseng root extract was not established beyond reasonable doubt. The widespread use of ginseng as a herbal remedy warranted more rigorous investigations to assess its efficacy and safety (Vogler, Pittler, and Ernst, 1999).

Ginseng is an herbal product that may act as a stimulant. In most well-designed and controlled experiments, researchers have not found a significant effect on performance for those taking ginseng versus placebo. Ginseng is very expensive, and the truth may be that most commercial preparations may contain little or no ginseng. The most common side effect of taking ginseng is **insomnia**, although some people have experienced **diarrhoea** and **skin eruptions**. Generally speaking, ginseng may be safe but ineffective and expensive (unknown, 2014h).

## Adverse effects

Nervousness and excitability may occur but decrease after the first few days. Ability to concentrate may decrease, and plasma glucose may become abnormally low (causing hypoglycaemia). Because ginseng has an oestrogen-like effect, women who are pregnant or breastfeeding should not take it, nor should children. Occasionally, there are reports of more serious effects, such as asthma attacks, increased BP, palpitations, and, in postmenopausal women, uterine bleeding. To many people, ginseng tastes unpleasant.

Ginseng can interact with antihyperglycaemic drugs, aspirin, other NSAIDs, corticosteroids, digoxin, oestrogens, monoamine oxidase inhibitors, and warfarin (merck, 2015).

## Adverse Reactions

It is estimated that more than 6 million people regularly ingest ginseng in the United States. There have been few reports of severe reactions, and a very low incidence of adverse events has been reported in clinical trials (Seely et al., 2008) Hypersensitivity and anaphylaxis have been reported (B. Barrett and D. J. Brown, 2007).

Inappropriate use of Panax ginseng has been described and caused symptoms such as hypertension, diarrhoea, sleeplessness, mastalgia, vaginal bleeding, skin rash, confusion, and depression. A ginseng abuse syndrome was described based on an uncontrolled study in which participants used up to 15 g ginseng daily. When the dosage was reduced to 1.7 g/day, adverse reactions resolved (WHO, 1999c), (Seely et al., 2008).

Oestrogenic effects have been reported in both pre- and postmenopausal women. However, studies with standardised extracts have shown no effect on oestrogenic receptors (rats) or progesterone receptors (humans) (WHO, 1999c), (Seely et al., 2008).

Common side-effects are mental status changes i.e. **nervousness**, **restlessness**, **excitation**, **insomnia**, **gastrointestinal problems**.

## Side Effects and Cautions

- Short-term use of ginseng at recommended doses appears to be safe for most people. Some sources suggest that prolonged use might cause side effects.
- The most common side effects are **headaches** and **insomnia** and **gastrointestinal problems**.
- Asian ginseng can cause allergic reactions.

- There have been reports of breast tenderness, menstrual irregularities, and high blood pressure associated with Asian ginseng products, but these products' components were not analyzed, so effects may have been due to another herb or drug in the product.
- Asian ginseng may lower levels of blood sugar; this effect may be seen more in people with diabetes. Therefore, people with diabetes should use extra caution with Asian ginseng, especially if they are using medicines to lower blood sugar or taking other herbs, such as bitter melon and fenugreek, that are also thought to lower blood sugar.
- Tell all your health care providers about any complementary health approaches you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care (NCCIH, 2012a).

## Possible side effects

All medicines may cause side effects, but many people have no, or minor, side effects. Check with your doctor if any of these most common side effects persist or become bothersome - **agitation, diarrhoea, headache, nervousness, insomnia**.

Seek medical attention right away if any of these severe side effects occur -

Severe allergic reactions **rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue**, **vaginal bleeding** This is not a complete list of all side effects that may occur. If you have questions about side effects, contact your health care provider. Call your doctor for medical advice about side effects.

Inappropriate use of ginseng or ginseng abuse syndrome includes symptoms such as **high blood pressure, diarrhoea, sleeplessness, breast pain, skin rash, confusion, and depression**.

Other side effects are rare, but may include -

- High blood pressure,
- Insomnia,
- Restlessness,
- Anxiety,
- Euphoria,
- Diarrhoea,
- Vomiting,
- Headache,
- Nose bleed,
- Breast pain,
- Vaginal bleeding (unknown, 2014c).

## If overdose is suspected

Symptoms may include **trouble sleeping or swelling of ankles, feet, face, or hands**.

## Proper storage of ginseng

Store ginseng at room temperature, between 59 and 86 degrees F (15 and 30 degrees C), in a cool, dry place. Store away from heat, moisture, and light. Do not store in the bathroom. Most herbal products are not in childproof containers. Keep ginseng out of the reach of children and away from pets.

## General information

- If you have any questions about ginseng, please talk with your doctor, pharmacist, or other health care provider.
- Ginseng is to be used only by the patient for whom it is prescribed. Do not share it with other people.
- If your symptoms do not improve or if they become worse, check with your doctor.
- Check with your pharmacist about how to dispose of unused medicine (CDI, 2015).

## What the Science Says

- Some studies have shown that Asian ginseng may lower blood glucose. Other studies indicate possible beneficial effects on immune function.
- Although Asian ginseng has been widely studied for a variety of uses, research results to date do not conclusively support health claims associated with the herb. Only a few large, high-quality clinical trials have been conducted. Most evidence is preliminary - i.e., based on laboratory research or small clinical trials.
- NCCIH supports studies to better understand the use of Asian ginseng. Areas of recent NCCIH-funded research include the herbs potential role in treating insulin resistance, cancer, and Alzheimers disease.

## Available Forms

White ginseng (dried, peeled) or Red ginseng (unpeeled root, steamed before drying) is available in water, water-and-alcohol, or alcohol liquid extracts, and in powders or capsules. Asian ginseng root is also available for making decoctions (boiling the root in water).

Read the label carefully to make sure you get the type of ginseng you want. If you are looking for Asian ginseng, make sure you buy Korean, Red, or Panax ginseng. If you are looking for American ginseng, you should buy Panax quinquefolius. Eleuthero (Eleutherococcus senticosus), which is sometimes called Siberian ginseng, does not have the same active ingredients as Asian or American ginseng (unknown, 2014c).

## Dosage

Ginseng root is standardised according to ginsenosides content, and can be chewed or taken as a powder, liquid extract, decoction, or infusion.

According to the Complete German Commission E Monographs, crude preparations of dried root powder 1 to 2 g can be taken daily for up to 3 months (Blumenthal, Gruenwald, et al., 1997). In numerous clinical trials, the dosage of crude root has ranged from 0.5 to 3 g/day and the dose of extracts has generally ranged from 100 to 400 mg (WHO, 1999c), (Kurihara and Kiruchi, 1973), (Ng, 2006). Other trials have used higher dosages (Vuksan, M. K. Sung, and Sievenpiper, 2008).

### Paediatric

Do not give ginseng to a child (unknown, 2014c).

### Adult

Asian ginseng comes in different forms and is often used in combination with other herbs or nutrients. Talk with an experienced health care practitioner to find the right dose for you.

Healthy people who want to boost physical or mental performance, prevent illness, or better resist stress should take Asian ginseng in cycles. For example, take every day for 2 to 3 weeks, then stop for 3 weeks, then start back (unknown, 2014c).

## Toxicology

Embryotoxicity due to ginsenosides Rb1, Rc, Re, and Rg1 has been demonstrated in rat embryos (Seely et al., 2008). In-vitro studies found no carcinogenicity, mutagenicity, or teratogenicity for Radix ginseng (WHO, 1999c).

A doping-control urinalysis was conducted under International Olympic Committee (IOC) doping control guidelines for CVT-E002 200 and found no IOC-banned substances that might induce a positive doping-control urinalysis (D. P. Goel et al., 2004).

## Commentary

*There are various chemical compositions in the commercial products, and differing pharmacological responses to Asian Ginseng, so it isn't possible to say how effective it is for oestrogenic effects.*

Chapter 5

# B's

## Basil

### Common names

Sweet Basil, Arabic = Rehahn, Chinese = Luo de, French = Basilic, German = Basilienkraut, German = Basilikum, Hindi = Babui tulsi, Italian = Basilico, Malay = Selasi, Russian = Bazilik, Sanskrit = Munjariki, Spanish = Albahaca, Tamil = Tirnirupachai, common basil, garden basil, St. Josephs wort, basilicon, joy of the mountain, Chinese = lo-le, Swedish = basilika, Japanese = barjiru.

### Latin name

*Ocimum basilicum*

Basil is a popular kitchen herb used for flavouring food. It is also widely regarded for its health-enhancing properties. Basil has been a staple of medicine for generations and the herb has been used to treat a variety of different conditions, from inflammation to bug bites (herbwisdom, 2015a).

It is said that basil was found growing around Jesus' tomb after the resurrection, and the Greek Orthodox Church uses it in the holy water. In Greece it's quite common to see the herb planted in front of houses since it's believed to bring good luck. In Western Europe during the Middle Ages it was considered the devil's herb and used in potions to protect against witches.

The herb was and still is used extensively in Ayurvedic (Indian) medicine for its antiseptic properties. Basil is also used medically in China, mainly to promote good blood circulation after birth, and to treat kidney problems and stomach cramps.

It has been used traditionally to alleviate and treat flatulence, abdominal cramps, colic, constipation, and indigestion. It can also be used to prevent nausea and vomiting, and to rid the body of intestinal worms.

Basil has a mild soothing and sedative effect that could make it useful in the treatment of nervous irritability, depression, anxiety and sleep difficulties.

Ocimum basilicum has anti-spasmodic, antiseptic, expectorant and antibacterial properties and it can be used for epilepsy, migraine, and fever associated with colds and flu. Additionally, the herb has a slight diuretic effect and has sometimes been used to treat arthritis, rheumatism and urinary problems.

The plant is traditionally used to increase production of breast milk in lactating mothers.

Basil may lower sugar values in both blood and urine. A 62-patients study, which was published in 1997, showed that consumption of basil reduced the amount of glucose by 17% compared with a control group that received a placebo. The amount of cholesterol and sugar in the urine were also reduced, but not significantly. More and larger studies are needed to determine whether basil may have a value as a glucose-lowering agent for diabetes patients.

The fresh leaves have been used as an insect repellant and the juice extracted from the leaves is used to treat snake bites and insect stings.

Used as a tea or a mouth rinse mixed with water, the herb can be used as an herbal remedy to relieve cough, whooping cough and sore throat, and fresh leaves can be chewed for fresher breath or to get rid of bad breath.

The leaves have been used to remove warts and other skin blemishes. The herb contains many viral inhibitory substances, which explains this traditional use.

In many cultures basil is regarded as a herb to promote menstruation, induce labour and as an aphrodisiac, but no evidence exist to substantiate this use (Resource, 2015b).

## Health Benefits

Basil has long been considered an anti-depressant. It makes an excellent tea that acts on the adrenal cortex, and it can help the body stimulate hormones that regulate the body's natural response to stress. For this reason, many people believe that basil has uplifting properties. Basil may also be able to improve memory, and it is often utilised to overcome the effects of jet lag. Basil has been commonly found in a variety of treatments for diarrhoea, intestinal parasites, fevers, and skin infections. It is also thought to imitate oestrogen, and may help regulate the menstrual cycle. In addition, basil may stimulate the immune system and lower the uric acid content that is responsible for arthritis and gout. Basil can also be used to treat the pain and inflammation of arthritis (herbwisdom, 2015a).

## Active Ingredients

Basil contains large quantities of E-Beta-CaryoPhyllene (BCP) which may be useful in treating arthritis or bowel diseases. BCP is one of the only products that naturally stimulates the body's cannabinoid receptors, and it can block the signals that lead to inflammation associated with arthritis. Basil also contains eugenol, cintronellol, linalool, and myrcene (herbwisdom, 2015a).

The plant contains 0.2% to 1% essential oil, which consists primarily of linalool and methyl chavicol, but it also contains small amounts of cineole, methyl cinnamate and other terpenes. Other constituents include tannins, monoterpenes, sesquiterpenes and phenylpropanoids (Resource, 2015b).

## Breastfeeding

### Summary of Use during Lactation

Basil (Ocimum basilicum) contains linalool, 1,8 cineole (eucalyptol), methylchavicol, methylcinnamate and an essential oil with high estragole content. Estragole might be a procarcinogen[225]. Basil is a purported galactogogue (Winterfeld et al., 2012); however, no scientifically valid clinical trials support this use. Galactogogues should never replace evaluation and counseling on modifiable factors that affect milk production (Breastfeeding Medicine Protocol Committee, 2011). No data exist on the excretion of any components of basil into breast-milk or on the safety and efficacy of basil in nursing mothers or infants. Basil is "generally recognized as safe" (GRAS) as a food by the US Food and Drug Administration. Basil appears to be safe during breastfeeding in the amounts found in foods, but many sources recommend that medicinal doses of basil not be used during lactation because of its estragole content and lack of safety information (Kopec, 1999).

Dietary supplements do not require extensive pre-marketing approval from the US Food and Drug Administration. Manufacturers are responsible to ensure the safety, but do not need to prove the safety and effectiveness of dietary supplements before they are marketed. Dietary supplements may contain multiple ingredients, and differences are often found between labeled and actual ingredients or their amounts. A manufacturer may contract with an independent organisation to verify the quality of a product or its ingredients, but that does not certify the safety or effectiveness of a product. Because of the above issues, clinical testing results on one product may not be applicable to other products.

[225] a chemical substance that becomes a carcinogen only after it is altered by metabolic processes

## Drug Levels

**Maternal Levels** - Twelve nursing mothers who were 19 weeks to 19 months postpartum[226] ingested 100 mg of 1,8 cineole (eucalyptol) in the form of delayed-release capsules (Soledum-Klosterfrau Vertriebs GmbH, Germany) that release the drug in the intestine. Then they pumped 1 to 4 milk samples at the time they perceived the smell of eucalyptus on their breath which had been previously shown to be approximately concurrent. A total of 21 milk samples were obtained. Odour was rated by a panel of 3 to 5 experts as either smelling like eucalyptus or not. Fourteen of the samples had a distinct eucalyptus-like odour. Chemical analysis of the positive odour tests found 1,8-cineole in concentrations from 70 to about 2090 mcg/kg of milk, most in the range of 100 to 500 mcg/kg of milk. Samples with negative odour tests contained concentrations in the range of 0.98 to about 20.23 mcg/kg of milk. In one woman who donated 3 samples, the highest concentration of 71 mcg/kg occurred at 1.5 hours after ingestion, with concentrations of 1 mcg/kg before ingestion and 15 mcg/kg at 9.5 hours after ingestion (Kirsch, Beauchamp, and Buettner, 2012). Eight women had their milk analyzed for 1,8-cineole metabolites. Ten metabolites and several enantiomers of these metabolites were detected (Kirsch and Buettner, 2013), (Kirsch, Horst, and Rohrig, 2013).

**Infant Levels** - Relevant published information has not been found.

## Effects in Breastfed Infants

Nursing mothers who were participating in an experiment on the excretion of 1,8-cineole (eucalyptol) in breastmilk took a 100 mg capsule of 1,8-cineole orally. Although instructed not to, 12 mothers breastfed their infants during the experiment. Mothers reported that none of their infants refused their milk or breastfed less than usual. Two mothers felt that their infants were more agitated a few hours after breastfeeding. A third mother reported that the infant stopped nursing from time to time and "looked puzzled", but resumed nursing. Upon repeating the experiment 6 weeks later, the infant did not react in an unusual way during breastfeeding (Kirsch, Beauchamp, and Buettner, 2012).

## Effects on Lactation and Breastmilk

Relevant published information has not been found (unknown, 2013a).

[226] the period beginning immediately after the birth of a child and extending for about six weeks

## Using Basil Leaves

Basil can be used in a variety of ways. The fresh leaves can be made into a poultice, or the seeds can be ground and added to meals. Basil also has antiseptic properties, and when the leaves are rubbed onto bug bites they can help reduce itching. Another outstanding use of basil is as an insect repellent. The herb is often made into tinctures, and because basil is an expectorant, it can help fight bronchitis and coughs. Basil is good for a wide variety of lung ailments, and when it is combined with elecampane and hyssop, it can be brewed into a tea that helps fight head colds. When consumed as a hot tea, basil can either be taken internally or inhaled, and the herb is often found in a variety of aromatherapy products (herbwisdom, 2015a).

### Basil Essential Oil

Basil is often found as an essential oil, and the product is said to fight mental fatigue. Basil oil is not taken internally, but it is used in aromatherapy and massage. When used in a massage, basil can increase blood flow and enhance the amount of nutrients that reach tired and fatigued muscles. The essential oil has also been used to fight headaches, reduce hay fever, allergies, or asthma, and it can even relieve the symptoms of hiccoughs (herbwisdom, 2015a).

### Culinary Uses

Basil is often used in tomato dishes, and it forms a crucial part of pesto. It is also said to complement the flavour of peaches very nicely. Just a few fresh leaves, or a sprinkling of dried leaves, are all that is needed to add a distinct flavour to any type of dish (herbwisdom, 2015a).

## Dosage

As a tea - 2 tablespoons of fresh ground leaves to one cup of boiling water. Steep for 15 minutes and then strain. Drink 1 to 2 cups daily (Resource, 2015b).

## Risks

The herb contains about 0.5% essential oil with up to 85% estragole. Estragole, after metabolic activation, has a mutagenic effect. Animal experiments indicated a carcinogenic effect, which demands further investigation. Because of the high estragole content in the essential oil, the herb should not be taken during pregnancy, nursing, by infants or toddlers, or over extended periods of time (herbalgram, 1992a).

### Side-effects

Because basil can enhance the effectiveness of insulin and blood glucose-lowering medications, people with diabetes and those using such medication should use the herb with caution and only under the guidance of a professional health care provider (Resource, 2015b).

### Toxicology

None known.

### Commentary

*Very little is known about this herb for its oestrogenic properties, and as such I would not use it on myself, except for culinary purposes.*

## Black Cohosh

### Common names

Black cohosh, black snakeroot, macrotys, bugbane, bugwort, rattle-root, rattleweed, baneberry, cimicifuga, rattletop, traubensilberberze, squawroot, wanzenkraut (Borrelli, Izzo, and Ernst, 2003), (J. E. Meyer, 1960), Richweed, Cimicifuga, Sheng ma, Chinese Black Cohosh.

### Latin names

*Actaea racemosa*, formerly known as *Cimicifuga racemosa*

### Overview

Black cohosh (known as both Actaea racemosa and Cimicifuga racemosa), a member of the buttercup family, is a perennial plant that is native to North America. Insects avoid it, which accounts for some of these common names.

Black cohosh, a member of the buttercup family, is a plant native to North America. It was used in Native American medicine and was a home remedy in 19th-century America. Black cohosh has a history of use for rheumatism (arthritis and muscle pain) but has been used more recently as a folk or traditional remedy for hot flashes, night sweats, vaginal dryness, and other symptoms that can occur during menopause. Black cohosh has also been used for menstrual irregularities and premenstrual syndrome, and to induce labour.

The underground stems and roots of black cohosh are commonly used fresh or dried to make strong teas (infusions), capsules, solid extracts used in pills, or liquid extracts (tinctures).

Black cohosh is the underground stem of a plant that can be ingested directly in powdered form or extracted into tablet or liquid form. It should be standardised to contain certain triterpenes. Black cohosh contains no phytoestrogens that can account for its purported oestrogen-like effects, but it contains small amounts of anti-inflammatory compounds, including salicylic acid (merck, 2009).

## Botany

The older name Cimicifuga racemosa L. (Nutt.) has been replaced by the synonym Actaea racemosa L., although both names are commonly used. Black cohosh grows in open woods at the edges of dense forests from Ontario, Canada to Tennessee and west to Missouri in the United States. This perennial grows to 2.5 m and is topped by a long plume of white flowers that bloom from June to September. Its leaflets are shaped irregularly with toothed edges. The word "black" refers to the dark color of the rhizome. The name "cohosh" comes from an Algonquian word meaning "rough," referring to the surface of the rhizome (I. N. Dobelis, 1986). The related species Cimicifuga foetida is used in traditional Chinese medicine, while Cimicifuga dahurica (Turcz.) Maximowicz and Cimicifuga heracleifolia Komarov are used in Japan. Polymerase chain reaction protocols have been developed for distinguishing and authenticating the species (Xue, D. Z. Li, and Q. Z. Wang, 2009), (Zerega et al., 2002), (drugs.com, 2015a).

Black cohosh Actaea racemosa (Cimicifuga racemosa) is equally at home in the perennial border as it is in its shaded haunts in the eastern deciduous forest. Pre-colonial botanical observers in America couldn't help but notice the handsome, robust foliage, with the tall spikes of brilliant white flowers, waving like a flag to attract attention. Native American groups looked deeper than its obvious beauty, believing that the thick, knobby, resin-scented roots hold medicinal value. Black cohosh fits into several categories including woodland wildflower, garden perennial, and medicinal herb. Backed by an intriguing botanical, horticultural, and medicinal history, a new generation of baby boomer women - at the steps of menopause - are discovering that this traditional First Nation remedy for female conditions is emerging as a new treatment for symptoms associated with menopause, backed by modern clinical research. Black cohosh is a rising star on the herbal horizon.

Black cohosh is a member of the buttercup family (Ranunculaceae) found in rich woods of the eastern deciduous forest from southern Ontario south to Georgia, west to Arkansas, north to Wisconsin. This perennial woodland plant likes the deep shade of moist hillsides; the home of other important medicinal plans such as goldenseal and ginseng. It has robust, three-

divided leaves, with three-lobed terminal leaflets. The middle lobe of the sharply-toothed leaflets is the largest. The plant is little-noticed until it sends up its tall spikes of showy white flowers, three to eight feet tall. Petals are not to be seen; the chief feature is tufts of conspicuous stamens surrounding the pistil in the center. In begins blooming in May in the southern part of its range, continuing to flower into September in more northerly regions. Black cohosh was first described in 1705. By 1732, it had been introduced into English gardens as a hardy ornamental perennial.

The root and rhizome are the parts used in herbal traditions. Most of the rhizome is wild-harvested, while some is grown commercially in Europe. The genus Actaea includes twenty-seven species, found in Europe, North America, and eastern Asia. Collectively, they are commonly known as bugbanes, primarily referring to the single native European species, Actaea europaea (Cimicifuga europaea) and the Asian species Actaea foetida (Cimicifuga foetida), which have strong, unpleasant smelling herbage, earning it a reputation as an insect-repelling plant. The genus name Cimicifuga, itself, honours this olfactory observation. It comes from the Latin cimex meaning bug (specifically the bed bug Cimex lectularius) and fugare "to drive-away" in reference to the insect-repelling attributes. These species are also known by the common names bugwort or bugbane. Bugbanes have been used independently as insect repellents throughout their extensive ranges from India to Western Europe to eastern Siberia. The herbage of the American black cohosh does not possess a strong odour.

## History

American Indians used black cohosh for the treatment of general malaise, kidney ailments, malaria, rheumatism, sore throat, and gynaecological disorders (eg, ease of labour, menstrual cramps). North American colonists used the herb for treating amenorrhoea, bronchitis, chorea, dropsy, fever, hysteria, itch, lumbago, nervous disorders, snakebite, yellow fever, and uterine disorders. In traditional Chinese medicine, the herb was valued for its anti-inflammatory, analgesic, and antipyretic properties. The plant has been used in Europe since the 17th century to treat joint pain, neuralgia, and pain in pregnancy and labour. Literature reports also document the use of black cohosh for treating influenza, smallpox, acute rheumatism, headache, cough, chorea, and other nervous system disorders (Low Dog, K. L. Powell, and Weisman, 2003), (Pepping, 1999), (Winterhoff et al., 2003). It was an important herb in the Eclectic medical movement[227] in the United States in the 19th century, under the name "macrotys" (Felter, 1900). The

[227] a branch of American medicine which made use of botanical remedies along with other substances and physical therapy practices, popular in the latter half of the 19th and first half of the 20th centuries

old-time remedy Lydia Pinkham's Vegetable Compound[228] (early 1900s) contained many natural ingredients, including black cohosh (V. E. Tyler, 1995). The roots and rhizomes[229] are used medicinally. A tea from the root has been recommended for sore throat. The Latin name cimicifuga means "bug repellent," and the plant has been used for this purpose. A variety of cimicifuga preparations are available commercially. However, Remifemin , the brand name of a standardised extract of the plant, has been widely studied and used in Germany for menopausal management since the mid-1950s (Low Dog, K. L. Powell, and Weisman, 2003), (M. Murray, 1997b), (drugs.com, 2015a).

Traditionally used by North American Indians for a variety of aches and pains as well as menopausal symptoms (Resource, 2015c).

## Black cohosh in History

American Indian groups of eastern North America used black cohosh to treat female conditions and for rheumatism, long before Europeans landed on American shores. The Delaware, whom were moved to the Indian Territories of modern Oklahoma a century ago, used black cohosh in combination with other herbs as a female tonic. The Iroquois used a strong tea of the root as a footbath, soaking the feet while bathing sore, stiff areas of the body to treat rheumatism. The Cherokee are said to have used the roots to treat rheumatism and various female conditions. They also valued it as a tonic and diuretic.

Early medical authors note that use of the plant was learned from Native Americans. The importance of black cohosh as a medicinal plant was recognized in the first works on American herbs, dating back to 1801. The root was an important folk medicine among American Indian groups and early settlers for menstrual irregularities and as an aid in childbirth. It was widely prescribed by physicians in nineteenth century America, where it had a great reputation as an anti-inflammatory for arthritis and rheumatism, and played an important role for normalizing suppressed menses, painful or difficult menses, and to relieve pain after childbirth. It was also used for nervous disorders. The root was an official drug of the United States Pharmacopoeia from 1820 to 1926. In historical works, information on the herb can be found under several names. Early editions of the United States Pharmacopoeia gave its official name as "black snakeroot," a name that persisted in medical books into the 1890s. Eclectic medical practitioners

[228] a commercially successful herbal-alcoholic "women's tonic" meant to relieve menstrual and menopausal pains. It contained Unicorn Root (Aletris farinosa L.) 8 ounces, Life Root (Senecio aureus L.) 6 ounces, Black Cohosh (Cimicifuga racemosa (L.) Nutt.) 6 ounces, Pleurisy Root (Asclepias tuberosa L.) 6 ounces, Fenugreek Seed (Trigonella foenum-graecum L.) 12 ounces, Alcohol (18%) to make 100 pints

[229] a horizontal stem that grows shallowly underground. At nodes along the rhizome, below-ground roots and above-ground shoots grow into new plants

of the late nineteenth and early twentieth centuries knew it by the name "macrotys" (a misspelling of the obsolete genus name Macrotrys, both a botanical and common name that was never widely recognised, and is lost in obscurity).

It was the Eclectics who championed the use of black cohosh, particularly Dr. John King, (1813-1893), who also first brought Echinacea to the attention of the medical community. Black cohosh was more important to King than Echinacea, since he was a professor of obstetrics at the old Eclectic medical college in Cincinnati (which closed its doors in 1943). He spoke about black cohosh to his students as his "favourite remedy." He had used it in his own clinical practice from 1832 until his death, as an important remedy in both acute and chronic cases of rheumatism and related inflammatory conditions, plus various lung and nervous affections. King recognized it as his primary treatment "in abnormal conditions of the principal organs of reproduction in the female." If King had not been such a strong proponent of the herb, it may have faded away into obscurity. Like several important herbs, such as Echinacea and saw palmetto, in the early part of this century, the Eclectic' extensive use and advocacy of black cohosh attracted the attention of the German medical community. As use of herbs faded in American medicine by the 1930s, the Germans picked-up the reins and catapulted these herbs into modern use.

More than two centuries ago, Native Americans discovered that the root of the black cohosh plant (Actaea racemosa, formerly known as Cimicifuga racemosa) helped relieve menstrual cramps and symptoms of menopause, such as hot flashes, irritability, mood swings, and sleep disturbances. Today, people use black cohosh for these same reasons. In fact, the herb has been widely used in Europe for more than 40 years and is approved in Germany for premenstrual discomfort, painful menstruation, and menopausal symptoms (unknown, 2014d).

Black Cohosh has been used by Native Americans for more than two hundred years, after they discovered the root of the plant helped relieve menstrual cramps and symptoms of menopause. These days it is still used for menopausal symptoms such as hot flashes/flushes, irritability, mood swings and sleep disturbances. It is also used for PMS, menstrual irregularities, uterine spasms and has been indicated for reducing inflammation associated with osteoarthritis, rheumatoid arthritis and neuralgia.

Herbal researcher Dr. James Duke has this to say about Black Cohosh -

> "Black cohosh really should be better known in this country, especially with our aging population and the millions of women who are now facing menopause. Recognised for its mild sedative and anti-inflammatory activity, black cohosh can help with hot flashes and other symptoms associated with that dramatic change of life called menopause. It's also reported to have some oestrogenic activity. Herbalist Steven Foster refers to a study that compared the effects of

> conventional oestrogen replacement therapy with black cohosh. That study looked at 60 women, younger than 40 years old, who had had complete hysterectomies and were experiencing abrupt menopause. In all groups, treatment with black cohosh compared favourably with conventional treatment."

> "Native Americans used the roots and rhizomes of this member of the buttercup family to treat kidney ailments, malaria, rheumatism, and sore throats. Early American settlers turned to it for bronchitis, dropsy, fever, hysteria and nervous disorders, lumbago, rattlesnake bites, and yellow fever. It's also reportedly well known for easing PMS and menstrual irregularities."

This oestrogenic activity, notes Dr. Duke, can contribute to a 'mastogenic' effect; the natural enlargement of the breasts. Black Cohosh has also been used to induce labour and should not be used during pregnancy (herbwisdom, 2015b).

A dozen studies or more conducted throughout the 1980s and 1990s confirm that the long-standing use of black cohosh for menopausal symptoms has scientific validity. For example, in a German study involving 629 women, black cohosh improved physical and psychological menopausal symptoms in more than 80% of the participants within four weeks. In a second study, 60 menopausal women were given black cohosh extract, conjugated oestrogens, or diazepam (a leading anti-anxiety medication) for three months. Those who received black cohosh reported feeling significantly less depressed and anxious than those who received either oestrogens or diazepam. *It should be noted however that diazepam is not a recognised treatment for menopausal symptoms. Its a bit like putting a sticking plaster on a crack in the wall, looks good but in reality, does bugger all!* In another study, 80 menopausal women were treated for 12 weeks with black cohosh extract, conjugated oestrogens, or placebo. Black cohosh improved anxiety, menopause and vaginal symptoms. In addition, the number of hot flashes dropped from 5 to less than 1 average daily occurrences in the black cohosh group compared to those taking oestrogen in whom hot flashes dropped from 5 to $3\frac{1}{2}$ daily occurrences.

Given these examples, and results of other studies, some experts have concluded that black cohosh may be a safe and effective alternative to oestrogen replacement therapy (ERT) for women who cannot or will not take ERT for menopause.

Preliminary studies also suggest that black cohosh may help reduce inflammation associated osteoarthritis and rheumatoid arthritis. In a review of scientific studies, researchers concluded that a combination of black cohosh, willow bark (Salix spp.), sarsaparilla (Smilax spp.), guaiacum (Guaiacum officinale) resin, and poplar bark (Populus tremuloides) may help relieve symptoms of osteoarthritis (herbwisdom, 2015b).

## What are the historical uses of black cohosh?

Black cohosh was used in North American Indian medicine for malaise, gynaecological disorders, kidney disorders, malaria, rheumatism, and sore throat (S. Foster, 1999). It was also used for colds, cough, constipation, hives, and backache and to induce lactation (Upton, 2002). In 19th-century America, black cohosh was a home remedy used for rheumatism and fever, as a diuretic, and to bring on menstruation. It was extremely popular among a group of alternative practitioners who called black cohosh "macrotys" and prescribed it for rheumatism, lung conditions, neurological conditions, and conditions that affected women's reproductive organs (including menstrual problems, inflammation of the uterus or ovaries, infertility, threatened miscarriage, and relief of labour pains) (Upton, 2002), (drugs.com, 2015a).

## Black Cohosh Today

Used in Europe for over 60 years, with experience in over a million cases, black cohosh is again becoming known in its native land as a possible alternative for reducing unpleasant symptoms associated with menopause. Efficacy and safety are confirmed by long-term clinical experience, as well as recent controlled clinical studies, along with acute toxicity studies that help to corroborate its safety. Black cohosh will become of increasing interest to women looking for an alternative to oestrogen therapy in the treatment of menopausal symptoms. Not only is it widely used in Europe, black cohosh and related species have a long history of use in both Asia and North America. Among women's herbs, black cohosh is the most important rising star (S. Foster, 2014).

Black cohosh is a plant native to eastern North America. The plant is found in rich, shady woods ranging from Maine to Ontario, and from Wisconsin south to Georgia and Missouri. Native Americans used the rhizome of black cohosh for general malaise, kidney ailments, malaria, rheumatism, sore throat, and for conditions specific to women, such as menstrual irregularities and childbirth. Black cohosh was adopted and used frequently by early settlers and herbal doctors, and in the 1840s by the Eclectic physicians, who used it for many symptoms, especially those associated with rheumatism and rheumatoid pain. Some of the early patent medicines contained high concentrations of black cohosh, and it was the main ingredient in Lydia Pinkham's famous 'Vegetable Compound,' drunk by women in the early nineteenth century to relieve menstrual stress and nervous tension (J. Duke, 1985), (Felter, 1922), (Snow, 1996). Currently, black cohosh has become the largest-selling herbal dietary supplement in the United States for reducing symptoms associated with menopause. Black cohosh influences the endocrine regulatory systems, with effects similar to one of the milder endogenous oestrogens, estriol[230]. For a short duration, it binds weakly with oestrogen receptors and is thought to exert its effects on

[230] estriol is one of the three main oestrogens produced by the human body

the vaginal lining (M. Murray, 1997a). A lack of oestrogen-like (hormonal) effect has been demonstrated in animal experiments (Boué, Wiese, and Nehls, 2003), and human pharmacological studies (Liske and Wüstenberg, 1999), (Liske and Wüstenberg, 1998).

Modern clinical studies have investigated the therapeutic efficacy and safety of black cohosh extracts for indications of the neurovegetative[231] symptoms caused by menopause. These studies used several internationally recognised and validated scales as controls, including the Kupperman index[232] for the quantitative determination of menopausal symptoms, the Self-evaluation Depression Scale, the Profile of Mood States[233], the hamilton anxiety scale[234], and the Clinical Global Impression scale (CGI), for evaluating the success and the risk-to-benefit assessment of the treatment. Somatic symptoms were determined using vaginal-cytological controls, such as vaginal smears, and measures of gonadotropin secretion (Beuscher, 1995).

Clinical studies using hormone replacement therapy (HRT) and black cohosh have been published based on a particular product called Remifemin*R* (Shaper & Brümmer, Germany), standardised on the basis of triterpene glycosides; each tablet contains 1 mg of triterpenes, calculated as 27-deoxyacteine and totalling 40 mg of black cohosh extract. In 1996, nearly ten million monthly units of Remifemin were sold in Germany, Australia, and the United States (M. Murray, 1997a). At least eight clinical studies have been published on the therapeutic effects of Remifemin in treating menopausal symptoms (S. Foster, 1999) although the total in the literature, according to the Napralert database, is 19.

Modern day use of black cohosh is most commonly for menopausal symptoms but also (PMS) and irregular periods (Resource, 2015c).

## Usage

Black cohosh has been used to help manage some symptoms of menopause and as an alternative to hormone replacement therapy (HRT). It may be useful for treatment of hypercholesteremia or peripheral arterial disease. Clinical studies do not support these uses.

[231] relating to the vegetative (autonomic) nervous system

[232] a rating scale that is used to measure the severity of the symptoms of menopause, including hot flashes, tingling or crawling skin, difficulty sleeping, nervousness, melancholy, dizziness, weakness, joint or muscle pain, headache, and abnormal heart beat

[233] a standard validated psychological test formulated by McNair in 1971

[234] a rating system that is used to measure the severity of the symptoms of anxiety (including worrying, restlessness, fearfulness, trouble sleeping, poor concentration or memory, depression, aches and pains, shortness of breath, nausea, sweating, and impotence)

Clinical trials have shown black cohosh to be useful in reducing hot flushes and night sweats associated with the menopause. Some studies have shown it to be as effective as conventional hormone treatments.

Some research has suggested that black cohosh in combination with St. Johns wort (Hypericum perforatum) is useful for both hot flushes and mood swings caused by the menopause.

It is often found in combination with other herbs thought to be of benefit for women's health e.g. menstrual cycle and menopause.

Contrary to traditional thinking, modern extracts of black cohosh do not contain natural hormones (oestrogen) and clinical studies have shown black cohosh to have no detrimental effect on the womb or breast tissue (Resource, 2015c).

Mild sedative, relaxant and anti-inflammatory. Diaphoretic, antipyretic, anti-fungal and antibacterial (herbwisdom, 2015b).

Cough/sore throat, dysmenorrhoea, dyspepsia, labour induction, menopausal symptoms, nervous tension, PMS, rheumatism (medscape, 2015a).

## Chemistry

German reports from the late 1960s discuss the contents of black cohosh (Linde, 1967a), (Linde, 1967b), (Linde, 1968). The key medicinal components include triterpene glycosides, phenolic acids, flavonoids, volatile oils, and tannins. High-performance liquid chromatography revealed the presence of caffeic acid, ferulic acid, isoferulic acid, cimicifugoside H-1, cimiracemoside A, cimicifugoside H-2, ( 26R )-actein, 26-deoxycimicifugoside, ( 26S )-actein, 23-epi-26-deoxyactein, 23-OAc-shengmanol-3- O -beta-D-xyloside, 26-deoxyactein, 25-OAc-cimigenol-3- O -beta-L-arabinoside, 25-OAc-cimigenol-3- O -beta-D-xyloside, cimigenol-3- O -beta-L-arabinoside, and cimigenol-3- O -beta-D-xyloside (S. N. Chen, Fabricant, Z., et al., 2002). Four phenylpropanoid esters, cimiracemates A-D (14), have been identified (S. N. Chen, Fabricant, Z. Z. Lu, et al., 2002), (W. Li et al., 2003). Black cohosh contains N-methylcytisine, as well as guanidine alkaloids (Gödecke, Lankin, and Nikolic, 2009a) and N-methyl-serotonin (Gödecke, Nikolic, and Lankin, 2009b). The terpenoid mixture consists of actein, 12-acetylactein, and cimigoside. Other constituents found in the plant include acetic, butyric, formic, oleic, palmitic, and salicylic acids; racemosin; formononetin (an isoflavone); phytosterols; acteina (resinous mixture); and volatile oil (C. A. Newall, L. A. Anderson, and Phillipson, 1996a). An amorphous resinous substance called cimicifugin (macrotin) accounts for approximately 15% to 20% of the root. Cimigoside (cimifugoside) and 27-deoxyacteine also have been isolated. The triterpene glycoside, 27-deoxyacteine, is used to standardise Remifemin (S. Berger, Junior, and Kopanski, 1988), (A. Huntley and Ernst, 2003a).

An efficient countercurrent chromatography isolation method for black cohosh saponins has been developed (Cicek et al., 2010). Quantitative chromatographic methods for determining triterpenes and formononetin in black cohosh rhizomes have been published (Kennelly, Baggett, and Nuntanakorn, 2002), (Avula et al., 2009). Stability of polyphenols and saponins in plant material has been evaluated (B. Jiang, Lyles, et al., 2008), and their content in an 85-year-old herbarium specimen has been determined (B. Jiang, H. Yang, et al., 2005). The pharmacokinetics of 23-epi-26-deoxyactein have been investigated in women administered black cohosh extract, with a measured half-life[235] of approximately 2 hours (Breemen, W. Liang, and Banuvar, 2010), (drugs.com, 2015a).

Black cohosh contains glycosides (sugar compounds), isoferulic acids (substances with anti-inflammatory effects), and, possibly, phytoestrogens, among several other active substances (unknown, 2014d).

Black cohosh's main constituents are cimicifugin, triterpene glycosides, isoflavones, tannins, isoferulic acid, salicylic acid, alkaloids (trace only), fatty acids, mucilage and starch (Resource, 2015c).

Contains glycosides (sugar compounds), isoferulic acids and, possibly, phytoestrogens (herbwisdom, 2015b).

## Uses and Pharmacology

Black cohosh has been used to control symptoms of menopause as an alternative to conventional HRT therapy. The plant seems to have no stimulatory effect on oestrogen-dependent cancers and may even exhibit inhibitory effects against the disease. Black cohosh may also be useful in other areas, such as treatment for HIV[236], hypercholesteremia, and peripheral arterial disease.

[235] the amount of time required for the amount of something to fall to half its initial value

[236] human immunodeficiency virus

## Menopause

### In-vitro studies

The isoflavone formononetin binds to oestrogen receptor preparations; however, it does not reduce serum levels of LH[237] in ovariectomized rats (Jarry, Harnischfeger, and E. Düker, 1985). N-methyl-serotonin was isolated from black cohosh and shown to bind to 5-HT [7] receptors and induce cyclic adenosine monophosphate (AMP) (S. L. Powell, Gödecke, and Nikolic, 2008).

### Animal data

The purported oestrogenic effects of the plant could not be reproduced in extensive tests in mice. In one study, there was no evidence of a direct or indirect influence on gonadal function. However, other studies indicate that methanol extracts of C. racemosa contain substances that bind to oestrogen receptors (Jarry, Metten, et al., 2003). Intraperitoneal injection of the extract in ovariectomized rats caused a selective reduction in LH level with almost no effect on follicle-stimulating hormone (FSH[238]) or prolactin levels (Jarry and Harnischfeger, 1985). One report found no signs of uterine growth or vaginal cornification[239] in ovariectomized rats given black cohosh extract (Einer-Jensen, J. Zhao, Andersen, et al., 1996). In a more recent study, standardised cimicifuga extract increased staining of oestrogen receptors in the endometrium of ovariectomized rats while lowering Ki67 protein levels. The increase in oestrogen receptors due to cimicifuga was less than that produced by estradiol, while estradiol increased Ki67 staining and cimicifuga lowered it (Alves, S. M. Lima, and Silva, 2008). Gene expression of oestrogen-receptor alpha was unchanged, while oestrogen-receptor beta expression was increased in the uterus of rats treated with cimicifuga (Seidlova-Wuttke, Jarry, and Wuttke, 2009). A model of hot flushes in ovariectomized rats that measured peripheral temperatures responded to both oestrogens and cimicifuga extract (Winterhoff et al., 2003). This suggests that conventional oestrogenic action is unlikely to be the explanation for the plant's beneficial effects on menopausal discomfort.

[237] luteinizing hormone - a hormone made in the brain that is important for the release of an egg from an ovary during the menstrual cycle and in making the hormones testosterone and oestrogen

[238] follicle-stimulating hormone - a hormone made by the pituitary gland (an organ at the base of the brain) that is used in reproduction and in making estrogen and sperm

[239] The changing of cells that line the internal and external surfaces of the body into an outer layer of flat cells that look like fish scales under a microscope). Also called keritinization

## Clinical data

In women treated for 8 weeks with the commercial product Remifemin and LH, but not FSH, levels were reduced. Remifemin is used for the management of menopausal hot flashes, with analysis identifying at least 3 fractions that contribute synergistically to the suppression of LH and bind to oestrogen receptors. These data suggest that black cohosh has a measurable effect on certain reproductive hormones. The product may offer an alternative to conventional HRT. In patient populations with a history of oestrogen-dependent cancers, Remifemin shows no stimulatory effects on established breast tumour cell lines dependent on oestrogen's presence (although it possesses some oestrogenic activity). Instead, inhibitory actions were seen. In addition, the product exerts no effect on the endometrium, so it is not necessary to oppose therapy with progesterone as with conventional HRT. The plant extract's action proves to be more like estriol than estradiol, which is associated with a higher risk of breast, ovarian, and endometrial cancers. Estriol exerts its effects mainly on the vaginal lining rather than on the uterine lining, as estradiol does (E. M. Düker et al., 1991b). Black cohosh was no more effective than placebo in reducing the intensity and number of menopausal hot flashes among breast cancer patients in a randomised, double-blind, placebo-controlled study. Of the 85 patients in the study, 42 were assigned to the treatment phase and 43 to placebo. Fifty-nine patients were using tamoxifen and 26 were not. Inclusion criteria included patients reporting menopausal symptoms, such as daily hot flashes, and completion of primary cancer therapy at least 2 months prior to entering the study. Exclusion criteria included using HRT for hot flashes, pregnancy, recurrent or metastatic breast cancer, or history of a major psychiatric illness. Patients were counseled to take one tablet by mouth twice daily with meals for 60 days. Before starting any study medication, each patient was asked to record the number of hot flashes, including their intensity. They were asked to do the same on days 27 to 30 and days 57 to 60 of the study. The average reported number of hot flashes declined for both groups; the overall decline from baseline to study completion was approximately 27%. The differences between treatment groups were not significant ( P = 0.86 via analysis of covariance adjusting for baseline number and for tamoxifen use; P = 0.44 via stratified Wilcoxon test in difference from baseline to completion). Other menopausal symptoms were analysed between the groups in a global rating of health and well-being on a 0 to 100 scale. These symptoms included headaches, poor sleep, heart palpitations, depression, irritability or nervousness, and excessive sweating. Overall, the global rating did not change significantly during the 2-month study (J. S. Jacobson, Troxel, and Evans, 2001). A clinical and endocrinologic study has been performed in 60 patients younger than 40 years of age who had hysterectomies. Four randomised treatment groups included estriol, conjugated oestrogens, oestrogen-gestagen sequential therapy, or black cohosh extract. Results showed no differences among groups in success of therapy (E. Lehmann-Willenbrock and Riedel, 1988).

A standardised preparation BNO 1055 (Klimadynon/Menofem, 40mg/day) was compared with conjugated oestrogens (0.6 mg/day) in a double-blind, placebo-controlled study and found a reduction in menopausal symptoms as well as the oestrogen levels; however, because each arm of the study was small (n = 20 to 22), the difference from placebo did not reach statistical significance (Wuttke, Seidlová-Wuttke, and C. Gorkow, 2003). Another study found that black cohosh had an effect on menopausal symptoms only in a subgroup of women with severe symptoms (kupperman index more than 20) (Frei-Kleiner et al., 2005).

A 12-week, randomised, placebo-controlled, double-blind study in the Netherlands found no effect on menopausal symptoms for a black cohosh and soy isoflavone combination (Verhoeven et al., 2005). A larger 5-arm study found no effect on menopausal vasomotor symptoms at 3, 6, and 12 months of treatment with black cohosh alone (160 mg daily) and in combination (Newton et al., 2006). A cross-over study of 20 mg black cohosh twice a day found no effect compared with placebo (Pockaj, Gallagher, and Loprinzi, 2006). A fixed combination of black cohosh and St. John's wort studied in women with menopausal complaints with a pronounced psychological component, on the other hand, found a highly significant reduction in symptom scores (Uebelhack et al., 2006).

The Herbal Alternatives for Menopause Study, in addition to examining primary end points, such as hot flash frequency (Newton et al., 2006), also studied vaginal cytology[240], dryness, menstrual cyclicity, and hormone profiles of the subjects; however, no effects were noted on vaginal epithelium, endometrium, or levels of reproductive hormones (Reed et al., 2008). A mechanistic study examined LH pulsatility and found a role for central opioid receptors in the actions of black cohosh. Naloxone treatment increased the frequency between LH pulses, especially at night (Reame et al., 2008). A study in Spain of overweight postmenopausal women given black cohosh evaluated quality of life measures, finding that menopause and health and psychic domains of the inventory were improved for the black cohosh group (Juliá Mollá et al., 2009). In a 12-month study from the United States, black cohosh failed to reduce vasomotor symptoms as effectively as placebo and did not improve other measures (Geller, Shulman, and Breemen, 2009).

Several systematic meta-analyses (Borrelli and Ernst, 2008b), (Palacio, Masri, and Mooradian, 2009), (Shams et al., 2010) have concluded that evidence is very weak for black cohosh effectiveness in ameliorating vasomotor symptoms in menopause. More recent trials have been conducted with standardised preparations and have been powered to detect important effects. These results concluded that black cohosh cannot be recommended for menopausal complaints.

[240]The study of cells using a microscope

Studied related uses include improvement of in-vitro fertilisation rates (Shahin, Ismail, and Shaaban, 2009) and osteoporosis (Bebenek et al., 2010). The latter use is supported by in-vitro studies on osteoblasts (Garcia-Pérez et al., 2009), (Chan et al., 2008) and in ovariectomized rats, where fracture healing was accelerated, albeit by less than those rats treated with oestrogens (Kolios, Schumann, and Sehmisch, 2010).

## Menopausal Symptoms

Studies confirm that black cohosh is effective for improving menopausal symptoms, although some have found no improvement. Early German studies found black cohosh improved physical and psychological menopausal symptoms, including anxiety, hot flashes, night sweats, and vaginal dryness.

In a study of 120 women with the menopausal symptoms, black cohosh was more effective in relieving hot flashes and night sweats than the antidepressant fluoxetine (Prozac).

Given the results of most clinical studies, many experts conclude that black cohosh may be a safe and effective alternative for women who cannot or will not take HRT for menopause. A 2010 review by researchers found that black cohosh provided a 26% reduction in hot flashes and night sweats (also known as vasomotor symptoms).

However, experts do not agree on the effectiveness and safety of using black cohosh to relieve symptoms of menopause. The American College of Obstetricians and Gynaecologists (ACOG) reports that many of the early studies were poorly designed and did not evaluate the safety and effectiveness of black cohosh beyond 6 months of use. A 2009 study reported that black cohosh did not relieve hot flashes any more than placebo did. Still, the ACOG recognizes the value of black cohosh for menopausal symptoms.

Until further studies are conducted, some doctors recommend only short-term (less than 6 months) use of this herb for the relief of hot flashes (unknown, 2014d).

## Premenstrual Syndrome

Some studies suggest black cohosh can help ease premenstrual syndrome and menstrual pain (unknown, 2014d).

## Hot Flashes Related to Breast Cancer Treatments

Breast cancer medications such as tamoxifen (Nolvadex) can cause hot flashes. While many breast cancer patients may take black cohosh to reduce the number and intensity of hot flashes, two well-designed studies concluded that the herb is no more effective than placebo. In addition, Yale researchers report that herbal medicines such as black cohosh may interfere with common breast cancer treatments, such as radiation and cancer therapy drugs.

There has been some concern that black cohosh may contain plant based oestrogens, or phytoestrogens, which can stimulate the growth of breast tumours. However, a case-control[241] clinical study of 949 breast cancer cases and 1,524 controls found that black cohosh use had significant protective effects against breast cancer development. More research is needed. Patients with a history of breast cancer, risk factors for breast cancer, or who are actively engaged in breast cancer treatment, should talk to their doctor before taking black cohosh (unknown, 2014d).

## Arthritis

Preliminary studies suggest that black cohosh may help reduce inflammation associated osteoarthritis and rheumatoid arthritis. In a review of scientific studies, researchers concluded that a combination of black cohosh, willow bark (Salix spp.), sarsaparilla (Smilax spp.), guaiacum (Guaiacum officinale) resin, and poplar bark (Populus tremuloides) may help relieve symptoms of osteoarthritis. However, there is not enough human research to support the use of black cohosh alone for arthritis (unknown, 2014d).

## Osteoporosis

Laboratory studies have found that plant-based oestrogens (called phytoestrogens) in black cohosh may inhibit bone loss, such as seen with osteoporosis. More research is needed (unknown, 2014d).

## Miscellaneous

Extracts of black cohosh inhibit the growth of prostate cancer cell lines (Jarry, Thelen, et al., 2005) and breast cancer cell lines (Einbond, Shimizu, and D. Xiao, 2004). Constituent actein has been shown to have a hypotensive effect in rabbits and cats and to cause peripheral vasodilation in

[241] A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition

dogs (Genazzani and Sorrentino, 1962). It has been identified as having anti-HIV activity (Sakurai, J. H. Wu, and Sashida, 2004), antimicrobial activity (Bukowiecki and Michalska, 1972), in-vivo hypocholesterolaemic activity, and therapeutic action in peripheral arterial disease by causing peripheral vasodilation and increasing blood flow (C. A. Newall, L. A. Anderson, and Phillipson, 1996a). In ovariectomized rats, black cohosh led to reduced weight gain and improved blood lipid profiles (Racho et al., 2008). Phenolic compounds from black cohosh have been identified with anti-inflammatory properties (Schmid, Gruber, and Woehs, 2009), (Schmid, Woehs, et al., 2009), (C. L. Yang et al., 2009).

## Claims

Black cohosh is said to be useful for menopausal symptoms (eg, hot flushes, mood lability, tachycardia, vaginal dryness), for menstrual symptoms, and for arthralgias in RA or osteoarthritis.

Scientific evidence regarding benefit in relieving menstrual symptoms is conflicting. There are few reliable data on its effectiveness for other disorders and symptoms (merck, 2009).

## Efficacy

- **Likely effective** for menopausal vasomotor symptoms,
- **Possibly effective** for PMS/dysmenorrhoea (medscape, 2015a).

## Contraindications

Breast cancer, endometrial cancer, endometriosis, hormone sensitive conditions, ovarian cancer, pregnancy, lactation, uterine fibroids (medscape, 2015a).

## Who should not take black cohosh?

- The use of black cohosh during pregnancy has not been rigorously studied. Thus, it would be prudent for pregnant women not to take black cohosh unless they do so under the supervision of their health care provider.
- Women with breast cancer may want to avoid black cohosh until its effects on breast tissue are understood.
- Individuals with liver disorders should avoid black cohosh.
- Individuals who develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice while taking the supplement should discontinue use and contact their doctor.

## Precautions

Some people who take high doses of black cohosh report side effects, including **abdominal pain**, **shortness of breath**, **diarrhoea**, **dizziness**, **headaches**, **joint pains**, **nausea**, **slow heart rate**, **tremors**, **visual dimness**, **vomiting**, and **weight gain**. You should not use black cohosh if you have a hormone-sensitive condition, such as breast cancer, endometriosis, ovarian cancer, uterine cancer, or fibroid tumours.

It is not clear whether black cohosh stimulates the growth of breast cancer cells or inhibits their growth. Research has been limited and has produced mixed results. Women with a history of breast cancer, and those at a high risk for developing breast cancer (for example, a strong family history like a mother or sister with breast cancer), should not take black cohosh without talking to a health care provider.

A few cases of liver toxicity have been reported, but a direct association with the ingestion of black cohosh has not been demonstrated. However, you should not use black cohosh if you have liver damage or drink alcohol in excessive quantities. Pregnant and breastfeeding women should avoid black cohosh as the herb may stimulate contractions and lead to premature labour. However, some homeopathic practitioners recommend the use of black cohosh to induce labour in pregnant women who are at or past term. Even then, pregnant women should never use black cohosh unless under the strict supervision of a knowledgeable physician (unknown, 2014d).

## Black cohosh products and liver toxicity: update

### Possible liver toxicity, a series of reports from Canada

- A previous issue of the Canadian Adverse Reaction Newsletter highlighted international reports of liver reactions suspected of being associated with the use of black cohosh products.
- In this update, 6 domestic reports of liver toxicity suspected of being associated with black cohosh are discussed.
- Analysis of some of the products identified in these reports revealed that they did not contain authentic black cohosh.

Black cohosh (Actaea racemosa, formerly Cimicifuga racemosa) is a herbal medicine used mainly to alleviate menopausal symptoms. In recent years, several international regulatory agencies have monitored a possible relationship between black cohosh and liver toxicity (T. Agency, 2006), (Administration, 2007), (E. M. Agency, 2006), (Mahady, Low Dog, and M. L. Barrett, 2008).

In 2005, an article in the Canadian Adverse Reaction Newsletter (Sheehy, Murty, and Pilon, 2005) was published to inform health care professionals of international reports of liver reactions suspected of being associated with the use of this natural health product. At the time of publication, Health

Canada had not received domestic reports of such reactions. To alert the public about this risk, Health Canada issued a public advisory (Canada, 2006) and a fact sheet (Canada, 2007), footnote 7, and required cautionary labelling on authorised black cohosh products.

From January 2005 to March 2009, Health Canada received 6 domestic reports of liver adverse reactions suspected of being associated with black cohosh. All 6 cases were reported as being serious, see the next table.

| Case | Age / Sex | Product / strength | Reactions ✚ | Outcome ✙ | Product analysis | Product status ✖ |
|---|---|---|---|---|---|---|
| 1 | Unknown / F | Swiss Herbal Natural HRT Extra Strength (not specified) | Ocular icterus | Unknown | Not authentic (sponsor analysis) | Voluntarily recalled |
| 2 | 47/F | Swiss Herbal Menopaus Natural HRT and Natural HRT Nighttime (not specified) | Autoimmune hepatitis, abnormal liver biopsy, elevated bilirubin, fatigue, jaundice | Not yet recovered | Not authentic (Health Canada analysis) | Voluntarily recalled |
| 3 | 56/F | Her Balance (not specified) | Upper abdominal pain, fatigue, increased hepatic enzymes | Not yet recovered | Unknown | Not authorized |
| 4 | 64F | Swiss Herbal Natural HRT Extra Strength (not specified) | Jaundice, upper abdominal pain | Recovered | Not authentic (sponsor analysis) | Voluntarily recalled |

| Case | Age / Sex | Product / strength | Reactions ✚ | Outcome ✙ | Product analysis | Product status ✖ |
|---|---|---|---|---|---|---|
| 5 | 51/F | Swiss Herbal Remedies Black Cohosh (100 mg) | Abdominal pain, increased liver enzymes, elevated bilirubin, jaundice | Recovered | Not authentic (Health Canada analysis) | Voluntarily recalled |
| 6 | 55/F | Black cohosh Health Balance (80 mg) | Lower abdominal pain, increased liver enzymes, increased bilirubin, fatigue, hepatic cirrhosis, chronic active hepatitis, jaundice | Recovered with sequelae | Unknown | Not authorized |

**Table 5.1** – ✠ Summary of reports of liver toxicity suspected of being associated with black cohosh that were received by Health Canada from Jan. 1, 2005 to Mar. 31, 2009

✠ - These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the health product was on the market has been taken into consideration.

✚ - Reaction terms are listed according to the *Medical Dictionary for Regulatory Activities* (MedDRA).

✙ - At the time of reporting.

✖ - *Voluntarily recalled* means that an analysis was conducted and the sponsor voluntarily recalled the product because it did not contain authentic black cohosh. *Not authorized* means that the suspected product was not authorised for sale by Health Canada, and data on herbal authenticity are not available. Natural health products authorised for sale in Canada have an 8-digit Natural Product Number (NPN) or a Homeopathic Medicine Number (DIN-HM) on the label. These numbers indicate that the

products have been assessed by Health Canada's Natural Health Products Directorate for safety, effectiveness and quality. Authorised natural health products are listed in Health Canada's searchable Licensed Natural Health Products Database.

Analysis by Health Canada laboratories of 3 products (one patient was taking 2 Swiss Herbal products) suspected in 2 adverse reactions identified in the reports revealed that these products did not contain authentic black cohosh. Their phytochemical profiles were consistent with the presence of other related herbal species. Although research has shown problems with the herbal identity of some products marketed in the United States as black cohosh (B. Jiang, Kronenberg, and Nuntanakorn, 2006), these domestic cases demonstrate that products not containing authentic black cohosh may be associated with liver adverse reactions (S. Jordan, Murty, and Perwaiz, 2008), and (Betz, L. Anderson, and Avigan, 2009).

A recent review of the herbal authenticity of all licensed products containing black cohosh in Canada was conducted; updated methods required for unequivocal identity testing were used (Canada, 2009). This review resulted in the voluntary withdrawal of several products that did not contain authentic black cohosh from the market, including products reported in 4 of the cases in the previous table (Painter, Perwaiz, and Murty, 2010).

## Adverse Reactions

In a review article on the safety of the herb, uncontrolled reports, postmarketing surveillance, and human clinical trials of more than 2,800 patients demonstrate a low incidence of adverse reactions (Low Dog, K. L. Powell, and Weisman, 2003).

Side effects with black cohosh are generally mild and rare. They include **stomach upsets** and **nausea**. Other side effects that have been noted are **low blood pressure**, **headache**, **dizziness** and **allergic reactions**.

Some black cohosh products have been associated with serious liver conditions but this has not been confirmed and is most likely to be due to low quality products.

There are no known interactions between this herb and conventional medicine although it is suggested not to take it with high blood pressure medication. Pregnant and breast-feeding women should not take this herb (Resource, 2015c).

Adverse effects are uncommon. The most likely are **headache** and gastrointestinal distress. **Dizziness**, **diaphoresis**, and **hypotension** (if high doses are taken) may occur (merck, 2009).

## Side Effects and Cautions

- United States Pharmacopeia experts suggest women should discontinue use of black cohosh and consult a health care practitioner if they have a liver disorder or develop symptoms of liver trouble, such as **abdominal pain, dark urine**, or **jaundice**. There have been several case reports of hepatitis, as well as liver failure, in women who were taking black cohosh. It is not known if black cohosh was responsible for these problems. Although these cases are very rare and the evidence is not definitive, scientists are concerned about the possible effects of black cohosh on the liver. Some people taking black cohosh have experienced side effects such as stomach discomfort, headache, or rash. In general, clinical trials of black cohosh for menopausal symptoms have not found serious side effects.
- Although concerns have been raised about possible interactions between black cohosh and various medications, a 2008 review of studies to date concluded that the risk of such interactions appears to be small.
- It is not clear if black cohosh is safe for women who have had hormone-sensitive conditions such as breast cancer or for pregnant women or nursing mothers.
- Black cohosh should not be confused with blue cohosh[242] (Caulophyllum thalictroides), which has different properties, treatment uses, and side effects than black cohosh. Black cohosh is sometimes used with blue cohosh to stimulate labour, but this therapy has caused adverse effects in newborns, which appear to be due to blue cohosh.
- Tell all your health care providers about any complementary health practices you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care (NCCIH, 2012d).

Side effects are rare with small to moderate amounts of black cohosh. Most studies have used black cohosh for less than 6 months and so the long term effects are not known.

The most common side effects are **stomach pain**, **feeling nauseous**, or actually **vomiting**, or **skin rashes**.

But very high doses (above 100mg) can cause -

- **A slowing of your heart rate**
- **Lowering of blood pressure**
- **Headaches**
- **Dizziness and light headedness**
- **Uterine contractions**

[242] A plant that has been used to treat menstrual disorders and to start labour. It may be unsafe and should not be confused with black cohosh. Latin name: *Caullophylum thalictroides*

- **Joint pain**

## Pregnancy/Lactation

Black cohosh should be used with caution in pregnancy (Dugoua et al., 2006). Large doses may cause premature birth (I. N. Dobelis, 1986), (C. A. Newall, L. A. Anderson, and Phillipson, 1996a).

## Can black cohosh be harmful?

Black cohosh can cause stomach discomfort and headaches (Kruse et al., 1999). Clinical trials comparing oestrogens with black cohosh preparations have shown a low incidence of adverse effects associated with black cohosh; headaches, gastric complaints, heaviness in the legs, and weight problems were the main adverse effects noted (Gruenwald, 1998).

A published case of acute[243] hepatitis involved a 47-year-old woman who used black cohosh for symptoms of menopause (Saiad and Borysov, 1979). She received a liver transplant three weeks after she started taking the herb. The report indicated the dose of black cohosh did not exceed the dosage recommended on the package; but no other dosage information was provided. No other cause for liver disease was found.

Black cohosh usually has not been used for long periods, and published studies have followed women for only 6 months or less. Recently, a large study that followed postmenopausal women taking combined oestrogen and progestin for an average of 5.2 years showed a small but significant increase in the risk of certain diseases, demonstrating the importance of long-term studies in revealing risks that may not be apparent in shorter studies (JAMA, 2002). If black cohosh is oestrogenic, long-term use may adversely affect uterine or breast tissue. No studies have been published on long-term safety in humans, particularly regarding abnormal stimulation of cells in the endometrium or breast.

There is a case report of neurological complications in a postterm baby after labour induction with a mixture of black cohosh and blue cohosh during a home birth (T. R. Gunn and I. M. Wright, 1996).

Other cases of adverse outcomes experienced by neonates born to women who reportedly used blue cohosh to induce labour have been published in peer-reviewed journals[244] (Finkle and Zarlengo, 2004), (T. K. Jones and B. M. Lawson, 1998).

[243] Sudden, severe, and not long lasting

[244] A scholarly or scientific publication in which an article is reviewed by a board of experts before it is published. The board members determine the accuracy of the article and approve or reject it

Liver damage has been reported in a few individuals using black cohosh, but millions of people have taken the herb without apparent adverse health effects (unknown, n.d.[b]). While studies of black cohosh have not provided scientific evidence to show that the herb causes liver damage, one country has added a warning to the label of all products containing black cohosh, stating that it may cause harm to the liver of some individuals and should not be used without medical supervision (unknown, n.d.[a]).

In the United States, the U.S. Pharmacopeia (the standards-setting organization for foods and drugs) advises that black cohosh products be labeled with the following cautionary statement -

> "Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice" (Mahady, Low- Dog, and M. L. Barrett, 2008).

## Interactions

Black cohosh may potentiate the effects of antihypertensive medications in rabbits, but not in dogs or humans (Pepping, 1999). Black cohosh constituents inhibit 4 cytochrome P450 enzymes (Y. Huang, B. Jiang, and Nuntanakorn, 2010), which may cause herb-drug interactions.

There are no known scientific reports of interactions between black cohosh and conventional medications. There is some concern about taking black cohosh along with medications that are toxic to the liver, based on the concern that black cohosh could potentially be harmful to the liver. See Precautions. Taking black cohosh can interact with other medicines, vitamins, and certain foods. Talk to your health care provider about possible interactions. Yale researchers also report that herbal medicines such as black cohosh may interfere with common breast cancer treatments, such as radiation and cancer therapy drugs (unknown, 2014d).

There is no evidence that black cohosh interferes with any drugs. Theoretically, black cohosh is contraindicated in patients with aspirin sensitivity, liver disease, hormone-sensitive cancers (eg, certain kinds of breast cancer), stroke, or high BP. The US Pharmacopeia (USP) has recommended that black cohosh products be labeled with a warning declaring that they may be hepatotoxic (merck, 2009).

## Does black cohosh interact with any drugs or laboratory tests?

Although black cohosh has not been reported to interact with any drugs or to influence laboratory tests, this has not been rigorously studied (ODS, 2008).

## What the Science Says

- Study results are mixed on whether black cohosh effectively relieves menopausal symptoms. An NCCAM-funded study found that black cohosh, whether used alone or with other botanicals, failed to relieve hot flashes and night sweats in postmenopausal women or those approaching menopause.
- Most studies to date have been less than 6 months long, so the safety of long-term use is uncertain.
- NCCAM is funding studies to further understand the potential effects of black cohosh on hot flashes and other menopausal symptoms.
- There are not enough reliable data to determine whether black cohosh is effective for rheumatism or other uses.

## What clinical studies have been done on black cohosh and its effect on menopausal symptoms?

Black cohosh is used primarily for hot flashes and other menopausal symptoms. A number of studies using various designs have been conducted to determine whether black cohosh affects menopausal symptoms (Saiad and Borysov, 1978). Few were placebo-controlled studies, and most assessed symptoms by using the kupperman index, a scale that combines measures of hot flashes, insomnia, and depression but not vaginal dryness. Those with the best study designs are described below.

A randomised, double-blind, placebo-controlled trial was done in breast cancer survivors because most of these women experience hot flashes and many use complementary or alternative remedies[245] (M. H. Chen, 1985). The women were over age 18 and had completed breast cancer treatment at least 2 months before the trial; 85 women (69 of whom completed the trial) took one tablet of placebo or 40 mg/day of black cohosh (as 20 mg twice daily) for 2 months to determine the effect on hot flashes, excessive sweating, palpitations, headaches, poor sleep, depression, and irritability [J.S. Jacobson, Columbia University, written communication, 2002]. Fifty-nine subjects were using tamoxifen (an antioestrogen treatment for breast cancer); tamoxifen users were distributed almost equally between the treatment and control groups[246]. The frequency and intensity of hot flashes decreased in both groups, with no statistical difference[247] between the

[245] A group of diverse medical and health care systems, practices, and products that are used in place of conventional medicine

[246] In a research study or clinical trial, the group that does not receive the new treatment being studied. This group is compared with the group that receives the new treatment, to see whether the new treatment works

[247] A mathematical measure of variation between groups that is greater than what might be expected to happen by chance alone

groups; excessive sweating decreased significantly more in the treatment group than the placebo group. Other symptoms improved equally in both groups, and scores on a health and well-being scale did not change significantly in either group.

A 24-week study in 60 women who had undergone hysterectomy but retained at least one ovary compared the effects of 8 mg/day of a black cohosh extract (as four 2-mg tablets daily; isopropanol extract version of Remifemin) with three oestrogen regimens: estriol (1 mg/day), conjugated oestrogens (1.25 mg/day), and oestrogen-progestin therapy (one daily Trisequens tablet containing 2 mg estradiol and 1 mg norethisterone acetate) (Stoll, 1987). In all groups a modified kupperman index measuring additional physical symptoms was significantly lower at 4, 8, 12, and 24 weeks after treatment began. Black cohosh decreased symptoms similarly to the other treatments, but this study was not placebo-controlled.

A randomised, double-blind, placebo-controlled trial in 80 menopausal women compared 8 mg/day of a black cohosh extract (as two 2-mg tablets of Remifemin twice daily) with placebo or conjugated oestrogens (0.625 mg/day) (Kurihara and Kiruchi, 1976). At 12 weeks, scores on the kupperman index and the hamilton anxiety scale were significantly lower in the treated groups than in the placebo group; the scores of participants using black cohosh were somewhat better than the scores of those receiving the oestrogen treatment. This is one of the few studies in which hot flashes were scored separately from other symptoms. Daily hot flashes decreased from 4.9 to 0.7 in the black cohosh group, 5.2 to 3.2 in the oestrogen group, and 5.1 to 3.1 in the placebo group.

A randomised, 12-week study of 55 menopausal women compared an ethanolic extract of black cohosh (40 drops twice daily) with conjugated oestrogens (0.6 mg/day) or diazepam (2 mg/day) (ACOG, 2001). Regardless of the treatment, all symptoms improved as measured by the kupperman index, a depression scale, and an anxiety scale. However, this was not a blinded, placebo-controlled trial and diazepam is not a usual treatment for menopausal symptoms.

Although some study results suggest that black cohosh may help relieve menopausal symptoms, other study results do not. Studies of black cohosh have yielded conflicting data, in part because of lack of rigor in study design and short study duration (6 months or less). In addition, interpretation of these studies is complicated by the fact that different amounts of black cohosh from different sources were used in the various studies and their outcome measures were different. To provide more definitive evidence on the effects of black cohosh on menopausal symptoms, NCCAM is funding a 12-month, randomised, placebo-controlled study to determine whether treatment with black cohosh is effective in reducing the frequency and intensity of menopausal hot flashes. The study will also assess whether black cohosh reduces the frequency of other menopausal symptoms and improves quality of life. The study will examine the possible mechanisms of action of black cohosh.

## How does black cohosh work?

How black cohosh works is not known. The possibility that black cohosh exhibits oestrogenic activity has been studied but the evidence is contradictory (Kruse et al., 1999), (E. M. Düker et al., 1991a), (J. Liu, Burdette, and H. Xu, 2001a), (Zava, Dollbaum, and Blen, 1998), (Dixon-Shanies and Shaikh, 1999), (Nesselhut et al., 1993), (Z. Liu et al., 2001) , (Einer-Jensen, J. Zhao, K. P. Anderson, et al., 1996), (Freudenstein, Dasenbrock, and Nisslein, 2002).

A compound[248] recently identified in black cohosh (fukinolic acid) was shown to have oestrogenic activity in-vitro (Kruse et al., 1999). Other active compounds appear to include triterpene glycosides (including actein and cimicifugoside), resins (including cimicifugin), and caffeic and isoferulic acids (S. Mills and Bone, 2000).

### Effect on hormone levels

Women who have reached menopause generally have lower levels of oestrogen and higher levels of two other hormones, LH and FSH, than do women who menstruate. Three of four studies show that black cohosh does not affect LH or FSH.

A study of 150 perimenopausal[249] women using two different doses of black cohosh (Remifemin tablets, 39 or 127.3 mg/day) found that 6 months of treatment caused no changes in LH, FSH, prolactin, estradiol, or sex-hormone-binding globulin[250] (Liske, Hanggi, and Henneicke-von Zepelin, 2002). Another trial of black cohosh in women with breast cancer found small but insignificant changes in LH levels (in 18 subjects) and FSH levels (in 33 subjects) (E Lehmann-Willenbrock and Riedel, 1988). In the third study, Remifemin (8 mg/day given as four 2-mg tablets) did not affect LH or FSH levels in 15 women who had undergone a hysterectomy who were part of a study comparing black cohosh with several oestrogens (Stoll, 1987).

The fourth study, which found an effect of black cohosh on LH levels, was a trial in 110 women with menopausal symptoms. Participants treated with Remifemin (8 mg/day) for 8 weeks had significantly lower average LH levels than did a control group (FSH levels were unchanged) (E. M. Düker et al., 1991a). However, the report of this study does not include the participants' hormone levels before the study began, so the two groups may have had different LH levels initially.

[248] in pharmacy, a substance that contains more than one ingredient

[249] referring to a period of a woman's life, age 45 to 55-ish, in which menstrual periods become irregular; perimenopause is immediately before, during and after menopause

[250] A protein made by the liver that carries a male hormone (testosterone) and a female hormone (estradiol, a form of oestrogen) through the blood to body tissues. Oestrogen causes levels of SHBG to increase; testosterone causes levels of SHBG to decrease

In-vitro studies used to examine the effect of black cohosh have given contradictory results. Black cohosh had no activity in oestrogen receptor (ER) binding assays[251] in Ishikawa (endometrial) and S30 (breast cancer) cell lines (J. Liu, Burdette, and H. Xu, 2001a). It did not show potent ER binding activity; slightly enhanced the growth of ER-positive[252] breast cancer cells[253] (T47D) but was not tested on ER-negative[254] cells (Zava, Dollbaum, and Blen, 1998). In another study black cohosh inhibited the growth of T47D (human breast cancer) cells (Dixon-Shanies and Shaikh, 1999). In ER-positive breast cancer cell line 435, black cohosh resulted in growth inhibition (Nesselhut et al., 1993). In ER-positive breast cancer cell line MCF-7, it inhibited estradiol-induced stimulation of cell proliferation in one study (Zierau et al., 2002) but isolated constituents of black cohosh increased proliferation in another (Kruse et al., 1999).

## Effect on the vagina

Because of the marked changes in hormone levels in women who have achieved menopause, numerous modifications occur in the structure and activity of vaginal and uterine tissues. Microscopically, vaginal cells look different after menopause because of decreased oestrogen. Studies have been mixed on whether black cohosh affects vaginal epithelium. One placebo-controlled, double-blind trial of black cohosh showed oestrogenic changes in vaginal epithelium of menopausal women (Warnecke, 1985), but another study of two Remifemin doses (39 or 127.3 mg/day) found that 6 months of treatment in perimenopausal and menopausal women caused no changes in vaginal cytology (Liske, Hanggi, and Henneicke-von Zepelin, 2002).

[251] A laboratory test to determine the presence of a protein found on cells of female reproductive tissue, some other tissues in the body, and some cancer cells. The hormone estrogen will attach (bind) to the receptors inside the cells and may cause the cells to grow

[252] Oestrogen receptor positive (ER+). Having to do with breast cancer cells that have a protein (a receptor molecule) to which oestrogen will attach. Breast cancer cells that are ER+ need the hormone oestrogen to grow and will usually respond to hormone (antioestrogen) therapy that blocks these receptor sites

[253] The individual unit that makes up the tissues of the body. All living things are made up of one or more cells, which are the smallest units of living structure capable of independent existence

[254] Oestrogen receptor negative (ER-). Having to do with breast cancer cells that do not have a protein (a receptor molecule) to which oestrogen will attach. Breast cancer cells that are ER- do not need the hormone oestrogen to grow and usually do not respond to hormone (antioestrogen) therapy that blocks these receptor sites

## Effect on the uterus

Menopause is associated with a thinning of the uterine lining (the endometrium). No human studies have adequately evaluated the effect of black cohosh on uterine endometrium.

When uterine weight of immature female mice and growth of ER-positive breast cancer cells (MCF-7) were used to measure the oestrogenic effect of black cohosh, black cohosh caused an increase in uterine weight and growth of cancer cells in culture, which the authors said reflected an oestrogenic effect (Z. Liu et al., 2001). Black cohosh did not exhibit oestrogenic effects in a study that measured uterine weight in immature mice and vaginal cell cornification (conversion of cells from columnar[255] to squamous[256]) in ovariectomized rats (Einer-Jensen, J. Zhao, K. P. Anderson, et al., 1996).

# What is the regulatory status of black cohosh in the United States?

In the United States, black cohosh is sold as a dietary supplement, and dietary supplements are regulated[257] as foods, not drugs. Manufacturers do not have to provide the Food and Drug Administration (FDA) with evidence that dietary supplements are effective or safe before marketing. Because dietary supplements are not always tested for manufacturing consistency, the composition may vary considerably from lot to lot.

# Key points

- Black cohosh is an herb sold as a dietary supplement in the United States.
- Black cohosh is used for hot flashes and other menopausal symptoms.
- Although preliminary evidence[258] is encouraging, the currently available data are not sufficient to support a recommendation on the use of black cohosh for menopausal symptoms. The National Center for Complementary and Alternative Medicine (NCCAM) at

[255] A type of cell that lines the internal and external surfaces of the body

[256] A type of cell that covers the inside and outside surfaces of the body. Squamous cells are flat cells that look like fish scales under a microscope. They are found in tissues that form the surface of the skin, the lining of hollow organs (such as the uterus), and passages of the respiratory tract (nose, throat, windpipe, and lungs) and digestive tract (mouth, esophagus, and rectum)

[257] To govern, make uniform, and bring under the control of a rule, principle, or legal system. In the United States, the FDA has the authority to regulate dietary supplements

[258] Information used to support the use of a particular screening procedure, treatment, or preventive measure. In medicine, evidence needed to determine effectiveness is provided by laboratory research, clinical trials, and other studies

the National Institutes of Health is funding a rigorous scientific study[259] to determine whether treatment with black cohosh reduces the frequency and intensity of hot flashes, and other menopausal symptoms.

- In 2001, the American College of Obstetricians and Gynaecologists stated, primarily on the basis of consensus and expert opinion[260], that black cohosh may be helpful in the short term (6 months or less) for women with vasomotor symptoms of menopause (S. N. Chen, W. Li, et al., 2001).
- Although few adverse events have been reported, long-term safety data[261] is not available.

## What are common black cohosh preparations?

Preparations of black cohosh are made from its roots and rhizomes. One commercial standardised black cohosh preparation is Remifemin, which contains black cohosh extract equivalent to 20mg of root per tablet. The manufacturer changed the formulation of this preparation from a solution (root extracted with ethanol, 60% by volume) to tablets (root extracted with isopropyl alcohol[262], 40% by volume), complicating the comparison of research results. Other preparations of black cohosh have been less well studied than Remifemin.

Extracts of black cohosh are standardised to 26-deoxyactein content (erroneously reported in the scientific literature as 27-deoxyactein (J. Duke, 2001)), a member of a group of chemicals known as saponins. Commercially available preparations of black cohosh usually contain 1mg of total triterpene saponins (expressed as 26-deoxyactein) in each 20mg dose of extract (nih, 2008).

Black cohosh is available in capsules, tablets, liquid tincture, and extracts that can be mixed in water, and dried root for a tea. A standardised preparation of black cohosh is recommended for use in menopause (unknown, 2014d).

Black cohosh should not be confused with blue cohosh, a nicotine-like herb that has similar effects but has not been thoroughly tested for its safety and effectiveness (unknown, 2014d).

---

[259] A method of gaining knowledge by making observations, proposing educated guesses (hypotheses) to explain the observations, and testing the hypotheses in ways that have reproducible results

[260] In medicine, the judgment of a respected healthcare professional, based on clinical experience or reports of expert committees. Expert opinions are important when results of controlled clinical trials and other scientific studies are not available to provide health care recommendations

[261] Information about unwanted symptoms or diseases related to the use of drugs, medical devices, dietary supplements, food, and cosmetics

[262] a substance used to kill germs and as a solvent. Also called isopropanol and rubbing alcohol

## Dosage

On the basis of clinical studies, to manage symptoms of menopause, the current recommended dose of black cohosh is a 40% to 60% ethanol or isopropanol extract in a daily dose of 40 to 80 mg standardised to contain 1 mg of the triterpene 27-deoxyactein per 20 mg tablet. Therapeutic effects generally begin after 2 weeks, with maximum effects usually within 8 weeks (Low Dog, K. L. Powell, and Weisman, 2003), (Pepping, 1999).

- **Dried root** - 300–2000 mg orally, three times a day,
- **Extract** - 0.3–2 ml orally daily; 1:1, 90% alcohol,
- **Tincture** - 2–4 ml orally daily; 1:10, 60% alcohol,
- **Tablet** - 20–80 mg orally, twice a day; standardised to 1 mg triterpene glycosides/20 mg tablet (medscape, 2015a).

### Paediatric

There are no known scientific reports on the paediatric use of black cohosh, and it is not currently recommended for children (unknown, 2014d).

### Adult

The recommended dose of black cohosh ranges from 20 to 80mg per day. The tablets should be standardised to contain 1 mg of 27-deoxyactein.

For black cohosh tincture, that equals 2 to 4 ml, 1 to 3 times per day in water or tea. Two capsules or tablets typically provide the recommended daily dose.

Although used traditionally, teas may not be as effective in relieving menopausal symptoms as the standardised extract of black cohosh. To make a black cohosh drink, put 20 g of dried root in 34 oz of water. Bring to a boil and then simmer 20 to 30 minutes until the liquid is reduced by a third. Strain, cover, and store in the refrigerator or a cool, dry place. The liquid keeps for up to 48 hours. Drink one cup 3 times daily (unknown, 2014d).

## Toxicology

Overdose of black cohosh may cause **nausea**, **vomiting**, **dizziness**, **nervous system and visual disturbances**, **reduced pulse rate**, and **increased perspiration**.

The constituent actein does not possess toxicity in animal studies (C. A. Newall, L. A. Anderson, and Phillipson, 1996b), (A. Huntley and Ernst, 2003b). The current major concern is hepatotoxicity. Numerous case reports of liver damage have been published (Whiting, Clouston, and Kerlin, 2002), (G. Guzman, Kallwitz, and Wojewoda, 2009), (Naser and Liske, 2009),

(Pierard, Coche, and Lanthier, 2009), (D. Joy, J. Joy, and Duane, 2008), (Lontos et al., 2003); however, prospective clinical studies of liver function in women taking black cohosh have failed to find negative effects on liver function (Nasr and Nafeh, 2009). Studies in rats have also failed to detect liver damage (Mazzanti, Di Sotto, and Franchitto, 2008). Critical analyses have generally failed to support a direct negative effect of black cohosh on the liver, (Borrelli and Ernst, 2008a), (Teschke and Schwarzenboeck, 2009), (Teschke, Bahre, et al., 2009), (Teschke, 2010) although a US Pharmacopeia panel recommended a cautionary label statement (Mahady, Low Dog, and M. L. Barrett, 2008). It has been suggested that the cases of hepatotoxicity may be due to black cohosh constituent-drug interactions (Y. Huang, B. Jiang, and Nuntanakorn, 2010). In addition to hepatotoxicity, cardiovascular and circulatory disorders and one case of convulsions have been documented (A. Huntley and Ernst, 2003b). A case report describes a 45-year-old woman who experienced seizures possibly related to consumption of an herbal preparation containing black cohosh (Shuster, 1996). Another case study[263] associated black cohosh use with coagulation activation and fluid retention (Zimmermann et al., 2010). A study in a mouse model of breast cancer found no effect of black cohosh on incidence or onset of cancer, but it did find an increase in frequency of lung metastases in the same mice (Davis, Jayo, and A. Ho, 2008).

### Commentary

*It can be used for breast enlargement, however it binds weakly with oestrogen receptors for a short time, but there is a lack of any oestrogen-like effect in human pharmacological studies (Liske and Wüstenberg, 1999), (Liske and Wüstenberg, 1998). It seems to be most effective in the treatment of hot flushes, and other menopausal symptoms, so it would appear to be ineffective for male-to-female transpeople, except perhaps as a placebo! However it could be very useful for female-to-male transpeople who may experience menopausal-like symptoms as their oestrogen levels drop during their pharmacological transition.*

## Borage

### Common names

Borage, burrage, common bugloss, bee-bread, bee fodder, ox's tongue, cool tankard, bee plant, borraja, bourrache, Bourrache Commune, Burage, Common Borage, Feuille de Bourrache, Fleur de Bourrache, Huile de Bourrache, Huile de Graines de Bourrache, Langue de Buf, Pain-des-

[263] involves an up-close, in-depth, and detailed examination of a subject (the case), as well as its related contextual conditions

Abeilles, Talewort, Starflower, German = Borretsch, German = Gurkenkraut, Italian = boragine, Italian = borandella, Russian = ogurecnik, Spanish = borraja, Swedish = gurkort, Brazilian = borragem, Danish = Hjulkrone, French = Bourrache.

## Latin name

*Borago officinalis*

## Overview

Borage is a plant. Its flowers and leaves, as well as the oil from its seeds are used as medicine.

Borage seed oil is used for skin disorders including eczema, seborrheic dermatitis, and neurodermatitis. It is also used for rheumatoid arthritis (RA), stress, PMS, diabetes, attention deficit-hyperactivity disorder (ADHD), acute respiratory distress syndrome (ARDS), alcoholism, pain and swelling (inflammation), and for preventing heart disease and stroke.

Borage flower and leaves are used for fever, cough, and depression.

Borage is also used for a hormone problem called adrenal insufficiency, for "blood purification", to increase urine flow, to prevent inflammation of the lungs, as a sedative, and to promote sweating. Borage is also used to increase breast milk production and to treat bronchitis and colds.

Borage is applied to the skin for infantile seborrheic dermatitis and is also used in a dressing to soften the skin.

In foods, borage is eaten in salads and soups.

In manufacturing, borage is used in skin care products (WMD, 2009a).

## Botany

Borage is an annual that grows to about 0.6 m in height. The stem and leaves are covered with coarse, prickly hairs, and the flowers are large, star-shaped, and bright blue with contrasting black anthers. It is a native of Europe but has been widely naturalized in other areas. The fresh plant has a salty flavour and a cucumber-like odour.

Borago officinalis is an annual plant of the Boraginaceae family (the borage or forget-me-not family). The plant is covered with stiff coarse hairs, and it can grow up to 70 cm high or 28 inches. The stem is erect with oval or lanceolate leaves that are rough and wrinkled.

The large star-shaped flowers are in sparse clusters. They have five petals that are purple at first but then soon turn blue. The flowering period is from July to August. The flowers produce a lot of nectar which makes them very attractive to bees.

The plant usually produces four seeds from each flower. The borage seeds contain around 30% oil that's used commercially. Unfortunately, the seeds ripen over a long period of time and fall to the ground when they are mature, which makes it difficult to harvest them in large quantities (Resource, 2015d).

## History

Borage leaves have been used as a potherb and in European herbal medicine since the Middle Ages, and are mentioned by Pliny (AD 61), Dioscorides (AD 40), and Galen (AD 129). Borage leaves and flowers were added to wine and lemon juice to make the popular beverages of claret cup and cool tankard. Borage leaves have been used to treat rheumatism, colds, and bronchitis, and to increase lactation in women. Infusions of the leaves were used to induce sweating and diuresis (Awang, 1990).

## Plant Parts Used

The leaves, flowers and the oil extracted from the seeds are used in herbal medicine. The leaves and flowers are usually used fresh. The dried herb must not be stored for more than a year since it quickly loses its medicinal effect (Resource, 2015d).

## Chemistry

The leaves and flowers contain mucilage, tannin, and a small amount of essential oil. The seed yields a fixed oil with a high content (20% to 26%) of gamma-linolenic acid (GLA), about twice the content of evening primrose oil, another commercial source (Gibson, Lines, and Neumann, 1992). The triacylglycerol structure of borage oil has been compared with evening primrose oil and other GLA sources, with GLA attached at position sn-3 in evening primrose oil but sn-2 in borage seed oil (L. D. Lawson and B. G. Hughes, 1988), (Ziboh, Naguwa, and Vang, 2004).

This difference explains the apparently poorer bioavailability[264] of GLA from borage seed oil compared with evening primrose oil (Fan, Chapkin, and Ramos, 1996). Numerous methods for analysis of GLA and other polyunsaturated fatty acids (PUFA) from borage seed oil and leaves have been published (L. D. Lawson and B. G. Hughes, 1988), (Wretensjö and Svensson, 1990), (Sewón and Tyystjärvi, 1993), (Laakso and Voutilainen, 1996).

Because of the occurrence of toxic pyrrolizidine alkaloids in other members of the Boraginaceae family, borage leaves, seeds, and seed oil have been carefully investigated for their alkaloid content. The unsaturated, potentially toxic alkaloids lycopsamine and amabiline are found in borage leaves, stems, and roots in relatively low concentration (Larson, Roby, and Stermitz, 1984). The seeds and flowers contain the saturated pyrrolizidine alkaloid thesinine, along with a trace of amabiline, supinine, and other alkaloids. Total alkaloid content of the plant is estimated as less than 0.001%, while mature seeds yield about 0.03% crude alkaloids (M. Herrmann, Joppe, and Schmaus, 2002), (Dodson and Stermitz, 1986). More sensitive trace analyses are required to measure the safety of borage seed oils. Antioxidant activity of borage has been attributed to rosmarinic acid found in the plant leaves. (Bandoniene and Murkovic, 2002).

Borage contains mucous substances, tannins, saponins, resins, essential oil, potassium, calcium, vitamin C and other substances. The borage leaves contain small amounts of pyrrolizidine alkaloids found to be toxic to the liver. However, the levels of those toxic alkaloids are extremely low.

The oil from the seeds is rich in GLA, an omega-6 fatty acid. Amount of GLA in the oil ranges from 20%–27%. The oil also contains about 10% alpha-linolenic acid (ALA), an omega-3 fatty acid (Resource, 2015d).

## Uses and Pharmacology

The 18-carbon fatty acid linoleic acid is considered essential in human nutrition because it must be obtained from the diet. It is converted by the enzyme delta-6-desaturase to GLA, which is considered rate-limiting in the pathway. GLA is further elaborated to the 20-carbon fatty acid dihomogamma-linolenic acid (DGLA), a key metabolite for the synthesis of the anti-inflammatory prostaglandins of the 1-series (eg, PGE1) and 15-(S) -hydroxy-8,11,13-eicosatrienoic acid (15HETrE) by different types of cells (Fan and Chapkin, 1998). Theoretically, supplementation with GLA might bypass the rate-limiting step in biosynthesis, providing more of these anti-inflammatory modulators. In addition, pathophysiological conditions

[264] the fraction of a dose of drug that is absorbed from its site of administration and reaches, in an unchanged form, the systemic circulation. This will differ when using a different route of administration

alter the ability to convert linoleic acid to GLA (Fan and Chapkin, 1998). Commercial sources of GLA include borage seed oil, evening primrose oil, and black currant seed oil, as well as the oil from the fungus Mucor javanicus (L. D. Lawson and B. G. Hughes, 1988).

Cloning of delta-6-desaturase enzymes into plants that do not typically possess them has been proposed as a means to increase dietary GLA (Palombo, DeMichele, J. W. Liu, et al., 2000).

## Animal data

Extensive research has demonstrated that dietary supplementation with GLA can alter lipid fatty acid profiles in experimental animals. GLA itself is not always elevated; however, DGLA can be highly elevated by GLA supplementation. Macrophage phospholipids of mice showed altered ratios of 20-carbon PUFA when they were fed borage seed oil (Chapkin, Somers, Schumacher, et al., 1988). DGLA was selectively increased in the same system (Chapkin, Somers, and Erickson, 1988). The particular phospholipid classes altered by GLA supplementation were examined in mice (Chapkin and S. L. Carmichael, 1990). GLA and DGLA in cutaneous phospholipids were markedly increased in guinea pigs after an 8-week feeding experiment, as well as the metabolites PGE 1 and 15HETrE (C. C. Miller and Ziboh, 1988), (C. C. Miller, Ziboh, et al., 1990), (C. C. Miller, W. Tang, et al., 1991). Borage seed oil and evening primrose oil were equivalent sources of GLA in rats despite the higher GLA content in borage oil (Raederstorff and Moser, 1992). Upon stimulation with zymosan, isolated mouse peritoneal macrophages increased PGE1 synthesis when the mice had been maintained on high GLA diets (Fan and Chapkin, 1992). Similar changes in hepatocyte PUFA were seen in Atlantic salmon smolts fed diets enriched with borage seed oil (Tocher et al., 1997). Analysis of the interaction of cholesterol metabolism with PUFA metabolism in rats showed that GLA had a smaller hypercholesterolemic effect than alpha-linolenic acid (Ihara-Watanabe et al., 1999). The effects of GLA supplementation in rats administered PUFA were different in immune tissues compared with other tissues (Kaku, Yunoki, and Ohkura, 2001). Other effects of GLA supplementation in animal models include an increase in Mn-superoxide dismutase in rats (Phylactos, Harbige, and Crawford, 1994), decrease in rat liver fatty acid oxidation[265], (Kumamoto and Ide, 1998) changes in mouse macrophage-vascular smooth muscle cell interactions, and inhibition of serum cholesterol in aged rats on high cholesterol diets (Fukushima, Ohhashi, and Ohno, 2001).

Changes in these mediators of inflammation might be expected to have an impact on a variety of diseases and conditions. Animal model experiments have been reported for some of them. Borage seed oil protected mice from experimental autoimmune encephalomyelitis, with improved clinical, biochemical, and histological parameters (Harbige et al., 2000). Neovascularization of chemically burned rabbit corneas was favourably

[265] a chemical process that can damage cells

modulated by dietary GLA (Ormerod et al., 1990). The use of enteral and parenteral feeding formulations supplemented with GLA and fish oil was investigated with rat and pig models of acute endotoxin and burn injuries. Rats demonstrated increases in plasma GLA and DGLA (Karlstad et al., 1993); however, lung microvascular permeability after endotoxin was not improved (Mancuso, J. Whelan, and DeMichele, 1997). Pulmonary eicosanoids were altered in endotoxic rats (Mancuso, J. Whelan, DeMichele, et al., 1997), but bacterial killing by macrophages was not changed (Palombo, DeMichele, and P. J. Boyce, 1999). In pigs, pulmonary surfactant function was not altered despite changes in PUFA composition of the surfactant (M. J. Murray et al., 2000). GLA supplementation in aged rats provided protection against ventricular fibrillation (Charnock, 2000). Thus, the link between dietary modulation of PUFA and functional changes remains tenuous in many cases.

## Clinical data

Investigations in humans have followed a similar pattern. Borage seed oil increased plasma phospholipid GLA and DGLA levels, while augmenting the arterial baroreflex control of vascular resistance in healthy humans, actions that may be useful in the treatment of hypertension (D. E. Mills et al., 1990). Proportions of different phospholipid types were unchanged, but DGLA was increased in platelets when borage seed oil was administered for 42 days (Barre and Holub, 1992). Neutrophils from subjects whose diets were supplemented with GLA mobilised 3-fold more DGLA after ionophore stimulation compared with controls (Chilton-Lopez et al., 1996). In older subjects, GLA had no effect on natural killer cell activity, while fish oil reduced it by 50% (Thies et al., 2001a). In contrast, T-lymphocyte proliferation was decreased by GLA and fish oil in the same type of population (Thies et al., 2001b). This effect on lymphocytes was reproduced by a second group for GLA in borage seed oil, where increases in plasma GLA and DGLA were observed. The release of pro-inflammatory leukotriene B4 from neutrophils with ionophore stimulation was reduced, while DGLA was elevated in healthy adults. The effects were greater at the higher of the 2 doses (Ziboh and Fletcher, 1992).

## Rheumatoid arthritis

Clinical trials have been performed with borage seed oil or purified GLA in several diseases. A 24-week randomised, double-blind, placebo-controlled trial of borage seed oil (GLA 1.4 g/day) in 37 individuals with rheumatoid arthritis found clinically important reduction in symptoms compared with a cotton seed oil placebo (Leventhal, E. G. Boyce, and Zurier, 1993). A trial in 56 subjects using a higher dose (GLA 2.8 g/day) included a 6-month, double-blind phase and a second 6-month, single-blind trial. Improvement

was found in arthritis symptoms for both groups, with the cohort receiving 12 months of GLA supplementation improving throughout both phases (Zurier, Rossetti, and E. W. Jacobson, 1996). No adverse effects were detected in any of these regimens.

A Cochrane review of trials from 1966 to 2000 suggests some benefit from GLA in rheumatoid arthritis, despite the relatively poor quality of the individual studies. There was a trend toward reduction of morning stiffness, joint tenderness, and pain. Sufficient evidence was found to warrant further larger trials to provide optimal dosage, information regarding outcome, and duration of therapy (Little and T. Parsons, 2001).

## Atopic eczema/dermatitis

A randomised clinical trial conducted in adults and children favoured placebo compared with borage oil for efficacy in atopic eczema (Takwale, Tan, and S. Agarwal, 2003). Other smaller trials noted a trend toward efficacy but without reaching clinical significance (Henz, Jablonska, and Van de Kerkhof, 1999), (Kapoor and Klimaszewski, 2000), (Henz, 2000), (Hoare, Li Wan Po, and H. Williams, 2000). In a trial designed to estimate degree of prevention of atopic dermatitis in infants with a familial risk, borage oil supplementation had no effect on dermatitis incidence or serum IgE and showed only a trend toward decreased severity of atopic dermatitis (Gool, Thijs, and Henquet, 2003). A small, open experiment in healthy elderly individuals reported improved cutaneous barrier function after 2 months of borage oil supplementation (Brosche and Platt, 2000).

## Respiratory distress syndrome

Compared with controls, a multicenter trial of fish oil and borage seed oil added to enteral feeding mixtures in patients with acute respiratory distress syndrome noted improvement in outcomes, with reduced major organ failures, shorter intensive care unit stays, and less ventilator support required (Gadek, DeMichele, and Karlstad, 1999). On the basis of this trial, Canadian practice guidelines for nutritional support in mechanically ventilated, critically ill patients, made the following recommendation: the use of products with fish oils, borage oils, and antioxidants should be considered in patients with adult respiratory distress syndrome (Heyland, Dhaliwal, and Drover, 2003).

## Other uses

### Osteoporosis

A pilot study of fish oil plus borage seed oil in elderly osteoporotic women found improved bone density in the treatment arm compared with placebo and improvement after crossover to all treatment in both groups (Kruger et al., 1998).

### Diabetes

An in-vivo experiment with borage oil failed to show an effect on insulin action and was associated with adversely affected lipid levels (Simoncikova, Wein, and Gasperikova, 2002).

### Neurodevelopment

No differences in neurodevelopment were found in a randomised, controlled trial with infants fed supplemented feeds. However, in planned subgroup analysis, boys fed the long-chain PUFA and borage oil-enriched formula scored higher on growth and neurodevelopment indicators (Fewtrell, Abbott, and K. Kennedy, 2004).

### Asthma

No clinical effect could be demonstrated in a randomised controlled trial of dietary supplementation versus placebo in asthma patients, despite measurable biochemical differences (Ziboh, Naguwa, and Vang, 2004).

## Uses

Borage has been used in European herbal medicine since the Middle Ages, alone and in combination with fish oil in rheumatoid arthritis, atopic eczema, and osteoporosis, although limited clinical evidence is available to support these uses.

The name "borage" derives from the medieval Latin "burra", meaning rough-coated, which refers to the hairs. An alternative explanation suggests a corruption of the Latin "corago" (courage), as in Gerard's rhyme "ego borago gaudia semper ago" (I, borage, bring alwaies courage), in line with its reputation as an herb to dispel melancholy.

## Anti-inflammatory/Arthritis/Eczema

Modern use of borage primarily comes from the use of the seeds to make borage seed oil, which contains a high content of the essential fatty acid known as GLA. Other current commercial sources of GLA include evening primrose oil, and blackcurrant seed oil. GLA is part of the inflammatory mediation process. Thus GLA supplements might be expected to have an impact on a variety of diseases and inflammatory conditions such as rheumatoid arthritis, and atopic eczema. Limited information involving the use of borage seed oil is available on treating any of these conditions. Most studies were done with other sources of GLA. Clinical tests verify that GLA has health and medical benefits.

## Other uses

Borage may also be useful in the treatment of osteoporosis. Fish oil plus borage seed oil has shown improvement in bone density in a study of elderly osteoporotic women. A review of trials of GLA for impaired nerve function in diabetics concluded that GLA may hold promise for treatment of diabetic neuropathy. Information is limited for the use of borage in these medical conditions (drugs.com, 2009c).

Treating joint pain and inflammation of arthritis and skin inflammation conditions (atopic dermatitis). It has also been used for symptoms of PMS. It may also have other uses. Check with your pharmacist for more details regarding the particular brand you use.

Preparations of borage flower and herb are used for blood purification and diuresis, as a preventative for inflammation of the lungs and peritoneum, for arthritis of the joints, as an expectorant, anti-inflammatory agent, for pain relief, cardiac tonic, sedative, diaphoretic, for increase of circulatory capacity and for phlebitis, and for menopausal disorders (herbalgram, 1991b).

The effectiveness for the claimed applications is not documented (herbalgram, 1991b).

Borage is an herbal product. It works by reducing inflammation in the body (drugs.com, 2015b).

The borage oil may help regulate the hormonal system, lowering blood pressure and cholesterol levels, strengthen the immune system, prevent allergies, premenstrual problems and prostate disorders.

The herb has been used traditionally as an herbal remedy to treat UTIs, cystitis, chronic kidney inflammation, catarrh, pneumonia, tuberculosis, gastritis, irritable bowel syndrome and depression.

The plant has also its traditional external uses. It has been used and may help as a treatment for itchy inflamed skin, wounds, eczema, rashes, arthritis and gout. As a mouthwash it is used to treat mouth and throat infections, mouth ulcers and bleeding gums.

The oil from the seeds is an alternative to evening primrose oil for atherosclerosis, rheumatic pain, PMS, menstrual problems, prostate disorders, allergies, arthritis, eczema and other skin problems.

Herbal tea made from borage may be helpful to treat acne and to reduce fever.

The tea can also act as an expectorant and clear the airways, therefore it's considered a useful remedy for colds, coughs, flu, sore throat, bronchitis and respiratory tract infections (Resource, 2015d).

## Do NOT use borage if

- you are allergic to any ingredient in borage.

Contact your doctor or health care provider right away if any of these apply to you.

## Before using borage

Some medical conditions may interact with borage. Tell your doctor or pharmacist if you have any medical conditions, especially if any of the following apply to you -

- if you are pregnant, planning to become pregnant, or are breast-feeding,
- if you are taking any prescription or nonprescription medicine, herbal preparation, or dietary supplement,
- if you have allergies to medicines, foods, or other substances,
- if you have schizophrenia or liver problems.

Some medicines may interact with borage. However, no specific interactions are known at this time.

This may not be a complete list of all interactions that may occur. Ask your health care provider if borage may interact with other medicines that you take. Check with your health care provider before you start, stop, or change the dose of any medicine.

## How to use borage

Use borage as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Dosing depends on the use and the source of the product.

- Use as directed on the package, unless instructed otherwise by your doctor.
- Borage oil should not be used for a long period of time unless directed by your doctor.
- If you miss taking a dose of borage for 1 or more days, there is no cause for concern. If your doctor recommended that you take it, try to remember your dose every day.

Ask your health care provider any questions you may have about how to use borage.

## Possibly Effective

- **Improving the function of the lungs in critically ill patients** - There is some evidence that borage seed oil, when taken by mouth in combination with eicosapentaenoic acid (EPA), might reduce the number of days spent in the intensive care unit (ICU) and the length of time a breathing machine is needed by patients with acute respiratory distress syndrome (ARDS).
- **Growth and development in premature infants** - Infant formula supplemented with fatty acids from borage oil and fish oils seems to improve growth and development of the nervous system in infants born early, especially boys.
- **Rheumatoid arthritis (RA)** - There is some evidence that taking borage seed oil in combination with conventional painkilling or anti-inflammatory medications might help decrease symptoms of RA after six weeks of treatment. The improvement appears to last for up to 24 weeks. Improvement is measured as a decrease in the number and severity of tender and swollen joints.

## Possibly Ineffective

- **Itchy, red skin (eczema)** - Taking borage seed oil by mouth does not seem to improve eczema in adults or children.

## Insufficient Evidence

- **Asthma** - Early research suggests that taking borage oil daily for 12 months does not improve asthma symptoms.
- **A dental condition called periodontitis** - Early research suggests that taking borage oil daily for 12 weeks improves gum inflammation but does not reduce plaque in people with periodontitis.
- **Skin conditions in infants** - There is some evidence that topical application of borage seed oil might be helpful for infantile seborrheic dermatitis. It seems to heal the condition within 1 to 3 weeks.
- **PMS**
- **Diabetes**

- **Attention deficit-hyperactivity disorder (ADHD)**
- **Alcoholism**
- **Heart disease**
- **Stroke**
- **Fever**
- **Cough**
- **Depression**
- **Dry skin**
- **Arthritis**
- **Pain relief**
- **Inflamed veins (phlebitis)**
- **Menopausal disorders**
- **Fluid retention**
- **Other conditions**

More evidence is needed to rate the effectiveness of borage for these uses (WMD, 2009a).

## Contraindications

Contraindications have not yet been identified.

## Adverse Reactions

No adverse effects have been reported. Although no direct evidence is available, caution is advised in patients with epilepsy because of reports of lowered seizure threshold with evening primrose oil (Z. Ma et al., 2005).

Although no side effects have been reported, borage leaves, flowers, and seeds contain small amounts of pyrrolizidine alkaloids that may be hepatotoxic especially at high doses for long periods of time (drugs.com, 2009c).

Borage seed oil is possibly safe when taken by mouth or applied to the skin appropriately.

Borage seed oil is likely unsafe when products containing a dangerous chemicals called pyrrolizidine alkaloids (PAs) are taken by mouth. Borage plant parts including the leaf, flower, and seed can contain PAs. PAs can damage the liver or cause cancer, especially when used in high doses or for a long time. Only use products that are certified and labeled PA-free (WMD, 2009a).

Seek medical attention right away if any of these SEVERE side effects occur:

Severe allergic reactions (**rash**; **hives**; **itching**; **difficulty breathing**; **tightness in the chest**; **swelling of the mouth, face, lips, or tongue**).

The contents of pyrrolizidin alkaloids found in plants of the Boraginaceae family cast doubt on the safety of borage as a culinary and medicinal herb, especially if large amounts of the leaves are consumed.

Borage contains small amounts pyrrolizidin alkaloids. In high concentrations these alkaloids have been shown to cause liver damage and liver cancer. The oil from the seeds of borage contain none or very small amounts of these compounds.

Apart from the seed oil, various herbal preparations of borage are therefore subject to sales restrictions in many countries, including Australia, New Zealand and Germany.

Borage must be used with caution, both as food and medicine, and not taken over a long period of time. Pregnant women or lactating mothers shouldn't use the herb.

People suffering from epilepsy, schizophrenia or those taking the drug Phenothiazine should not use this herb. Some plants of the Boraginaceae family like borage may cause skin dermatitis and inflammation so exercise caution when collecting and drying the plant. It's safe to say this herb should only be used in consultation with trained health care professionals (Resource, 2015d).

It is not recommended that Borage be taken long term internally because of the concentration of alkaloids in Borage that can damage the liver. Do not take Borage if you are taking anti-coagulants without discussing it with your doctor first. **Nausea**, **cramping**, **bloating** and **headache** are side effects that Borage can cause, although they are relatively mild (herbwisdom, 2015c).

## Pregnancy/Lactation

Documented adverse effects (pyrrolizidine alkaloids). Avoid use (Rotblatt and Ziment, 2002), (F. J. Brinker, 1998b), (C. A. Newall, L. A. Anderson, and Phillipson, 1996b), (Arao et al., 1995), (M. Herrmann, Joppe, and Schmaus, 2002).

Borage seed oil is likely unsafe during pregnancy and while breast-feeding. It is important to avoid borage products that might contain pyrrolizidine alkaloids (PAs). PAs are a risk to the mother because they can cause serious liver disease and might cause cancer. PAs are also a risk to the infant because they might cause birth defects and they can pass into breast milk. Researchers are not sure if borage products that are certified PA-free are safe during pregnancy and breast-feeding. It is best to stay safe and avoid using borage (WMD, 2009a).

## Special Precautions & Warnings

### Children

Borage seed oil is possibly safe when taken by mouth appropriately. Borage seed oil is likely unsafe when products containing PA are taken by mouth.

### Bleeding disorders

There is some concern that borage seed oil might prolong bleeding time and increase the risk of bruising and bleeding. If you have a bleeding disorder, use borage with caution.

### Liver disease

Borage products containing hepatotoxic pyrrolizidine alkaloids (PA) might make liver disease worse.

### Surgery

Borage might increase the risk of bleeding during and after surgery. Stop taking borage at least 2 weeks before a scheduled surgery (WMD, 2009a)

## Interactions

None well documented.

### Moderate Interaction

**Be cautious with this combination**

- Medications that increase the break down of other medications by the liver (Cytochrome P450 3A4 (CYP3A4) inducers) interacts with borage.
  Borage is broken down by the liver. Some chemicals that form when the liver breaks down borage seed oil can be harmful. Medications that cause the liver to break down borage seed oil might enhance the toxic effects of chemicals contained in borage seed oil.
  Some of these medicines include carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin), rifampin, rifabutin (Mycobutin), and others.
- Medications that slow blood clotting (anti-coagulant / anti-platelet drugs) interacts with BORAGE

Borage seed oil might slow blood clotting. Taking borage seed oil along with medications that also slow clotting might increase the chances of bruising and bleeding.
Borage seed oil contains GLA. GLA is the part of borage seed oil that might slow blood clotting.
Some medications that slow blood clotting include aspirin, clopidogrel (Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.

- Medications used during surgery (Anesthesia) interacts with borage.
  Borage seed oil might interact with medications used during surgery. Be sure to tell your doctor what natural products you are taking before having surgery. To be on the safe side, you should stop taking borage seed oil at least two weeks before surgery.

## Minor Interaction

**Be watchful with this combination**

- Nonsteroidal anti-inflammatory drugs (NSAID)s interacts with borage.
  - NSAIDs are anti-inflammatory medications used to decrease pain and swelling. Borage seed oil is also used as an anti-inflammatory medication. Sometimes NSAIDs and borage seed oil are used together for rheumatoid arthritis. But borage seed oil seems to work in a different way than NSAIDs. Some scientists think that taking NSAIDs along with borage seed oil might decrease the effectiveness of borage seed oil. But it is too soon to know if this is true.

  Some NSAIDs include ibuprofen (Advil, Motrin, Nuprin, others), indomethacin (Indocin), naproxen (Aleve, Anaprox, Naprelan, Naprosyn), piroxicam (Feldene), aspirin, and others (WMD, 2009a).

# Dosage

Borage seed oil has been given in doses of 1.4 to 2.8 g/day in several clinical trials for arthritis and other inflammatory conditions. The content of GLA is between 20% and 26% of the oil (drugs.com, 2009c).

For rheumatoid arthritis - 1.1 or 1.4 grams of borage seed oil daily for up to 24 weeks (WMD, 2009a).

Studies suggest that borage oil has a teratogenic effect and that its prostaglandin E agonist action may cause premature labour in females. Seizures have been reported as a complication of ingestion of borage oil in doses of 1,500 to 3,000 mg daily, (Al-Khamees, 2011) although a mixed review of borage oil's effect on seizure thresholds indicates that borage

oil quality varies (Spinella, 2001). A specific extraction process may offer purified products with 50%+ GLA content. Borage oil has been investigated along with evening primrose oil in the treatment of eczema, and it was found that there is a lack of effect on eczema; improvement was similar to respective placebos used in trials (Bamford, 2013).

Herbal tea can be made by pouring a teacup of boiling water over one or two teaspoons of the dried herb and allow it to soak for 5 to 10 minutes.

Some herbalists recommend drinking up to three cups a day and as a tincture three times a day (Resource, 2015d).

Borage can be found in a caplet form, or as a liquid extract of the plant. Borage oil is distilled from the seeds of the plant and used topically or taken internally. It is not recommended to be taken long term internally due to the concentration of alkaloids in Borage that can damage the liver. A typical dose of the caplet or extract form is one to two grams per day. The dried leaves can be brewed into a tea, which has been said to have a refreshing cucumber-like flavour (herbwisdom, 2015c).

## Important safety information

- Have your liver function tested regularly while you are taking borage oil.
- This product has not been approved by the FDA as safe and effective for any medical condition. The long-term safety of herbal products is not known. Before using any alternative medicine, talk with your doctor or pharmacist.
- Pregnancy and breast-feeding - Use of borage is not recommended if you are pregnant. Consult your doctor before using this product. If you are or will be breast-feeding while you are using borage oil, check with your doctor or pharmacist to discuss the risks to your baby (drugs.com, 2015b).

## Toxicology

The presence of unsaturated pyrrolizidine alkaloids in leaves, flowers, and seeds of borage (Larson, Roby, and Stermitz, 1984), (Dodson and Stermitz, 1986) suggests a potential for hepatotoxicity, although the total plant alkaloid content is low (M. Herrmann, Joppe, and Schmaus, 2002), (Langer and Franz, 1997).

## Commentary

*There is insufficient evidence for the usage of borage as a herbal hormone, as there is no proven benefit for taking it for that purpose. In other words, its a waste of time and money taking it as a herbal hormone.*

Chapter 6

# C's

## Caraway

### Common Names

ALcaravea, Anis Canadien, Anis des Prés, Anis des Vosges, Apium carvi, Carraway, Carum carvi, Carum velenovskyi, Carvi, Carvi Commun, Carvi Fructus, Cumin des Montagnes, Cumin des Prés, Faux Anis, Haravi, Jeera, Jira, Kala Jira, Karwiya, Krishan Jeeraka, Krishnajiraka, Kummel, Kummich, Roman Cumin, Semen Cumini Pratensis, Semences de Carvi, Shahijra, Shiajira, Wiesen-Feldkummel, Wild Cumin, Carroway, carvies, karve, Persian cumin, Arabic = Karawiya, Chinese = Shan chu tsai, Dutch = Karwij, French = Carvi cumin des pres, French = Faux anis, German = Kummel, Hindi = Shia jira, Persian = Karoya, Russian = Tmin obyknovennyj, Sanskrit = Sushavi, Swedish = Kummin, Spanish = alcaravea

### Latin name

*Carum carvi*

Caraway is a plant that has an interesting place in legend. Superstitions held that caraway had the power to prevent the theft of any object that contained the seed and to keep lovers from losing interest in one another. These days, some people think caraway has healing power, and they use the oil, fruit, and seeds as medicine.

Caraway is used for digestive problems including heartburn, bloating, wind, loss of appetite, and mild spasms of the stomach and intestines. Caraway oil is also used to help people cough up phlegm, improve control of urination, kill bacteria in the body, and relieve constipation.

Women use caraway oil to start menstruation and relieve menstrual cramps; nursing mothers use it to increase the flow of breast milk.

Caraway is used in mouthwashes and in skin rubs to improve local blood flow.

In foods, caraway is used as a cooking spice.

In manufacturing, caraway oil is used to flavour certain medications. It is also commonly used as a fragrance in toothpaste, soap, and cosmetics.

## Plant Parts Used

The caraway seeds and fruit are the plant part that are mostly used for health benefits. However, leaves and roots are also used in some medical preparations (Resource, 2015e).

## Contains

The caraway seeds contain 2–7% of essential oil consisting of carvone (45–65%), smaller amounts of limonene, carveol and some other substances. Furthermore, the seeds contain around 20% fatty oil. Plants that grow in the wild usually contain more oil than plants that are cultivated and have therefore a stronger flavour. The leaves of caraway are rich in vitamin B and C, as well as iron (Resource, 2015e).

## History

Caraway has been cultivated for a very long time and it was known and described by many ancient civilizations. The seeds of the plant have been found in human settlements dating from the Stone Age, and also in Egyptian tombs (Resource, 2015e).

## Uses

Caraway has various medicinal properties such as antihistaminic[266], antiseptic, anti-spasmodic, carminative, and vermifuge[267], and digestive.

This medicinal herb has been utilised to get rid of toothaches and it is commonly used as a carminative.

An herbal tea prepared from the seeds of caraway is used as an herbal remedy for digestive disorders, heartburn, loss of appetite, and to dispel worms.

Caraway seems to be a natural treatment for dyspepsia, hysteria, and similar disorders. Also it is believed to be an effective stomachic.

[266] opposes the activity of histamine receptors in the body

[267] an agent that destroys or expels parasitic worms

Distilled water extracted from caraway is believed to be an effective herbal remedy for flatulent colic[268] in infants.

A poultice made from the powdered seeds is believed to be an effective herbal remedy for wounds.

An infusion prepared from the caraway seeds can help aid digestion, menstrual cramps, and relieve wind.

The caraway seed oil is sometimes utilised orally to get rid of halitosis, bad breath or bad taste. In addition, the oil contains an effective anthelmintic[269] agent, especially against hookworms (Resource, 2015e).

Dyspeptic problems such as mild, spastic conditions of the gastrointestinal tract, bloating, and fullness.

It's been used to stimulate milk production in mothers as well as treat infant colic and is often used to flavour children's medicines. Today, caraway is still recommended as a treatment for flatulence (unknown, 2014k). Recent research is showing promise of it being effective in cases of triple-negative breast cancer (K. M. Sutton, 2014).

## How does it work?

Caraway oil might improve digestion and relieve spasms in the stomach and intestines.

## Uses & Effectiveness

### Possibly Effective for

- Heartburn, when used in combination with other herbs. Taking caraway oil as part of a specific combination with peppermint oil (Enteroplant, Spitzner Arzneimittel) seems to relieve heartburn, including symptoms of fullness and mild gastrointestinal spasms, about as well as a drug called cisapride. This peppermint oil/caraway oil combination is not available in the US. Another combination product that contains caraway plus clown's mustard plant, peppermint leaf, German chamomile, liquorice, milk thistle, angelica, celandine, and lemon balm (Iberogast, Medical Futures, Inc) also seems to improve symptoms of upset stomach. This combination seems to significantly help acid stomach, cramping, nausea, and vomiting.

[268] severe abdominal pain caused by spasm, obstruction, or distension of any of the hollow viscera, such as the intestines

[269] can expel parasitic worms and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host

### Insufficient Evidence for

- Asthma. Early research suggests that drinking tea containing chamomile, saffron, anise, fennel, caraway, liquorice, cardamom, and black seed twice daily for 6 months reduces symptoms of allergic asthma, including sleep discomfort and coughing.
- Poor appetite.
- Constipation.
- Wind, otherwise known as "flatus".
- Bloating.
- Spasms of stomach and intestines.
- Menstrual cramps.
- Poor blood flow.
- Infection.
- Starting menstruation.
- Increasing milk flow in nursing mothers.
- Other conditions.

More evidence is needed to rate the effectiveness of caraway for these uses.

## Side Effects & Safety

Caraway is likely safe when taken by mouth in food amounts. Caraway is possibly safe for most people when taken by mouth in medicinal amounts for up to 8 weeks.

Caraway oil can cause **belching**, **heartburn**, and nausea when used with peppermint oil. It can cause **skin rashes** and **itching** in sensitive people when applied to the skin.

Caraway seeds contains highly volatile essential oils that if taken in large dosage over a long period can cause **liver damage** and **kidney damage**.

## Special Precautions & Warnings

### Pregnancy and breast-feeding

It is possibly unsafe to take caraway in medicinal amounts. Caraway oil has been used to start menstruation, and this might cause a miscarriage. Don't use it.

Not enough is known about the safety of using caraway during breast-feeding. Stay on the safe side and avoid use.

In very high dose, the oil can be an abortifacient and it may be neurotoxic[270]; therefore, it should be avoided by pregnant women (Resource, 2015e).

[270] poisonous or destructive to nerve tissue

### Paediatric

It is not safe to use the purified essential oil by children below two years, because, it may cause skin and mucous membranes irritation (Resource, 2015e).

### Diabetes

There is a concern that caraway might lower blood sugar. If you have diabetes and use caraway, watch your blood sugar carefully. The dose of the medications you use for diabetes might need to be adjusted.

### Too much iron in the body (heamochromatosis)

Caraway extract might increase the absorption of iron. Overuse of caraway extract with iron supplements or iron-containing food might increase iron levels in the body. This may be a problem for people who already have too much iron in the body.

### Surgery

Caraway might lower blood sugar levels. There is a concern that it might interfere with blood sugar control during and after surgery. Stop using caraway at least 2 weeks before a scheduled surgery.

## Interactions

### Moderate Interaction

Be cautious with this combination.

- Medications for diabetes (Antidiabetes drugs) interacts with caraway.
- Caraway might decrease blood sugar. Diabetes medications are also used to lower blood sugar. Taking caraway along with diabetes medications might cause your blood sugar to go too low. Monitor your blood sugar closely. The dose of your diabetes medication might need to be changed. Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others. Before taking caraway, talk with your healthcare professional if you take any medications.

## Dosage

The following doses have been studied in scientific research -

### Orally

- For heartburn - 50–100 mg of caraway oil per day has been used in combination with peppermint oil. A specific combination product containing caraway (Iberogast, Medical Futures, Inc) and several other herbs has been used in a dose of 1 mL three times daily (WMD, 2009b).

### Tea

For preparing a herbal tea or tisane, it is recommended to use about 0.5–2 grams of powdered fruit; you may drink the herbal tea three times a day (Resource, 2015e).

Use 1.5–6 g of seeds (herbalgram, 1990b).

### Tinctures

The tinctures prepared from the extracts of the herb can be used 0.5–4 ml three times a day (Resource, 2015e).

### Essential oil

The essential oil can be taken 0.05–0.2 ml three times a day for petulant bowel syndrome (Resource, 2015e).

For gassy indigestion, one to four drops of the volatile oil with sufficient quantity of sugar and a teaspoonful of pure water seems to be very effective (WMD, 2009b).

Use 3–6 drops (herbalgram, 1990c).

## Commentary

*There is insufficient evidence for the usage of Caraway as a herbal hormone, as there is no proven benefit for taking it for that purpose. In other words, its a waste of time and money taking it as a herbal hormone.*

# Chaste Tree/Berry

## Common Names

CHasteberry, chaste-tree berry, vitex, monk's pepper, Chaste tree, agnus castus, gattilier, Indian spice, lilac chaste tree, sage tree hemp, wild pepper, Abraham's balm, chaste lamb-tree, safe tree, Nirgundi, Sambhalu, Monk's Berry, cloister pepper, Indrani, Nochi, Arabic = Fitex, Arabic = Ibrahim, Arabic = Kaf mariyam, Arabic = Shajarat, Finnish = Siveydenpuu, French = gattilier agneau-chaste, German = Keuschbaum, German = Mönchspfeffer, Icelandic = munkapipar, Italian = Agno casto, Italian = Albero del pepe, Italian = Pepe falso, Russian = Avraamovo derevo, Russian = Prutnjak obyknovennyj, Spanish = sauzgatillo, Swedish = kyskhetsträd.

## Latin Name

*Vitex agnus-castus*

## Botany

The chaste tree is a small (6 to 7 m) tree or shrub native to river banks in southern Europe and the Mediterranean region. The plant is cultivated in China. It blooms in summer, developing light purple flowers and palm-shaped leaves. The dark brown to black fruits are the size of peppercorns. These fruits have a pepperish aroma and flavour and are collected in autumn (USDA, 2011), (Chevallier, 1996).

The dried ripe chasteberry is used to prepare liquid extracts or solid extracts that are put into capsules and tablets.

## History

The dried, ripe fruit is used in traditional medicine. The plant has been recognized since antiquity and has been described in works by Hippocrates (AD 460), Dioscorides (AD 40), and Theophrastus (AD 372). In Homer's epic "The Iliad", the plant was featured as a symbol of chastity, capable of warding off evil. Early physicians recognised its effect on the female reproductive system, suggesting its use in controlling haemorrhages and expelling the placenta after birth. Monks have chewed it to decrease sexual desire (Chevallier, 1996), (S. Christie and A. Walker, 1998), (Hobbs, 1991).

Chaste tree got its name from the anaphrodisiac quality purported since its early use. Monks used to chew the berries and leaves of this tree to reduce the urges of the flesh. This use isn't scientifically proven, but it has deep roots traditionally. Syrup of the berries was even given at convents to nuns to reduce the chances of succumbing to sexual desires.

This plant has been used for menstrual difficulties for over 2500 years, with its earliest uses documented during early Roman and Greek history (Resource, 2015f).

## Plant Parts Used

The fruit/berries, leaves, tender stem parts, and leaves are all used from this plant (Resource, 2015f).

## Properties

- **Leaves** - Anti-parasitical[271], alterative, aromatic, vermifuge, pain reliever (herbwisdom, 2015d).
- **Root** - Tonic, febrifuge[272], expectorant, diuretic (herbwisdom, 2015d).
- **Fruit** - Nervine, cephalic[273], emmenagogue (herbwisdom, 2015d).

## Chemistry

Vitex agnus-castus contains iridoids, flavonoids, diterpenoids, progestins, essential oils, and ketosteroids. Iridoid glycosides have been isolated from the leaves and fruit of the plant and include agnuside and aucubin. Flavonoid content (including kaempferol, quercetagetin, and casticin) has been identified in chaste tree leaves, flowers, and fruits. Flavonoids were isolated from the root bark.

The alkaloid vitricine is present in the plant. Vitex lactam A, a labdane diterpene, has been isolated from the fruit of Vitex agnus-castus. In-vitro studies show that labdane diterpenes have dopamine receptor affinity.

Clerodadienols are potent inhibitors of prolactin release. Although present in only trace amounts, progesterone, hydroxyprogesterone, testosterone, and androstenedione have been isolated from the leaves and flowers of Vitex agnus-castus. Numerous fatty acids also have been found (Kuruüzüm-Uz et al., 2003), (Hirobe et al., 1997), (Hoberg et al., 1999), (J. Liu, Burdette, and Sun, 2004), (Ono, Eguchi, and Konoshita, 2011), (B. Ahmad et al., 2010), (Choudhary and Jalil, 2009), (S. N. Chen, Friesen, and D. Webster, 2011), (N. A. Ibrahim et al., 2008), (Marongiu, Piras, and Porcedda, 2010), (Mesaik, Azizuddin, and Murad, 2009), (Sarikurkcu et al., 2009).

The berries contain various alkaloids and flavonoids, as well as substances that are precursors of steroidal hormones. Studies have indicated that the health properties of the herb aren't due to one substance in particular but to several compounds interacting together (Resource, 2015f).

[271] indicated for the treatment of parasitic diseases

[272] serving to dispel or reduce fever

[273] relating to the head

## Uses and Pharmacology

There is evidence that aqueous-alcoholic extracts of chaste tree fruit inhibit secretion of prolactin in-vitro. In human pharmacology there are no data about the lowering of prolactin levels. There is no knowledge regarding pharmacokinetics (herbalgram, 1992b).

## Mastalgia/Cyclic breast pain

### Animal data

The widespread use of chaste tree extracts and the relatively safe profile of the preparations make data from animal studies largely irrelevant. The plant has been approved for this condition by the Complete German Commission E Monographs (Blumenthal, Goldberg, and Brinckmann, 2000).

In-vitro experimental studies suggest dopaminergic activity of the plant's diterpenes, similar to bromocriptine, may result in decreases in serum prolactin. Additionally, oestrogen receptor binding by phytoestrogens or linoleic acid from the fruits has been postulated as a possible mechanism for effect (Roemheld-Hamm, 2005), (Tamagno, 2009), (A. R. Carmichael, 2008).

### Clinical data

A limited number of controlled clinical trials have been conducted, and reviews of these trials are concordant in finding a benefit for treatment with Vitex agnus-castus. Decreased pain and shorter durations of pain have been demonstrated when chaste tree preparations are used for at least 3 cycles (Roemheld-Hamm, 2005), (A. R. Carmichael, 2008), (Die et al., 2009).

## Menopause

### Animal data

The widespread use of chaste tree extracts and the relatively safe profile of the preparations make data from animal studies largely irrelevant. With regard to menopausal symptoms, effects of chemical constituents of chaste tree on dopamine receptors, opioid receptors, and melatonin were described in animal experiments and in-vitro studies (Die et al., 2009), (D. E. Webster et al., 2011), (Wuttke, Jarry, et al., 2003), (Chopin Lucks, 2003), (Jarry et al., 1994a).

## Clinical data

Few controlled clinical trials have evaluated the efficacy of Vitex agnus-castus as a single agent in the management of menopausal symptoms (Die et al., 2009). Chaste tree was evaluated in combination with other natural products in the "Herbal Alternatives for Menopause Trial". Other observational studies and pharmacological experiments suggest Vitex agnus-castus may be a suitable alternative to standard management, such as HRT, but quality clinical trials are required to support a definitive role in therapy (Die et al., 2009).

# Premenstrual syndrome

## Animal data

The widespread use of chaste tree extracts and the relatively safe profile of the preparations make data from animal studies largely irrelevant. The plant has been approved for this condition by the Complete German Commission E Monographs (Blumenthal, Goldberg, and Brinckmann, 2000).

## Clinical data

A limited number of high-quality, controlled clinical trials have evaluated the efficacy of Vitex agnus-castus preparations in treating symptoms associated with PMS (moderate to severe), (Schellenberg, 2001), (D. Berger et al., 2000), (Z. He, R. Chen, and Y. Zhou, 2009), (L. Ma, S. Lin, R. Chen, and X. Wang, 2010), (L. Ma, S. Lin, R. Chen, Y. Zhang, et al., 2010), (Atmaca, Kumru, and Tezcan, 2003), with most conducted in Germany and China (E. W. Freeman, 2010). Despite a large placebo response observed in these trials (approximately 50%) and heterogeneity in trial conditions, a systematic review found that chaste tree extract demonstrated an overall benefit in reducing adverse physical symptoms and poor mood (Roemheld-Hamm, 2005), (Dante and Facchinetti, 2011). The number needed to treat for improvement in global symptoms score in 1 person was determined to be "4" in a quality controlled trial involving 104 women followed for at least 3 menstrual cycles (Roemheld-Hamm, 2005), (Schellenberg, 2001). Chaste tree has also been favourably compared with fluoxetine in the management of depression associated with PMS (Atmaca, Kumru, and Tezcan, 2003). The clinical studies have found the preparations to be well tolerated with few adverse effects, although data from larger controlled trials are still needed (Roemheld-Hamm, 2005), (E. W. Freeman, 2010), (Dante and Facchinetti, 2011).

## Other effects

### Amenorrhoea/Infertility

There have been case reports for the reinstatement of regular cycles in amenorrhoea; however, information from controlled clinical trials is lacking (Roemheld-Hamm, 2005), (Die et al., 2009), (Gerhard et al., 1998).

### Cancer

Ethanol extracts from the fruit of Vitex agnus-castus have shown in-vitro cytotoxic activity against various human cancer cell lines, including cervical, ovarian, breast, and gastric cancer, and small cell lung carcinoma. Numerous mechanisms of action may be involved in inducing apoptosis (A. R. Carmichael, 2008), (Ohyama et al., 2005), (Imai et al., 2009).

### Immune system

Experimental studies suggest immunomodulatory effects of chaste tree flavonoids, diterpenes, and other chemical constituents (B. Ahmad et al., 2010), (Choudhary and Jalil, 2009), (S. N. Chen, Friesen, and D. Webster, 2011), (Mesaik, Azizuddin, and Murad, 2009).

### Orchiectomy

Inhibition of testosterone in rats and bone-sparing effects in castrated rats have been demonstrated by extracts of chaste tree (Nasri et al., 2007), (Sehmisch, Boeckhoff, and Wille, 2009).

## Efficacy

Possibly effective for treating Premenstrual Dysphoric Disorder (PMDD) and PMS (medscape, 2015b).

## Uses

Chaste tree extract has been used to manage symptoms related to PMS and cyclic mastalgia and may be a suitable alternative to standard pharmacological management. Although the Complete German Commission E Monographs supports its use for PMS and cyclic mastalgia, there are limited clinical trials to support these uses. Limited evidence exists for its use in menopause.

Chaste tree is used for irregularities of the menstrual cycle, PMS, and breast pain. It may also have other uses. Check with your pharmacist for details regarding the particular brand you use (drugs.com, 2015c).

Modern uses of chaste tree berry include reduction of PMS, menstrual cramps and other pre-menopausal symptoms. Studies have shown a reduction in breast tenderness and pressure, headaches, bloating and fatigue in women who took the herb regularly and over some time.

Chaste tree is often used in combination with other herbs depending on the ailment. It can be used with black cohosh (Cimicifuga racemosa) or golden seal (Hydrastis canadensis) to treat PMS and menopause symptoms, with echinacea (Echinacea sp.) to treat acne caused by hormone imbalances and with feverfew (Tanacetum parthenium) for menstrual migraine.

This herb has also been used to increase stimulation of breast milk production.

Chaste tree berries are used as an herbal treatment for infertility associated with mild corpus luteum insufficiency.

This plant may also be beneficial in combating breast cancer.

Chaste tree berry has been shown to help balance the progesterone and oestrogen levels. This is why it has been referred to as a "female" herb. It also has a negative effect (anti-androgenic[274]) on male hormones. In males it reduces sex drive and, therefore, men seldom use it.

The berries may also be dried and used as a substitute for pepper. They are also used in various spice blends in the Middle East.

The aromatic leaves can also be used as a seasoning. The plant is one of the ingredients in a legendary Moroccan spice blend called "ras el hanout".

A perfume is made from the flowers. The young stems have been used to make baskets and a yellow plant dye can be obtained from the leaves, seeds and roots (Resource, 2015f).

One of its properties was to reduce sexual desire and it is recorded that Roman wives whose husbands were abroad with the legions spread the aromatic leaves on their couches for this purpose. It became known as the chasteberry tree. During the Middle Ages, Chasteberry's supposed effect on sexual desire led to it becoming a food spice at monasteries, where it was called "Monk's pepper" or "Cloister pepper" (herbwisdom, 2015d).

[274] having the ability to block the male hormone testosterone from binding to androgen receptors

## Traditional/Ethnobotanical uses

Chasteberry has been used for thousands of years, mostly by women to ease menstrual problems and to stimulate the production of breast milk. Currently, chasteberry is still used as a folk or traditional remedy for menstrual problems, such as PMS, as well as for symptoms of menopause, some types of infertility, and acne (NIH, 2012a).

Acne, BPH, fibrocystic breast disease, impotence, female infertility, lactation, menopausal symptoms, menstrual irregularities, PMS, progesterone insufficiency (medscape, 2015b).

Chaste tree is an herbal product. It is thought to work by regulating hormone production through the pituitary gland in the brain (drugs.com, 2015c).

Do NOT use chaste tree if -

- you are allergic to any ingredient in chaste tree,
- you are pregnant.

Contact your doctor or health care provider right away if any of these apply to you (NIH, 2012a).

## Before using chaste tree

Some medical conditions may interact with chaste tree. Tell your doctor or pharmacist if you have any medical conditions, especially if any of the following apply to you -

- if you are planning to become pregnant or are breast-feeding,
- if you are taking any prescription or nonprescription medicine, herbal preparation, or dietary supplement,
- if you have allergies to medicines, foods, or other substances (drugs.com, 2015c)

## How to use chaste tree

Use chaste tree as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Dosing depends on the use and the source of the product,
- Use as directed on the package, unless instructed otherwise by your doctor,
- It may take several days to months for this product to work,
- If you miss taking a dose of chaste tree for 1 or more days, there is no cause for concern. If your doctor recommended that you take it, try to remember your dose every day (NIH, 2012a).

## Important safety information

- Chaste tree may reduce the effectiveness of birth control pills. Use an additional form of contraception (eg, condoms) while you are taking this product.
- If you will be taking this product for irregularities of the menstrual cycle or for breast pain and swelling, consult your doctor first. It is important to receive an accurate diagnosis of your symptoms before taking this product.
- This product has not been approved by the FDA as safe and effective for any medical condition. The long-term safety of herbal products is not known. Before using any alternative medicine, talk with your doctor or pharmacist.
- **Pregnancy and breast-feeding** Do not take this product if you are pregnant. If you are or will be breast-feeding while you are using this product, check with your doctor or pharmacist to discuss the risks to your baby (drugs.com, 2015c).

## What the Science Says

- A few studies of chasteberry for PMS have found a benefit. However, most of these studies were not well designed, so firm conclusions cannot be drawn.
- Small studies suggest that chasteberry may help with breast pain and some types of infertility, but there is not enough reliable scientific evidence to determine whether chasteberry has any effect on these conditions.
- NCCIH has funded studies on chasteberry. Projects have explored how chasteberry works in the body and how it might affect symptoms of PMS (NIH, 2012a).

## Chaste Tree and hormones

In latent hyperprolactinemia, excessive secretion of prolactin may cause breast swelling and breast pain (H. P. Schneider and Bohnet, 1981). Studies have determined that chaste berry may help to correct prolactin levels through effects on dopamine receptors (Jarry, 1991), (Jarry et al., 1994b). Chaste berry also affects beneficially 'luteal phase defect,' a condition marked by short menstrual cycles, thought to be caused by insufficient progesterone secretion consequent to deficits in the corpus luteum (Mühlenstedt et al., 1978). Drugs that lower prolactin secretion have been shown to prolong the luteal phase of the menstrual cycle, as chaste berry has also been shown to do (Schulz, Hänsel, and V. E. Tyler, 1998), (Milewicz, 1993).

Both hyperprolactinemia and luteal phase defect have been pointed to as causal to PMS and cyclic mastalgia. In clinical trials, chaste berry was shown to relieve both PMS, and, especially, breast swelling and pain (Wuttke, J. Gorkow, and Jarry, 1995). Compared to vitamin B[6], chaste berry was superior in reducing mastalgia, premenstrual fluid retention, headache, and fatigue (Lauritzen, 1997), (herbalgram, 2000).

Traditionally, it has been an important European remedy for controlling and regulating the female reproductive system. Long used to regularise monthly periods and treat amenorrhoea and dysmenorrhoea, it was used to help ease menopausal problems and aid the birth process. Hippocrates, Dioscorides, and Theophrastus mention the use of chaste tree for a wide variety of conditions, including haemorrhage following childbirth, and also to assist with the 'passing of afterbirth'. Decoctions of the fruit and plant were also used in sitz baths[275] for diseases of the uterus.

Because of the intact herbal culture in Germany and other parts of Europe, chaste tree has not lost its popularity. In fact it remains probably the most commonly used herb for regulating hormones and relieving menstrual difficulties and is considered to be the best herb for ailments such as fibroid cysts of the uterus and endometriosis.

Chaste tree has not been significantly investigated for its therapeutic effects. However, preliminary investigations do indeed show the presence of compounds which are able to adjust the production of female hormones. Studies have shown that extracts of chaste tree can stimulate the release of LH and inhibit the release of FSH. This suggests that the volatile oil has a progesterone-like effect. Its benefits stem from its actions upon the pituitary gland specifically on the production of LH. This increases progesterone production and helps regulate a woman's cycle. Chaste tree may also regulate prolactin secretion. The ability to decrease excessive prolactin levels may benefit infertile women (herbwisdom, 2015d).

## Anxiety and PMS

A double-blind study conducted in London showed a 60% group reduction or elimination of PMS symptoms such as anxiety, nervous tension, insomnia, or mood changes, from subjects who were taking dried chaste tree capsules.

Employing an aqueous extract from the fruit, a 1979 study reported good results on premenstrual water retention. Women were able to sustain a good level of milk production for breastfeeding while taking this herb. While it took some time for the drug to take effect, the women were able to continue the use of the drug for months without harmful side effects (herbwisdom, 2015d).

[275] a warm-water bath covering the hips and buttocks

## Contraindications

Patients who have an allergy to or are hypersensitive to chaste tree or patients who are pregnant or breast-feeding should avoid use. Safe use in children has not been established. Breast cancer, endometriosis, hormone sensitive conditions, ovarian cancer, uterine cancer, uterine fibroids (medscape, 2015b).

## Adverse Reactions

Generally regarded as safe; mild and reversible adverse effects include **gastrointestinal reactions**, **itching**, **rash**, **headache**, **fatigue**, **acne**, and **menstrual disturbances**.

Chaste tree administration is generally regarded as safe for use because it has not been associated with any major adverse reactions. Minor and reversible adverse effects reported in clinical trials and surveillance include gastrointestinal reactions, **pruritus**[276], **rash**, **headache**, **fatigue**, **acne**, and menstrual disturbances (Roemheld-Hamm, 2005), (Daniele et al., 2005).

All medicines may cause side effects, but many people have no, or minor, side effects. Check with your doctor if any of these most common side effects persist or become bothersome -

- **Acne**, **cramping**, **diarrhoea**, **hair loss**, **headache** **increased menstrual flow**, **stomach pain**, **tiredness**.

Seek medical attention right away if any of these severe side effects occur -

- Severe allergic reactions (**rash**, **hives**, **itching**, **difficulty breathing**, **tightness in the chest**, **swelling of the mouth, face, lips, or tongue**).

This is not a complete list of all side effects that may occur. If you have questions about side effects, contact your health care provider. Call your doctor for medical advice about side effects (NIH, 2012a).

## Side Effects and Cautions

- Chasteberry has not been associated with serious side effects. However, it can cause **gastrointestinal problems**, **acne-like rashes**, and **dizziness**.
- Chasteberry may affect certain hormone levels. Women who are pregnant or taking birth control pills or who have a hormone-sensitive condition (such as breast cancer) should not use chasteberry.

[276] intense chronic itching in the anal region

- Because chasteberry may affect the dopamine system in the brain, people taking dopamine-related medications, such as certain antipsychotic drugs and Parkinson's disease medications, should avoid using chasteberry.
- Tell all your health care providers about any complementary health practices you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care (NIH, 2012a).

Although deemed safe through numerous studies, chaste tree berry use has shown some mild side effects. These include **gastrointestinal discomfort**, **diarrhoea**, **nausea**, **transitory headaches** and **mild skin reactions** (Resource, 2015f). Side effects of using chaste tree are rare. Minor gastrointestinal upset and a mild skin rash with itching have been reported in less than 2% of the women monitored while taking chaste tree (herbwisdom, 2015d).

## Pregnancy/Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking. However, chaste tree may have oestrogenic, progesterogenic, and/or uterine stimulant activity and should be avoided in pregnancy (Roemheld-Hamm, 2005), (F. J. Brinker, 1998c), (Cherdshewasart, Cheewasopit, and Picha, 2004a), (Dugoua et al., 2008).

No consensus exists regarding the efficacy of extracts in increasing milk production (Roemheld-Hamm, 2005), (D. J. Brown, 1994). When analysed chemically, human breast milk revealed no compositional changes after chaste tree use (M. Taylor, 2001). Despite low toxicity and a lack of evidence that chemical constituents pass into the milk, chaste tree products should be avoided during breast-feeding because safety has not been established (Roemheld-Hamm, 2005), (Dugoua et al., 2008).

## Interactions

None well documented.

Some medicines may interact with chaste tree. Tell your health care provider if you are taking any other medicines, especially any of the following -

- Dopamine agonists (eg, bromocriptine, levodopa) because side effects may be increased by chaste tree.

This may not be a complete list of all interactions that may occur. Ask your health care provider if chaste tree may interact with other medicines that you take (drugs.com, 2015c)

Case reports are lacking; however, chaste tree has dopamine agonist activity. An interaction with dopamine agonists (eg, bromocriptine, levodopa), dopamine receptor antagonists, and fertility and contraceptive drugs may be theoretically possible (M. Taylor, 2001), (Sliutz et al., 1993), (Russell et al., 2002), (Daniele et al., 2005).

This plant doesn't show any interaction with other herbs or medication, but due to it's hormonal influences it shouldn't be taken in conjunction with other female hormonal medications without consulting a physician or herbal practitioner (Resource, 2015f).

## How it works

Increase progesterone:oestrogen ratio by decreasing FSH release (medscape, 2015b).

## Proper storage of chaste tree

Store at room temperature away from heat, moisture, and light unless otherwise directed on the package label. Do not store in the bathroom. Most herbal products are not in childproof containers. Keep chaste tree out of the reach of children and away from pets.

## General information

- If you have any questions about chaste tree, please talk with your doctor, pharmacist, or other health care provider.
- Chaste tree is to be used only by the patient for whom it is prescribed. Do not share it with other people.
- If your symptoms do not improve or if they become worse, check with your doctor.
- Check with your pharmacist about how to dispose of unused medicine (drugs.com, 2015c).

## Notes

Chaste tree stimulates LH production, which can in turn increase levels of progesterone secreted by the endocrine system. However, a component of Black Cohosh also has a LH suppressing action, so if these two are taken together they can end up working against one another (unknown, 2014g).

## Dosage

The effect of chaste tree extract on hormones in women may be dose-dependent[277]. Some studies suggest lower doses result in increases in prolactin and oestrogen as well as decreases in progesterone, while higher doses decrease prolactin levels (Roemheld-Hamm, 2005).

Daily doses of chaste tree fruit extract are typically 20 to 40 mg, although dosages of up to 1,800 mg/day have been used (Roemheld-Hamm, 2005). Chaste tree fruit is available in several different extracts standardised to casticin or agnuside content (S. Christie and A. Walker, 1998), (Huddleston and E. A. Jackson, 2001), (Loch, Selle, and Boblitz, 2000).

Chaste tree berry does not give immediate results and must be used over a long period of time. In most cases the herb should be used for four to six months to obtain the desired effect.

The leaves, flowers and berries can be used in a decoction, traditional tincture, cider vinegar tincture, syrup, elixir[278], or just eaten right off the tree. It's also available in capsule and tablet form as well. The common dose of this supplement is 40 drops of the liquid extract daily, usually in a single dose (Resource, 2015f).

Daily dosage of an aqueous-alcoholic extracts corresponding to 30–40mg of the drug (herbalgram, 1992b).

Aqueous-alcoholic extracts (50–70% its concentration in volume/volume percent (V/V)[279]) from the crushed fruits taken as liquid or dry extract (herbalgram, 1992b). With its emphasis on long-term balancing of a woman's hormonal system, chaste tree is not a fast-acting herb. For PMS or frequent or heavy periods, chaste tree can be used continuously for four to six months. Women with amenorrhoea and infertility can remain on chaste tree for twelve to eighteen months, unless pregnancy occurs during treatment (herbwisdom, 2015d).

- **Crude herb extract** - 20–240 mg a day orally, in divided doses twice, or three, times a day,
- **Fluid extract** - 40 drops a day, orally,
- **Dried fruit extract** - 1.6–3 mg orally, twice a day,
- **Tincture** - 35–45 drops orally, three times a day,
  - **Other Information**
  - **PMS** - 4–20 mg a day,
  - **PMDD** - 20–40 mg a day.
- No more than 1800 mg a day (medscape, 2015b).

[277] effects change when the dose of the treatment is changed

[278] a sweetened, aromatic solution of alcohol and water containing, or used as a vehicle for, medicinal substances

[279] its concentration in volume/volume percent

### Toxicology

Information is limited. The safety of the plant's use in children has not been determined (Kurihara and Kikuchi, 1975) (drugs.com, 2009d).

Systematic studies about toxicology are unknown (herbalgram, 1992b).

### Commentary

*Progesterone and testosterone are present in the leaves and flowers, but only in very small amounts. There is a suggestion that chaste tree may be a suitable alternative to HRT, but clinical trials have not yet been done to make this a positive yet. It has been found that chaste tree extract does provide an overall benefit in reducing adverse PMS symptoms and poor mood.*

## Cranberry

### Common Names

AGrio, Airelle à Gros Fruits, Airelle Canneberge, Airelle Européenne, Airelle Rouge, American Cranberry, Arándano, Arándano Americano, Arándano Rojo, Arándano Trepador, Atoca, Atoka, Bearberry, black cranberry, Bog cranberry, Bounceberry, Canneberge, Canneberge à Feuillage Persistant, Canneberge d'Amérique, Canneberge Européenne, Cocktail au Jus de Canneberge, Cranberry Extract, Cranberry Fruit, Cranberry Fruit Juice, Cranberry Juice, Cranberry Juice Cocktail, Cranberry Juice Concentrate, Cranberry Powder, Cranberry Powdered Extract, Craneberry, Da Guo Yue Jie, Da Guo Yue Ju, Da Guo Suan Guo Man Yue Ju, European Cranberry, Extrait de Canneberge, GroSSe Moosbeere, Gros Atoca, Grosse Moosbeere, Jus de Canneberge, Jus de Canneberge à Base de Concentré, Jus de Canneberge Frais, Kliukva, Kliukva Obyknovennaia, Kranbeere, Large Cranberry, low cranberry, Man Yue Ju, Man Yue Mei, Moosebeere, Mossberry, Oomi No Tsuruko Kemomo, Oxycoccus hagerupii, Oxycoccus macrocarpos, Oxycoccus microcarpus, Oxycoccus palustris, Oxycoccus quadripetalus, Petite Cannberge, Pois de Fagne, Pomme des Prés, Ronce d'Amerique, Sirop de Canneberge, Small Cranberry, Trailing Swamp Cranberry, Tsuru-Kokemomo, Vaccinium edule, Vaccinium erythrocarpum, Vaccinium hagerupii, Vaccinium macrocarpon, Vaccinium microcarpum, Vaccinium oxycoccos, Vaccinium palustre, Vaccinium vitis, Finnish = Karpalo, Finnish = Pikkukarpalo, French = Airelle, French = Airelle des marais, German = Kranbeere, German = Moosbeere, Swedish = Myrbär

## Latin Name

*Vaccinium macrocarpon*

## What is it?

Cranberry is a small, evergreen shrub grown throughout North America. Cranberry has a long history of use among native American Indian tribes, primarily for treating urinary conditions. Juice and extracts from the fruit (berry) are used as medicine.

Cranberry is most commonly used for prevention and treatment of UTI. Cranberry juice seems to help prevent UTIs, but so far it doesn't seem to be effective in treating UTIs.

Cranberry is also used for neurogenic bladder (a bladder disease), as well as to deodorise urine in people with urinary incontinence (difficulty controlling urination). Some people use cranberry to increase urine flow, kill germs, speed skin healing, and reduce fever.

Some people use cranberry for type 2 diabetes, chronic fatigue syndrome (CFS), scurvy, inflammation of the lining around the lung (pleurisy), and cancer.

In foods, cranberry fruit is used in cranberry juice, cranberry juice cocktail, jelly, and sauce. Cranberry juice cocktail is approximately 26% to 33% pure cranberry juice, sweetened with fructose or artificial sweetener.

These red berries are used in foods and in herbal products. Historically, cranberry fruits and leaves were used for a variety of problems, such as wounds, urinary disorders, diarrhoea, diabetes, stomach ailments, and liver problems. More recently, cranberry has been used as a folk or traditional remedy for UTIs or Helicobacter pylori (H. pylori) infections that can lead to stomach ulcers, or to prevent dental plaque. Cranberry has also been reported to have antioxidant and anticancer activity.

The berries are used to produce beverages and many other food products, as well as dietary supplements in the form of extracts, capsules, or tablets.

Some evidence exists for the use of cranberry in preventing, but not treating, UTIs. Other possible roles for cranberry, with limited evidence include reduction of the risk of cardiovascular disease and cancer treatment.

Cranberry has been used as both food and medicine for centuries. It is native to North America and was used by Native Americans to treat bladder and kidney diseases. Early settlers from England learned to use the berry both raw and cooked for many conditions, including appetite loss, stomach problems, blood disorders, and scurvy caused by not getting enough vitamin C.

Cranberry is best known for preventing UTIs, commonly caused by bacteria known as Escherichia coli (E. coli). At first doctors thought cranberry worked by making urine acidic enough to kill the bacteria. Now, studies show that cranberry may prevent bacteria from attaching to the walls of the urinary tract. Good scientific studies support using cranberry either in capsules or as juice, for preventing, though not treating, UTIs (unknown, 2014e).

## Botany

The cranberry plant is native to eastern North America (N. USDA, 2008), (Dugoua, Seely, Perri, Millis, et al., 2008). Some research on the plant can be found under the older name Oxycoccus macrocarpus (Aiton) Pursh. A number of related cranberries are found in areas ranging from damp bogs to mountain forests. These plants grow from Alaska to Tennessee as small, trailing evergreen shrubs. Their flowers vary from pink to purple and bloom from May to August depending on the species. The genus Vaccinium also includes the blueberry (Vitex angustifolium Ait.), deerberry (Vitex stamineum L.), the bilberry (Vitex myrtillus), and the cowberry (Vitex vitis-idaea L.) (N. USDA, 2008). They should not to be confused with another highbush cranberry, Viburnum opulus L. (family: Caprifoliaceae) (I. Dobelis, 1986).

Found primarily in North America and grown in bogs, cranberry is an evergreen shrub related to blueberry, buckberry, huckleberry, and bilberry. The cranberry bush has upright branches with leaves that are speckled underneath by tiny dots. Pink flowers blossom and red-black fruits appear during June and July.

Cranberry fruit is high in antioxidants, partly from substances called proanthocyanidins, which give cranberries their vibrant colour. Antioxidants neutralise particles in the body known as free radicals, which damage DNA and are thought to contribute to heart disease, diabetes, cancer, and other conditions.

Cranberries are also an excellent source of vitamin C, another important antioxidant. Scientists are researching to see if the antioxidants in cranberries will help protect against heart disease and cancer (unknown, 2014e).

## History

The cranberry was primarily used as a traditional medicine for the treatment of bladder and kidney ailments among American Indians (Dugoua, Seely, Perri, Millis, et al., 2008). The berries were also used as a fabric and food dye, and as a poultice to treat wounds and blood poisoning (McKay and Blumberg, 2007). Sailors used the berries as a scurvy preventative. Despite a general lack of scientific evidence to indicate that cranberries or their

juice are effective urinary acidifiers, interest persists among the public in the medicinal use of cranberries. Cranberries are used in eastern European cultures because of their folkloric role in the treatment of cancers and to reduce fever.

## Properties

Antioxidant, anti-bilious[280], anti-putrid[281], diuretic, laxative, refrigerant[282], sub-astringent[283], vasodilator.

## Chemistry

The berries contain about 88% water (Lentner, 1991). Cranberries are a rich source of phenolic phytochemicals including phenolic acids (benzoic, hydroxycinnamic, sinapic, caffeic, and ferulic acids) and flavonoids (quercetin, myericetin, cyanidin, and peonidin) (McKay and Blumberg, 2007), (Neto, 2007b). Cranberries also contain anthocyanins and proanthocyanins, catechin, triterpenoids, lutein and zeaxanthin, and small amounts of protein, fibre, sodium potassium, selenium, and vitamins A, C, and E (2 to 10 mg) (McKay and Blumberg, 2007), (Melgalve, 1976). Dried berries contain little sodium or fat (McKay and Blumberg, 2007). The major organic acids are citric, malic (Borukh, Kirbaba, and Senchuk, 1972), and quinic acids, with small amounts of oxalate[284], and benzoic and glucuronic acids. The glycoside leptosine and several related compounds have been isolated (Jankowski, 1983), along with small amounts of alkaloids (Jankowski, 1973). The peel contains substantial amounts of triterpenoid ursolic acid (Neto, 2007b).

Cranberries contain many phytochemicals that are biologically active like proanthocyanidins, quinic acid, hippuric acid, tannins, Vitamin C, pterostilbene, and other antioxidants (Resource, 2015g).

## Uses and Pharmacology

The widespread consumption of cranberries makes the results of animal trials largely irrelevant.

UTI (prevention), urinary deodoriser for incontinent patients, type 2 diabetes, chronic fatigue syndrome, scurvy, pleurisy, as a diuretic, antiseptic, antipyretic, and cancer (medscape, 2015c).

[280] serving to prevent or cure biliousness

[281] having the ability to arrest putrefaction

[282] cooling, possessing the ability to reduce slight fevers

[283] mildly astringent, causing contraction or arresting discharges

[284] a salt of oxalic acid

Candida and other bacterial conditions, diarrhoea, dropsy, fevers, scurvy, stomach ulcers, UTIs of the bladder and urethra, urolithiasis.

Cranberries contain chemicals called oxalates, which may contribute to the formation of kidney stones. Drinking large amounts of cranberry juice (more than about a litre per day) or taking concentrated cranberry supplements may increase the risk of developing kidney stones. Therefore, individuals who have or who ever have had kidney stones should not consume very large amounts of cranberries or use supplemental cranberry products (Resource, 2015g).

## How it works

Proanthocyanidins, other compounds prevent bacterial adherence to urothelium.

Does not significantly decrease urine pH (medscape, 2015c).

## Urinary tract infections

Traditionally, cranberry products have been used to prevent and treat UTI. Though in the past many not well controlled and too small studies have been done to investigate the ability of cranberry juice to prevent UTIs gave inconclusive results, there is more and more data accumulating that cranberries can indeed be beneficial in the prevention of UTIs.

The mechanism is not fully understood but many in-vitro tests have shown that the proanthocyanidins contained in cranberries can inhibit the bacterium E. coli, which is responsible for 70–80% for all UTIs from adhering to the cells that line the bladder. This adhesion of the bacteria is a necessary first step before they are able to establish an infection.

Two other compounds found in cranberries, quinic acid, and hippuric acid, might also help in the prevention of UTIs. These substances are weak acids that unlike other organic acids are not degraded in the body, but secreted intact by the kidneys. They therefore make the urine slightly acidic, which can help keeping bacteria from growing in the urinary tract. However, no study to date has shown that drinking cranberry juice can treat an established bladder infection.

Since untreated bladder infection can lead to a more serious kidney infection, a doctor should be consulted if symptoms like frequent and painful urinating and urgency are observed (Resource, 2015g).

Two main mechanisms of action have been postulated. A change in the pH of urine by the conversion of benzoic acid to hippuric acid has been suggested. Consequent acidification of the urine was demonstrated in some studies (Blatherwick, 1923), (Raz, Chazan, and Dan, 2004). Hippuric acid is also considered to be bacteriostatic[285], but the amount of benzoic acid in the fruit rarely results in the production of sufficient hippuric acid to be effective as a urinary bacteriostatic agent (Raz, Chazan, and Dan, 2004).

The other mechanism by which cranberry may act is via properties that inhibit the adhesion of the pathogen (E. coli) to urinary epithelial cells (Howell et al., 1998), (Ofek et al., 1991), (Ahuja, Kaack, and J. Roberts, 1998). Preliminary data suggest that concentrated cranberry juice has some antibacterial activity, but whether sufficient urinary concentrations of the active ingredients can be achieved needs further investigation (Raz, Chazan, and Dan, 2004), (Y. L. Lee et al., 2000).

In the early 1920s, American scientists discovered that people who eat large amounts of cranberries have more acid in their urine than those who do not eat high amounts of the berry. Because bacteria cannot survive in an acidic environment, the researchers speculated that a diet rich in cranberries may help prevent and treat UTIs, which are commonly caused by bacteria known as Escherichia coli. In time, the popularity of cranberry for UTIs soared and many women reported satisfactory results from drinking cranberry juice.

UTIs are a serious health problem affecting millions of people each year. Infections of the urinary tract are common; only respiratory infections occur more often. Each year, UTIs account for about 9.6 million doctor visits. One woman in five develops a UTI during her lifetime; UTIs in men are not so common. Nearly 20% of women who have a UTI will have more than one and 30% of those will have more than two. Most infections arise from one type of bacteria, Escherichia coli, which normally live in the colon. Usually, the latest infection stems from a strain or type of bacteria that is different from the infection before it, indicating a separate infection.

NIH-funded research suggests that one factor behind recurrent UTIs may be the ability of bacteria to attach to cells lining the urinary tract. Current belief is that the prevention of UTI is achieved by inhibiting the infecting bacteria, E. coli, from adhering to uroepithelial cells. Bacterial adherence to these cells is a critical step in the development of infection, without which the causative bacteria are flushed, preventing their colonisation of the urinary tract.

An Israeli research group looked at chemical fractions of a number of fruit juices. They found that fructose, a common sugar in many fruit juices, had some anti-adherence effect on the bacterium. They also found that a nondialyzable polymeric compound isolated from cranberry juice (and blueberry juice) had the most potent effect. In 1991 Israeli researchers, publishing in The New England Journal of Medicine, duplicated the previous studies and confirmed the results.

[285] the prevention of the further growth of bacteria

Further laboratory studies indicated that cranberries also prevent another microorganism known as Helicobacter pylori from adhering to cell walls. H. pylori is a bacteria that can cause stomach ulcers, so it is possible that cranberries may eventually prove to play a role in the prevention of this condition. Studies also suggest that cranberries may help prevent bacteria from adhering to gums and around the teeth.

Cranberry also appears to be more effective than certain probiotics in preventing recurrent UTIs. They are often used as a supplement to try to prevent or fight UTIs (herbwisdom, 2015e).

Several studies indicate that cranberry helps prevent UTIs of the bladder and urethra, especially for women who have frequent UTIs. In one study of older women, cranberry juice reduced the amount of bacteria in the bladder compared to placebo. Another study showed that younger women with a history of frequent UTIs who took cranberry capsules had fewer UTIs compared to those who took placebo.

However, studies suggest that cranberry does not work once you have a UTI. That is because it helps keep bacteria from attaching to the urinary tract. But it is less effective once the bacteria have already attached. That is why cranberry is better at preventing UTIs than treating them. UTIs should be treated with conventional antibiotics (unknown, 2014e).

## Treatment

A systematic review found no well-designed trials assessing evidence for effect in the treatment of UTIs. Methodological issues include study design, measurement of outcomes and dosage, and duration of treatment. The use of cranberries for the treatment of UTIs remains unsupported (Raz, Chazan, and Dan, 2004), (Jepson, Mihaljevic, and J. Craig, 2004), (Tong, Heong, and S. Chang, 2006), (Waites et al., 2004).

## Prevention

A systematic review found a reduction in the incidence of UTIs at 12 months compared with placebo (relative risk [RR] 0.65; 95% confidence interval [CI], 0.46 to 0.90) (Jepson and J. C. Craig, 2008). A greater effect was found for reducing the incidence of recurrent UTIs in women, than among elderly men and women, or people requiring catheterisation (Jepson and J. C. Craig, 2008), (unknown, 2003b), (Franco, 2005), (Donabedian, 2006). A large number among the participants dropped out of the studies, and optimal dosage was unclear.

Among patients with spinal cord injury, no preventative effect was found for cranberry consumption in treating neurogenic bladders in two small trials (B. B. Lee, Haran, and L. M. Hunt, 2007), (Linsenmeyer, Harrison, and Oakley, 2004).

## Other effects

### Cancer

Cranberry phytochemicals, especially proanthocyanidins, quercetin, and ursolic acid, are being investigated for a role in cancer treatment. Induction of apoptosis and inhibition of tumour proliferation have been suggested. Clinical studies are limited (Neto, 2007b), (Duthie, Jenkinson, and Crozier, 2006).

The cranberry fruit is high in antioxidants, partly from substances called proanthocyanidins. Antioxidants scavenge damaging particles in the body known as free radicals. Environmental toxins (including ultraviolet light, radiation, cigarette smoking, and air pollution) can increase the number of free radicals in the body, which are believed to contribute to the aging process as well as the development of a number of health problems such as heart disease, cancer, and infections. Antioxidants can neutralise free radicals and may reduce or even help prevent some of the damage they cause. Cranberries are an excellent source of vitamin C as well, another important antioxidant. The juice is excellent against scurvy and to allay fevers. Cranberries also contain a potent vasodilator and have been used for breathing problems.

Several studies have measured high levels of antioxidants in people after drinking cranberry juice. Research is underway to determine if the antioxidant ability of cranberries will translate into protection from heart disease. Adding to cranberry's potential health benefits, a recent study found that an extract of cranberry inhibited an enzyme, and this has been associated with a reduction in cancer risk (herbwisdom, 2015e).

### Cardiovascular

Reviews suggest that the high polyphenolic content of cranberry may contribute to a reduction in the risk of cardiovascular disease. Suggested mechanisms, based mainly on animal studies, include increased resistance of LDL to oxidation, inhibition of platelet aggregation, and reduced blood pressure (McKay and Blumberg, 2007), (Duthie, Jenkinson, and Crozier, 2006), (Neto, 2007a).

### Diabetes

A small trial investigated the effect of daily cranberry consumption among patients with type 2 diabetes. Lower insulin levels compared with placebo were found in the experiment arm at 12 weeks (McKay and Blumberg, 2007), (Chambers and Camire, 2003).

### Gastrointestinal/antibacterial

Trials investigating the efficacy of cranberry in H. pylori eradication have been of varying methodological quality (Shmuely, Yahav, and Samra, 2007), (L. Zhang et al., 2005). In-vitro studies evaluated the effect of cranberry on gastrointestinal bacteria, as well as on nasopharyngeal bacteria (Puupponen-Pimia et al., 2005), (Kontiokari et al., 2005).

## Ulcers

Two studies showed that cranberry may also prevent the bacteria Helicobacter pylori (H. pylori) from attaching to stomach walls. H. pylori can cause stomach ulcers. So cranberries may play a role in preventing stomach ulcers. More research is needed to be sure cranberry helps (unknown, 2014e).

## Other uses

Scientists are still studying cranberry for the following conditions. More research is needed.

- **Cancer** - Some test tube and animal studies suggest cranberry may help stop cancer cells from growing.
- **High cholesterol** - One preliminary study found that drinking cranberry juice raised HDL (good) cholesterol levels.
- **Viruses** - Cranberry seems to fight some viruses in test tubes. Studies in people are needed.
- **Bacterial illnesses** - Cranberry has been shown to inhibit common forms of bacteria, such as Escherichia coli (E. coli) and Listeria monocytogenes (unknown, 2014e).

## Contraindications

Predisposition to nephrolithiasis.

History of kidney stones (medscape, 2015c).

## Precautions

Cranberry juice as a beverage (in normal amounts) is generally considered safe to drink with no serious side effects, even for pregnant women. Cranberry supplements are considered safe for most people, although pregnant and breastfeeding women should ask their doctor before taking any supplement, including cranberry.

Cranberry has relatively high levels of oxalate, chemicals that may raise the risk of kidney stones in some people. If you have kidney stones, talk to your doctor before taking cranberry supplements or drinking a lot of cranberry juice.

DO NOT use cranberry if you already have a UTI. You should see a doctor for prescription antibiotics.

Most cranberry juice has added sugar. People who have diabetes should look for brands that are artificially sweetened or should be careful how much sweetened juice they drink.

People who are allergic to aspirin may also be allergic to cranberry (unknown, 2014e).

## Efficacy

- Studies show significant reduction in the risk of recurrent UTI's in the elderly, hospitalized patients, and pregnant women.
- No reliable evidence shows effectiveness for treating UTI.
- **Urinary odour** - Preliminary research shows there may be a reduction in urinary odour in patients receiving oral cranberry.
- **Diabetes** - Clinical studies show NO improvement in fasting blood glucose, HbA1c, fructosamine, triglyceride, HDL cholesterol, or LDL cholesterol levels in patients with type 2 diabetes (medscape, 2015c).

## What the Science Says

- There is some evidence that cranberry can help to **prevent** UTIs; however, the evidence is not definitive, and more research is needed. Cranberry has not been shown to be effective as a **treatment** for an existing UTI.
- Research shows that components found in cranberry may prevent bacteria, such as E. coli, from clinging to the cells along the walls of the urinary tract and causing infection. There is also preliminary evidence that cranberry may reduce the ability of H. pylori bacteria to live in the stomach and cause ulcers.
- Findings from a few laboratory studies suggest that cranberry may have antioxidant properties and may also be able to reduce dental plaque (a cause of gum disease).
- NCCIH is funding studies of cranberry, primarily to better understand its effects on urinary tract infection. The Office of Dietary Supplements and other National Institutes of Health (NIH) agencies are also supporting cranberry research; for example, the National Institute on Aging is funding a laboratory study of potential anti-aging effects.

## How effective is it?

*Natural Medicines Comprehensive Database* rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

The effectiveness ratings for **Cranberry** are as follows -

### Possibly effective for...

- **Preventing UTIs** - Most research shows that drinking cranberry juice or taking certain cranberry extracts can lower the risk of repeated UTIs in some people. Evidence suggests that taking cranberry products can reduce the occurrence of UTIs in women, most children, and people who are hospitalized. It is not clear if drinking cranberry juice or taking supplements of cranberry extract is more effective. Although most research shows that cranberry is beneficial for UTIs, there is some evidence that it might not benefit children with a history of UTIs. Also, there is no strong evidence that cranberry can treat an existing UTI.

### Possibly ineffective for...

- **Diabetes** - Research shows that taking cranberry supplements by mouth does not lower blood sugar in people with diabetes.

### Insufficient evidence to rate effectiveness for...

- **Benign prostatic hyperplasia (BPH)** - Early research shows that taking dried cranberry capsules, three times daily for 6 months, might improve urinary symptoms and reduce levels of certain biomarkers associated with BPH.
- **Clogged arteries (coronary artery disease)** - Early evidence suggests that drinking cranberry juice daily for 4 weeks does not improve blood flow in people with clogged arteries.
- **Stomach ulcers caused by Helicobacter pylori (H pylori) infection** - There is inconsistent evidence regarding the ability of cranberry juice to eliminate a certain bacteria (H. pylori) in the stomach that can cause stomach ulcers. Some research suggests that drinking cranberry juice daily for 90 days can help eliminate H. pylori more quickly. However, other early research shows that drinking cranberry juice while taking conventional medication used to treat H. pylori infections does not improve healing time compared to taking the medication alone.

- **Kidney stones (nephrolithiasis)** - There is inconsistent evidence on the use of cranberry to lower the risk of kidney stones. Some early evidence suggests that drinking cranberry juice might lower the risk of kidney stones forming. However, other early evidence suggests that drinking cranberry juice or taking cranberry extracts might actually increase the risk of kidney stones.
- **Memory** - Some early evidence suggests that drinking cranberry juice twice daily for 6 weeks does not improve memory.
- **Metabolic syndrome** - Early research suggests that drinking cranberry juice (Ocean Spray) twice daily does not appear to affect blood pressure, blood sugar, or cholesterol levels in people with metabolic syndrome.
- **Urine odour** - Early research shows that drinking cranberry juice might reduce the odour of urine.
- **Skin healing**
- **Pleurisy**
- **Cancer**
- **Chronic fatigue syndrome (CFS)**
- **Other conditions**

More evidence is needed to rate cranberry for these uses.

## How does it work?

People used to think that cranberry worked for UTIs by making the urine acidic and, therefore, unlikely to support the growth of bacteria. But researchers don't believe this explanation any more. They now think that some of the chemicals in cranberries keep bacteria from sticking to the cells that line the urinary tract where they can multiply. Cranberry, however, does not seem to have the ability to release bacteria which are already stuck to these cells. This may explain why cranberry is possibly effective in preventing UTIs, but possibly ineffective in treating them.

Cranberry, as well as many other fruits and vegetables, contains significant amounts of salicylic acid, which is an important ingredient in aspirin. Drinking cranberry juice regularly increases the amount of salicylic acid in the body. Salicylic acid can reduce swelling, prevent blood clots, and can have anti-tumour effects.

## Adverse Reactions

Gastrointestinal upset, diarrhoea, kidney stones at high doses.

Increased risk of cancer oxalate uroliths in predisposed patients (medscape, 2015c).

The ingestion of large amounts (more than 3 to 4 L per day) of cranberry juice may result in diarrhoea and other gastrointestinal symptoms; however, trials record few adverse reactions (Jepson, Mihaljevic, and J. Craig, 2004).

Controversy exists over cranberry as a risk factor for the formation of calcium oxalate kidney stones. A case report suggested that concentrated cranberry tablets caused urinary tract stones in a man with a history of nephrolithiasis[286] (Terris, Issa, and Tacker, 2001). However, a randomised, cross-over study conducted among healthy adults found reduced oxalate and phosphate excretion, and increased urinary citrate excretion conditions unfavourable for calcium oxalate stone formation (McHarg, Rodgers, and Charlton, 2003). The amount of oxalate ingested daily from cranberry juice was approximately equivalent to 86 mg/L in the cross-over study, compared with delivery of approximately 363 mg from the concentrated cranberry tablet (McHarg, Rodgers, and Charlton, 2003), (Brinkley et al., 1981). Bioavailability of oxalate from the food source may be limited (McHarg, Rodgers, and Charlton, 2003), (Brinkley et al., 1981).

The berries and juice have few adverse reactions associated with their consumption. Large doses (more than 3 to 4 L per day) may produce gastrointestinal symptoms such as diarrhoea. Concentrated cranberry tablets may predispose patients to calcium oxalate stone formation (drugs.com, 2009e).

## Side-effects

Get emergency medical help if you have any of these signs of an allergic reaction while taking cranberry - **hives**, **difficult breathing**, **swelling of your face, lips, tongue, or throat**.

Stop using cranberry and call your doctor at once if you have -

- **continued pain or burning when you urinate**,
- **vomiting**, **severe stomach pain**, or
- signs of a kidney stone - **painful or difficult urination**, **pink or red urine**, **nausea**, **vomiting**, and waves of **sharp pain** in your side or back spreading to your lower stomach and groin.

Common side effects may include -

- **upset stomach**,
- **nausea**, and/or **vomiting**,
- **diarrhoea** (drugs.com, 2015d).

- Drinking cranberry juice products appears to be safe, although excessive amounts could cause gastrointestinal upset or diarrhoea.
- People who think they have a UTI should see a health care provider for proper diagnosis and treatment. Cranberry products should not be used to treat infection.

[286] kidney stones

- There are some indications that cranberry should be used cautiously by people who take blood-thinning drugs (such as warfarin), medications that affect the liver, or aspirin.
- Tell all your health care providers about any complementary health approaches you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care (NCCIH, 2012b).

- Atrophic gastritis, hypochlorhydria.
- Potential interaction with warfarin and increased bleeding risk.
- Potential hypersensitivity.
- No evidence for efficacy in treatment (medscape, 2015c).

## Pregnancy/Lactation

No direct evidence of safety or harm to the mother or fetus has been found. Indirect evidence suggests minimal risk in pregnancy. There were insufficient data to evaluate risk during lactation. Because of its common use, when ingested at normal food consumption amounts, cranberries are considered safe during pregnancy (Dugoua, Seely, Perri, Millis, et al., 2008).

Information is limited; however, at normal consumption dosages as food, cranberry is considered relatively safe in pregnancy. Safety during lactation is unknown (drugs.com, 2009e).

## Interactions

Cranberry is reported to interact with warfarin, based on a number of case reports. The Committee on Safety of Medicines issued a warning in 2004 against the consumption of cranberry products and juice in patients taking warfarin (csmmhpra, 2004). However, a systematic literature review[287] found no available data to suggest a clinically relevant interaction, also noting that the case reports failed to identify cranberry as the sole cause of international normalized ratio (INR) elevations (D. Q. Pham and A. Q. Pham, 2007). A number of trials have been conducted to establish the effect of cranberry on CYP-450 2C9, the enzyme responsible for the metabolism of the active S -enantiomer of warfarin. Among healthy participants, no pharmacokinetic effect on CYP2C9 was established (Greenblatt, Moltke, and Perloff, 2006). In patients with atrial fibrillation taking warfarin for 3 months, no difference in INR was found with daily

[287] provides a coherent, persuasive and updated synthesis of studies in a particular area of scientific inquiry. A critical consideration of studies is an integral part of the reviewing process. This would include an appropriate critique of methodological issues relating to the work reviewed, although these are discussed mainly with regard to the area of inquiry in general. Ultimately, systematic literature reviews should lead to new levels of understanding, conclusions and recommendations in the chosen area

intake of 250 mL cranberry juice (Z. Li, Seeram, and Carpenter, 2006). A theoretical antithrombotic[288] effect may be possible because of flavonoid action on platelet function, but this has not been demonstrated (D. Q. Pham and A. Q. Pham, 2007).

An interaction between cranberry and warfarin has been suggested in case reports; however, evidence of a causal relationship is lacking (drugs.com, 2009e).

## Warfarin (Coumadin)

Cranberry may raise the risk of bleeding, especially if you already take medications to thin the blood such as warfarin. It increases the amount of time that warfarin stays in your body. The evidence is mixed and not completely clear, so it is best to ask your doctor before you take cranberry or drink a lot of juice.

## Aspirin

Like aspirin, cranberries contain salicylic acid. If you take aspirin regularly, as a blood-thinner, for example, or if you are allergic to aspirin, you should not take cranberry supplements or drink a lot of juice.

## Other medications

Cranberry may interact with medications that are broken down by the liver. To be safe, if you take any medications, ask your doctor before taking cranberry (unknown, 2014e).

## Are there interactions with medications?

## Major

Do not take this combination.

- **Warfarin (Coumadin)** - Warfarin (Coumadin) is used to slow blood clotting. Cranberry might increase how long warfarin (Coumadin) is in the body, and increase the chances of bruising and bleeding. Be sure to have your blood checked regularly. The dose of your warfarin (Coumadin) might need to be changed (drugs.com, 2009e).

## Minor

Be watchful with this combination.

[288] reduces the formation of blood clots

- **Medications changed by the liver (Cytochrome P450 2C9 (CYP2C9) substrates[289])** - Some medications are changed and broken down by the liver. Cranberry might decrease how quickly the liver breaks down some medications. Taking cranberry along with some medications that are broken down by the liver can increase the effects and side effects of some medications. Before taking cranberry, talk to your healthcare provider if you take any medications that are changed by the liver.
  Some medications that are changed by the liver include amitriptyline (Elavil), diazepam (Valium), zileuton (Zyflo), celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), warfarin (Coumadin), and others (drugs.com, 2009e).

There are no known interactions with herbs and supplements (drugs.com, 2009e).

There are no known interactions with foods (drugs.com, 2009e).

## Available Forms

You can get cranberries fresh or frozen, and in juice and concentrate forms. Dried berries are also available as tablets or capsules. Pure cranberry juice is very sour, so most juices contain a mixture of cranberries, vitamin C, and sweeteners, which may make the juice less healthy. Look for a brand of cranberry juice that has the lowest amount of added sugar or is sugar-free (unknown, 2014e).

## Dosage

A lack of consistency in clinical trials makes dosage guidance difficult (drugs.com, 2009e).

Cranberry juice, juice concentrate, and dried extract have been extensively studied in UTIs. Doses of juice studied have ranged from 120 to 4,000 mL/day. Concentrated cranberry extract in the form of tablets is available (Kontiokari et al., 2005).

### Paediatric

Cranberry juice is considered safe for children to drink. However, there is not enough evidence to say what would be a safe dose for children who tend to get UTIs. A child with a UTI should be seen by a doctor.

[289] a substrate is a drug that is metabolized by an enzyme system (Nursinglink, 2015)

A trial in children used 5 mL/kg (up to 300 mL) daily in divided doses (Kontiokari et al., 2005).

Do not give children cranberry supplements.

- **For preventing UTIs** - 15ml/kg daily as 30% cranberry concentrate has been used (MedlinePlus, 2014c).

### Adult

- **Juice** - Studies have used 3 or more fluid oz. of pure juice per day, or about 10 oz. of cranberry juice cocktail, for preventing UTIs. Ask your doctor about the right dose for you.
- **Fresh or frozen cranberries** - 1.5 oz (unknown, 2014e).

### Prevention of UTI's

- **Juice**
  - **Cranberry juice cocktail** - 26% cranberry juice - 10–16 ounces, orally per day,
  - **Cranberry juice** - 15 ml orally, twice a day (medscape, 2015c).
  - **Cranberry juice** - 1–10 ounces per day has been used. However, the ideal dose has not yet been determined (MedlinePlus, 2014c).
- **Capsule**
  - 400 mg orally, twice a day (medscape, 2015c).

### Urinary Deodoriser for Incontinent Patients

- **Cranberry juice cocktail**
  - 3–6 ounces a day, orally (medscape, 2015c).
  - 3–6 oz per day of cranberry juice (MedlinePlus, 2014c).

### For type 2 Diabetic Patients

- Six capsules (equivalent to 240 mL cranberry juice cocktail) daily for 12 weeks. Encapsulated formulations are often taken in doses of 300–400 mg twice daily (MedlinePlus, 2014c).

## Are there safety concerns?

Cranberry is **likely safe** for most people when taken by mouth. Cranberry juice and cranberry extracts have been used safely in people. Cranberry juice is **likely safe** for children. However, drinking too much cranberry juice can cause some side effects such as mild stomach upset and diarrhoea. Drinking more than 1 litre per day for a long period of time might increase the chance of getting kidney stones.

## Special precautions & warnings

- **Pregnancy and breast-feeding** - Cranberries and cranberry juice are safe to consume during pregnancy and breast-feeding. However, do not use dietary supplements that contain cranberry products. It is not known if these are safe to use during pregnancy and breast-feeding.
- **Aspirin allergy** - Cranberries contain significant amounts of salicylic acid. Salicylic acid is similar to aspirin. Avoid drinking large quantities of cranberry juice if you are allergic to aspirin.
- **Inflammation of the stomach lining (Atrophic gastritis)** - Cranberry juice might increase how much vitamin B12 the body absorbs for people with atrophic gastritis.
- **Diabetes** - Some cranberry juice products are sweetened with extra sugar. If you have diabetes, stick with cranberry products that are sweetened with artificial sweeteners.
- **Low stomach acid (hypochlorhydria)** - Cranberry juice might increase how much vitamin B12 the body absorbs for people with low levels of stomach acid.
- **Kidney stones** - Cranberry juice and cranberry extracts contain a large amount of a chemical called oxalate. In fact, there is some evidence that some cranberry extract tablets can boost the level of oxalate in the urine by as much as 43%. Since kidney stones are made primarily from oxalate combined with calcium, healthcare providers worry that cranberry might increase the risk of kidney stones. To be on the safe side, avoid taking cranberry extract products or drinking a lot of cranberry juice if you have a history of kidney stones.

## Toxicology

Information is lacking (drugs.com, 2009e).

## Commentary

*Most research has been done with regard to cranberries and UTI's, and little research elsewhere. So there is insufficient evidence for the usage of cranberry as a herbal hormone. In other words, its a probably a waste of time and money taking it as a herbal hormone.*

Chapter 7

# D's

## Damiana

### Common Names

Damiana, Herba de la pastora, Mexican damiana, Old woman's broom, Rosemary (not to be confused with the spice Rosmarinus officinalis L.) (drugs.com, 2009f). French = Thé bourriqu, Spanish = chac-mixib, Spanish = misibcoc, Mexican = pastorcita, Bolivian = hierba del ahorcado, Guatemalan = mejorana, oreganillo, Mexican holly, damiana de Guerrero, damin, Mizibcoc.

### Latin Name

*Turnera diffusa*.

### Overview

Damiana leaves have been used as an aphrodisiac and to boost sexual potency by the native peoples of Mexico, including the Mayan Indians and is used for both male and female sexual stimulation, increased energy, asthma, depression, impotence and menstrual problems.

Damiana is a small shrub with aromatic leaves found on dry, sunny, rocky hillsides in south Texas, Southern California, Mexico, and Central America. Damiana leaves have been used as an aphrodisiac and to boost sexual potency by the native peoples of Mexico, including the Mayan Indians. The two species used in herbal healing, both of which are referred to as damiana, are Turnera aphrodisiaca and Turnera diffusa.

Historically damiana has been used to relieve anxiety, nervousness, and mild depression, especially if these symptoms have a sexual component. The herb is also used as a general tonic to improve wellness.

Damiana has also been used traditionally to improve digestion and to treat constipation, as in larger doses it is thought to have a mild laxative effect.

It is well known in southwestern cultures as a sexuality tonic and is recommended by many top herbalists. It stimulates the intestinal tract and brings oxygen to the genital area. It also increases energy levels which does a lot to restore libido and desire. In women, Damiana often restores the ability to achieve orgasm. Damiana is used primarily as an energy tonic and an aphrodisiac for both men and women.

Damiana has a dual effect. It can work quickly to stimulate the genital area by enriching the oxygen supply. Longer term use can improve sexual fitness and performance.

The libido-boosting power of damiana hasn't been tested in humans, although a liquor made from the leaves has long been used as an aphrodisiac in Mexico. In animal studies, extracts of damiana speeded up the mating behaviour of "sexually sluggish" or impotent male rats. It had no effect on sexually potent rats.

How damiana works as an aphrodisiac is currently not known. It is also claimed that when drank as a tea it has a relaxing effect not-unlike low doses of cannabis (herbwisdom, 2015f).

Damiana has both diuretic and antiseptic properties and has been used as an herbal treatment for UTIs such as bladder and urethral inflammation. This effect is partly due to the substance arbutin found in the plant, which is converted to hydroquinone (a powerful antiseptic) in the ureters.

Damiana is a mild laxative and can be useful in the treatment of constipation due to relaxed gastrointestinal muscles.

It's used in folk medicine to treat asthma and bronchitis, particularly in Indian herbal medicine (Resource, 2015h).

## Botany

Damiana is a Mexican shrub also found throughout the southern US and many parts of South America. It has small, yellow-brown aromatic leaves. The leaves are broadly lanceolate, 10 to 25 mm long with three to six teeth along the margins. The red-brown twigs are often found mixed in the crude drug along with the spherical fruits (drugs.com, 2009f).

## History

The scientific literature on the plant dates back more than 100 years when reports described its aphrodisiac effects (unknown, 1875). Damiana history began with its early use by the Maya (under the name mizibcoc) in the treatment of giddiness and loss of balance. Its primary use in the last century has been as an aphrodisiac (V. E. Tyler, 1983). Father Juan Maria

de Salvatierra, a Spanish missionary, first reported that the Mexican Indians made a drink from the damiana leaves, added sugar and drank it for its love-enhancing properties. In the 1870s, it was imported into the US as a tincture and advertised as a powerful aphrodisiac, to improve the sexual ability of the enfeebled and the aged and to provide increased activity to all the pelvic secretions. Suffice to say that in this patent medicine era, it enjoyed some success.

Damiana was admitted into the first edition of the National Formulary (NF) in 1888 as an elixir and fluid extract. However, it never made it into the US Pharmacopeia and the elixir was finally dropped from the NF in 1916. The fluid extract and the crude drug (leaves) were listed in the NF until 1947. Although some commercial companies continued to sell it to the American market, damiana had almost disappeared until the 1960s "hippy" movement brought it back into popularity.

Today, damiana has found its way into a number of herbal OTC products, in particular those claiming to induce a legal herbal "high." In the Caribbean, damiana leaves are boiled in water and the vapours inhaled for the relief of headaches. Teas are said to aid in the control of bed wetting (Eldridge, 1975).

## Properties

Mild purgative, diuretic, tonic, stimulant, hypochondriasis, aphrodisiac, alterative, aperient[290], carminative, cholagogue, emmenagogue, laxative, nervine, urinary antiseptic and yang tonic (herbwisdom, 2015f).

## Chemistry

Damiana contains from 0.5% to 1% of a complex volatile oil that gives the plant its characteristic odour and taste. Analysis of the oil has identified a low-boiling fraction composed mainly of 1,8-cineol and pinenes, but their consistent presence in all forms of the plant has been disputed (Dominquez and Hinojosa, 1976). A fraction with a higher boiling point is believed to contain thymol and a number of sesquiterpenes. In addition, the plant contains gonzalitosin, a cyanogenic glycoside and a brown amorphous, bitter substance (damianin) among other components (Leung, 1980).

The chemical composition of damiana is complex and all of the components have not been completely identified. However, the known make-up is 0.5-1% volatile oil, flavonoids, gonzalitosin, arbutin, tannin and damianin (a brown bitter substance). It also contains essential oils (containing cineol, cymol, pinene), cyanogenic glycosides, thymol and trace amounts of phosphorus (herbwisdom, 2015f).

[290] having a gentle laxative effect

The leaves contain substances like essential oil, resins, tannins, starch, arbutin, barterin and a bitter substance known as damianin (Resource, 2015h).

## Uses and Pharmacology

Damiana is reportedly an aphrodisiac and hallucinogen[291] (drugs.com, 2009f).

Reportedly has stimulant, antidepressant, thymoleptic[292], testosteromimetic[293], euphoric[294] and nervous restorative properties (medscape, 2015d).

Damiana preparations are used as an aphrodisiac, for prophylaxis[295] and treatment of sexual disturbances, for strengthening and stimulation during exertion (overwork), also for boosting and maintaining mental and physical capacity (herbalgram, 1989).

Headache, bedwetting, depression, nervous dyspepsia, atonic constipation, for prophylaxis and treatment of sexual disturbances, strengthening and stimulation during exertion, boosting and maintaining mental and physical capacity, and as an aphrodisiac (medscape, 2015d).

### Aphrodisiac

No substantive data is available to support the aphrodisiac effects of damiana. Although it has been postulated that the plant may contain the central nervous system stimulant caffeine, the aphrodisiac effect has not been attributed to any specific components. The volatile oil in damiana might be sufficiently irritating to the urethral mucous membranes to account for its so-called aphrodisiac effects. Despite containing a complex mixture of components, there is no evidence to support claims for an aphrodisiac effect (V. E. Tyler, 1983).

### Hallucinogen

Despite containing a complex mixture of components, there is no evidence to support claims for a hallucinogenic effect (drugs.com, 2009f).

---

[291] a psychoactive agent which can cause hallucinations, perception anomalies, and other substantial subjective changes in thoughts

[292] having the ability to modify a patient's mood

[293] mimics the action of testosterone

[294] having the ability to induce a state of happiness and confident well-being

[295] a measure taken to maintain health and prevent the spread of disease

## Contraindications

Contraindications have not yet been identified (drugs.com, 2009f).

## Adverse Reactions

No significant adverse effects have been reported in the literature. However, people claiming to experience damiana-induced hallucinations should be monitored closely and the possibility of ingestion of other drugs should be considered (drugs.com, 2009f).

Damiana is relatively safe in regular doses although the long-term effects of its use have not been tested. Damiana does have a traditional background as an abortifacient; therefore, pregnant women shouldn't take it. The herb's safety in children has not been tested so don't give it to children.

Damiana does have a mild hypoglycaemic effect so those on diabetes medication or those who suffer from hypoglycaemia must use this plant with caution. It may interfere with the body's absorption of iron, so monitor iron levels while on this herb (Resource, 2015h).

## Side-effects

Excessive doses may cause **insomnia** and **headache** (medscape, 2015d).

It is thought that large quantities of Damiana taken internally may cause insomnia and headaches and in some cases liver damage. However, no rigorous scientific studies have examined the effects of long-term use of this herb (herbwisdom, 2015f).

## Pregnancy/Lactation

Documented adverse effects include cyanogenetic[296] glycosides and risk of cyanide toxicity in high doses. Avoid use (C. A. Newall, L. A. Anderson, and Phillipson, 1996b).

## Interactions

None well documented.

[296] potentially poisonous cyanide radicals are found in plants in the form of cyanogenetic glycosides, in which form they are not poisonous. The glycosides may be broken down by plant enzymes or by rumen microorganisms and the material then releases its cyanide

### Efficacy

Insufficient reliable information to rate efficacy (medscape, 2015d).

### Dosage

Damiana can be administered in an infusion of the dried leaves, as a fluid extract from the leaves or a capsule of the crushed dry leaves (Resource, 2015h).

There are no recent clinical studies of damiana that provide a basis for dosage recommendations, though it has been studied in combination with other agents. Classical dosage of the leaf was 2 g.

Since the effectiveness of Damiana preparations for the claimed applications is not documented, a therapeutic administration cannot be recommended (herbalgram, 1989).

- **Infusion** - 1 cup of the infusion two to three times daily.
- **Fluid extract** - 2 to 4 mls twice daily.
- **Capsules** - 3 to 4 grams twice daily (Resource, 2015h).

### Toxicology

Research reveals little or no information regarding toxicology with the use of this product (drugs.com, 2009f).

### Commentary

*There is no viable research on damiana to establish it as a herbal hormone, and it seems to contain no recognised phytoestrogens so taking it doesn't really seem worthwhile.*

## Dill

### Common Names

Anethi herba, Anethi fructus, Anethum, dill herb, dill weed, dill seed, dilla, anise, shubit, Arabic = bisbas, Chinese = hui hsiang, Chinese = shih lo, Danish = dild, French = aneth, German = gurkenkraut, Greek = anethon, Italian = oneto, Polish = koper ogrodowy, Russian = ukrop, Spanish = anís alemán , Spanish = eneldo.

### Latin Name

*Anethum graveolens*

## Plant Description

Dill is a plant belonging to the celery family (Apiaceae) that can grow up to 40–60 cm in height. It has slender stems and alternate and finely divided, softly delicate leaves around 10–20 cm long. Leaf divisions are 1–2 mm broad, slightly broader than the similar leaves of fennel, which are thread like, but harder in texture. The flowers are white to yellow. The seeds are 4–5 mm long and 1 mm thick, and straight to slightly curved with a longitudinally ridged surface. Dill is in leaf from May to November, in flower from April to July, and the seeds ripen from July to August (Resource, 2015i).

## History

Dill has been used both as food and medicine for a very long time. The herb was already mentioned in "The Ebers Papyrus", an Egyptian papyrus of herbal medicine knowledge dating to about 1550 BC, where it was described as a remedy for flatulence, dyspepsia and constipation. The ancient Egyptians also used it in the production of cosmetics and perfumes.

In Ancient Rome, dill was a well known and widely used herb. The Roman gladiators rubbed the dill oil into their skin and they used the burned seeds on wounds to speed up healing. From the Roman Empire the herb was spread to North Europe by monks and the first European settlers took the dill plant with them to North America (Resource, 2015i).

## Plant Parts Used

Leaves, flowers, seeds. The leaves should be picked fresh, usually after the plant has reached 8.5 cm in height. The leaves are often difficult to dry successfully, and the dried leaves must be stored in closed containers in order to retain some of the flavour.

The seeds should be collected when fully mature and then spread out and air dried. An essential oil can be extracted both from the fresh leaves and from the seeds, these two oils differ slightly in terms of scent and taste (Resource, 2015i).

## Actions

Anti-spasmodic, bacteriostatic (herbalgram, 1987), (herbalgram, 1990d).

## Composition of Drug

Dill seed consists of the dried fruit of Anethum graveolens L. s.l. [Fam. Apiaceae], as well as its preparations in effective dosage.

The drug contains essential oil rich in carvone.

## Uses

Dill herb is used for prevention and treatment of diseases and disorders of the gastrointestinal tract, kidney and urinary tract, for sleep disorders, and for spasms.

The effectiveness of the claimed indications is not documented.

Used in the treatment of dyspepsia.

Dill is used as an appetiser. It is believed to stimulate peristaltic motion of the intestine and it has been used as an herbal remedy for heartburn.

It is used as an herbal remedy for insomnia. The flavonoids and vitamin-B complex which dill is rich of are believed to activate the secretion of certain enzymes and hormones which have calming effect.

Monoterpenes and flavonoids present in its essential oils are germicidal or bactericidal in nature. They can help treat diarrhoea by inhibiting microbial infections.

Dill is high in calcium which promotes healthy teeth and bones. Also, dill seeds and leaves are very good mouth fresheners due to its antimicrobial nature.

The herb is high in substances known as monoterpenes which have been shown to have anti-cancer properties.

It may help to protect the stomach lining. It has shown significant reduction of stomach acid secretions in mice, but has not yet been tested on humans for this effect.

Substances known as polyacetylenes found in the herb have been shown to have antibacterial and anti-fungal activity as well as anti-inflammatory effects. Additionally, the herb contains dietary fibre and it is a good source of the minerals manganese, iron and magnesium.

It has been thought to help lactating women increase the flow of milk.

For menstrual disorders the flavonoids in the essential oils of dill are believed to stimulate secretion of certain hormones which in turn help maintain proper menstrual cycles.

The herb is commonly added to cough, cold and flu remedies and it is speculated that it may be useful as a treatment for some types of asthma. An extract made from the seed has been used in the treatment of acid reflux, peptic ulcer, UTI and headaches.

Externally, extracts of the seeds were used to treat head lice and haemorrhoids. Furthermore, the essential oil is said to be a good remedy for earache (Resource, 2015i).

## Heartburn

Dill has been known to stimulate the lining of the oesophagus and assist with removal of acid that normally causes the burning associated with heartburn. It does not actually rid the tube of the stomach acid that comes up but rather invigorates the muscles to work a bit harder to ingest the agitating acid back into the stomach (herbwisdom, 2015g).

## Insomnia

Dill provides a healthy alternative towards relieving the body and the mind of insomnia. Certain flavonoids and vitamins that are abundant within the herb assist with speeding up the production of hormones within the body and, in turn, provide a relaxing and calming feeling (herbwisdom, 2015g).

## Stomach Ailments

Dill is well known for containing an immense amount of dietary fibre and certain flavonoids that have bactericidal tendencies. Combine this with Dill also being a key source of minerals, such as magnesium, and you have an herb that can naturally assist you with the pain and discomfort that comes with stomach ailments and diarrhoea (herbwisdom, 2015g).

## Cancer

Cancer is one of the leading causes of death in today's society. Most cancer victims will attest that when it comes to herbal supplements, Dill is high on their list in regards to its ability to ward off the spread of the disease. Dill is known to have high amounts of monoterpenes which have been documented and shown to have properties associated with attacking and limiting the growth of cancer cells within the body (herbwisdom, 2015g).

## Bone/Teeth Enhancements

Growing up in today's society, we have always been told to drink milk to build stronger bones and have healthier teeth. This consumption of milk revolves around the amount of calcium found within it. Dill also contains high amounts of calcium and is therefore considered a fantastic herbal supplement for helping strengthen the durability of bones in the human body (herbwisdom, 2015g).

### Cold/Flu Remedies

Everyone has had symptoms of the common cold, such as a runny nose or a productive cough. Dill plays a strong part in the herbal community as being a supplement added to most cold remedies to assist in reducing the amount of time a cold lingers within the body (herbwisdom, 2015g).

### Bad Breath

Components found within the structure of the dill herb have been known to assist with being a fast cure for bad breath. Dill seeds can be chewed in similar fashion to gum and breath mints and provide a health alternative for fresh clean breath that will not play a part in destroying the integrity of your teeth (herbwisdom, 2015g).

### Essential Oil

Essential Oil can also be extracted from the seeds and leaves/stem (Dillweed), and this has a wide variety of uses including: easing stomach conditions, reducing nervousness, aiding bronchial and respiratory health, to support the pancreas in reducing glucose and normalising insulin, which is obviously important for diabetics (herbwisdom, 2015g).

## Contraindications

None known.

## Side-effects

Side-effects from the consumption of dill are very rare. If the herb is consumed in high levels, there is a possibility that the skin can become extra sensitive to light and a rash may occur. If this happens during the consumption of dill or herbal supplements containing dill, consult your herbal supplement provider or your physician to determine a different approach towards including dill in your overall diet (herbwisdom, 2015g).

People with epilepsy should NOT use Dill Essential Oil (herbwisdom, 2015g).

Reports on the side effects of dill are limited. The most common side effect is dermatitis but it is considered very rare and usually only when dealing with large quantities of the live plant outdoors in the presence of ultra-violet light (Resource, 2015i).

## Interactions with Other Drugs

None known.

## Evaluation

Since the effectiveness for the claimed applications is not documented, the therapeutic administration of this herb cannot be recommended.

## Administration

Since dill is so widely used and recognised as a spice or flavouring agent, it is best to use it as that. Dill is a unique plant in that both its leaves and seeds are used as a seasoning. The green leaves are wispy and fernlike and have a soft, sweet taste.

Dried dill seeds are light brown in colour and oval in shape. The seeds are similar in taste to caraway, with a flavour that is aromatic, sweet and citrusy, and slightly bitter.

Leaves are best used fresh, while the seeds are most commonly used dried. The flowers of the dill plant are also sometimes used to flavour soups and salads. As it is also common to chew the dried seeds at any time as a breath freshener (Resource, 2015i).

Dill can be consumed in a variety of different ways. More often than not, someone will find dill as being an ingredient in a popular food dish. Dill comes across in most foods as having a sweet taste that adds a citrus-type atmosphere to most dishes. Outside of being added as an ingredient, dill seeds and oils can be found within most herbal supplement stores and are provided with directions on the amounts that can be taken on a daily basis.

Dill Essential Oil can be applied directly to the skin or inhaled (herbwisdom, 2015g).

Whole seeds for teas and other galenical preparations[297] for internal application.

## Dosage

Unless otherwise prescribed -

### Average daily dosage

- Seed, 3 g;
- essential oil, 0.1 - 0.3 g;

[297] preparations of botanical drugs

- equivalent preparations.

## Commentary

*There is insufficient evidence for Dill to be regarded as a herbal hormone. Save your money and don't take it except as part of your diet when its used as a flavouring.*

# Dong Quai

## Common names

ANgelica China, Angelica sinensis, Angelica polymorpha var. sinensis, Angelicae Gigantis Radix, Angélique Chinoise, Angélique de Chine, Chinese Angelica, Danggui, Danngui, Dong Qua, Danguia, Don Quai, Doong Quai, Female ginseng, Kara Toki, Kinesisk Kvan, Ligustilides, Radix Angelicae Gigantis, Radix Angelicae Sinensis, Tang Kwei, Tan Kue Bai Zhi, Tanggwi, Toki. Can qui, dangdanggui, dang gui, duong qui handanggui, hashyshat almalak, kara toki, langdu danggui, min-gui, Qinqui, tang-kuei, tangkuei tân qui, Women's Ginseng, Yungui, Chinese = dang qui, European = Chinese angelica, Finnish = kiinanvaeinoenputki, German = Chinesische Engelwurz, Japanese = Toki, Korean = Tanggwi, Swedish = Kinesisk angelikarot, Vietnamese = duong qui.

## Latin name

*Angelica sinensis*

## Overview

Dong Quai (Angelica sinensis) is also known as Chinese Angelica and is primarily known for it's uses in treating women's problems including lack of sexual desire, the symptoms of menopause, cramps and PMS. For this reason also commonly known "female ginseng". It aids in increasing the effects of hormones in both men and women and is widely used as an aphrodisiac. Dong Quai is particularly useful in helping to end hot flashes and menstrual cramps. It is also used as a liver tonic and in treating sciatica and shingles. It is one of the most widely consumed herbs in China, used as frequently as ginseng and liquorice. Dong quai has been used by the Chinese for more than two thousand years, as a strengthener of the heart, lung, spleen, liver and kidney meridians and as a tonic for the blood. It is traditionally characterized as a warm atmospheric energy that promotes blood circulation.

The root has earned a reputation as the "ultimate herb" for women. It is widely used among Chinese women as a fortifying daily tonic, much as Chinese men rely on ginseng. Women in other parts of the world have also discovered this 5,000 year old tradition that naturally provides balancing and normalising support for women's unique rhythms, cycles and body systems. It is not recommended during pregnancy or menstruation or for people taking blood thinning agents. Reports indicate that dong quai may lower blood pressure in some individuals.

Dong quai contains compounds that, in laboratory tests, have demonstrated activities that may translate into reduction of pain, dilation of blood vessels and stimulation as well as relaxation of uterine muscles. Animal studies suggest that dong quai may treat abnormal heart rhythm, prevent accumulation of platelets in blood vessels (contributing to plaque formation or atherosclerosis), protect the liver, promote urination, act as a mild laxative, promote sleep, fight infection and soothe ulcers. The data consists primarily of laboratory and animal studies with a few preliminary studies in people. More studies are needed to determine the herb's safety and effectiveness in humans.

Other studies suggest that dong quai offers some value when used in conjunction with other Chinese herbs, particularly black cohosh, to treat PMS. When used in combination with ginseng (Asian ginseng) and astragalus (Astragalus membranaceus), dong quai decreased symptoms of chest pain and improved exercise tolerance in a small group of people with heart disease. A series of reports published in China indicate that the use of dong quai just following a stroke demonstrated a decrease in the amount of brain damage.

It has also been indicated for constipation, migraines, pain and liver disorders though studies are lacking (herbwisdom, 2015h).

Dong quai (Angelica sinensis) root has been used for more than one thousand years as a spice, tonic, and medicine in China, Korea, and Japan. It is still used often in Traditional Chinese Medicine (TCM), where it is usually combined with other herbs. TCM practitioners often prescribe dong quai to treat women's reproductive problems, such as dysmenorrhoea, and to improve blood flow.

Dong quai is sometimes called the "female ginseng." Although there are few scientific studies on dong quai, it is sometimes suggested to relieve cramps, irregular menstrual cycles, infrequent periods, PMS, and menopausal symptoms (unknown, 2015d).

Clinical tests performed by Kaiser Permanente showed it has no oestrogenic or phytoestrogenic effects. Another component acts as a muscle relaxant, which explains why it helps ease PMS cramps for women. As a component of HRT[298], however, it is no more effective than a placebo. Dong quai is a plant. People use the root to make medicine.

[298] Hormone Replacement Therapy

## Botany

Angelica sinensis (Oliv.) Diels is synonymous with Angelica polymorpha var. sinensis (Oliv.). Three species of angelica are monographed separately in the Pharmacopoeia of the People's Republic of China : dong quai, the root of Angelica sinensis ; bai zi, the root of Angelica dahurica (Fisch.) Benth. et. Hook. f. or Angelica dahurica var. formosana (Boiss.) Shan et Yuan; and du huo, the root of Angelica pubescens Maxim. f. biserrata Shan et Yuan. In Korea, Angelica gigas Nakai is used medicinally, while in Japan, Angelica acutiloba Kitagawa is used. The European Angelica archangelic L. is used to flavour liqueurs and confections. While botanically related, the various species of Angelica, which differ in chemistry, pharmacology, and toxicology should not be confused. A molecular biology study of Angelica acutiloba may lead to efficient methods for distinguishing raw materials (A. USDA, 2009), (W. Tang and Eisenbrand, 1992), (Mizukami, 1995).

It is found growing wild in China, Korea and Japan. In China it has been cultivable for more than 1500 years, mostly in the southern and western parts of the country.

Dong quai is a member of the Umbelliferae family and is a fragrant perennial plant which can grow up to 2 metres tall, and produces white flowers in early summer. Dong quai is typically found growing in damp mountain ravines, meadows, river banks, and near the sea (Resource, 2015j).

## History

Dong quai has been used for thousands of years in traditional Chinese, Korean, and Japanese medicine and continues to be popular in China and elsewhere. It is used primarily for health issues in women and has been termed "female ginseng." It is reported to be a blood strengthener and has been used for cardiovascular conditions, inflammation, headache, infections, and nerve pain (medlineplus, 2015a). It is also used to treat a wide range of conditions including menstrual disorders and other gynaecological issues, as an analgesic in rheumatism, and in suppressing allergy symptoms. It is promoted for similar uses in the American herb market (Haines et al., 2008).

## Plant Parts Used

Root. Powdered /dried root/root slices, fluid extracts, tinctures, decoctions and dried leaf preparations are available to be taken by mouth. Topical preparations can also be used (Resource, 2015j).

## Properties

Mild laxative, warming and restorative, antiseptic, diuretic, diaphoretic, expectorant, anti-spasmodic (herbwisdom, 2015h).

## Chemistry

The chemistry of Angelica sinensis is distinct from that of other species in the genus. While coumarins have been reported from this species (Hata, Kozawa, and Ikeshiro, 1967), a comparative study of commercial dong quai products and related species (Zschocke et al., 1998) found coumarins to be lacking, while the lactone Z -ligustilide was a major constituent (Q. C. Chen, J. Lee, and W. Jin, 2007). In this study, Angelica sinensis more closely resembled Levisticum officinale in chemical composition than other species of Angelica. Thus, there is justification for terming the latter plant European dong quai. Several other lactones related to ligustilide have been found in Angelica sinensis (Sheu et al., 1987), (Hon et al., 1990), (Y. Chen, 1984). Ferulic acid and its esters were also found in Angelica sinensis. A capillary electrophoresis method for measuring ferulic acid in Angelica sinensis has been published (Ji, Y. F. Chai, and Y. T. Wu, 1999).

In contrast, the roots of Angelica dahurica were found to contain an abundance of coumarins. Imperatorin and isoimperatorin are the major constituents, with many other related compounds (eg, bergapten, phellopterin, scopoletin) reported (Okuyama et al., 1990). Ferulic acid was also detected in this species (Kwon et al., 1997).

The root of Angelica pubescens contains coumarins, but with some differences from Angelica dahurica. The simple prenylcoumarin, osthole, and the linear furocoumarins, columbianadin and columbianetin acetate, are the major constituents, while the coumarins, angelols A-H, are characteristic of the species (Kozawa et al., 1980), (Baba, Matsuyama, and Kozama, 1982).

The common polyacetylene falcarindiol has been isolated from various species of Angelica (Zschocke et al., 1998). Polysaccharides have been isolated from different species of Angelica; however, they have not been characterised sufficiently to permit comparison (Choy et al., 1994). Simple plant sterols and lipids have also been found (Tani, Fujiwara, and Kato, 1984).

## Uses and Pharmacology

Stimulate normal menstrual flow, prevent menstrual cramps.

Anaemia, constipation, dysmenorrhoea, hypertension, psoriasis, rheumatism, skin depigmentation, ulcers (medscape, 2015e).

Dong quai is widely used in the United States to treat hot flashes and other symptoms of menopause, despite a lack of clinical data.

Dong quai is used for menstrual cramps, PMS, and menopausal symptoms. It is also used orally as a "blood purifier"; to manage hypertension, infertility, joint pain, ulcers, "tired blood" (anaemia), and constipation; and in the prevention and treatment of allergic attacks. Dong quai is also used orally for the treatment of loss of skin colour (depigmentation) and psoriasis.

Some men apply dong quai to the skin of the penis as part of a multi-ingredient preparation for treating premature ejaculation.

In Southeast Asia, other Angelica species are sometimes substituted for dong quai (Angelica sinensis). Most often these include Angelica acutiloba, which is predominantly found in Japan; and Angelica gigas, which is mainly found in Korea. Although these three species are similar, the chemicals they contain are different. Don't think of these species as interchangeable.

## Cardiac

The root of Angelica sinensis contains active compounds that increase the cardiac rest period between heartbeats and relax blood pressure inside the arteries which in turn helps to increase blood flow. Dong quai may reduce spasms in the smooth muscles around the arteries which could help improve blood flow to the veins.

Animal testing indicates that dong quai reduces the formation of plaque in the blood vessel walls and the herb could therefore be relevant as a preventive agent against atherosclerosis, angina pectoris, myocardial infarction (heart attack) and hypertension. These effects are believed to be due to the substances coumarins and ferulic acid found in the root (Resource, 2015j).

## Dysmenorrhoea

In-vivo animal studies suggest that the basis for dong quai use in dysmenorrhoea lies in its action of increasing excitability of the uterus; the rhythm of contraction changed from fast, weak, and irregular to slow, strong, and more regular (W. C. Ko, 1980). It has been postulated that the anti-spasmodic effects of dong quai are related to the volatile oil constituents ligustilide, butylidenephthalide, and butylphthalide, while the uterine-stimulating effect is due to the water-soluble components (W. C. Ko, 1980). Clinical trials are lacking.

## Menstrual migraine

Among women with either menstrual migraine or simple migraine without aura, a combination preparation of soy isoflavones, black cohosh, and dong quai taken daily for 24 weeks decreased the frequency and severity of attacks (Burke, Olson, and Cusack, 2002). Dong quai has not been investigated alone for its effect in this indication.

## Menopausal vasomotor symptoms

Randomised, double-blind, placebo-controlled trials of A. sinensis as a single agent and in combination found no difference for dong quai over placebo for menopausal vasomotor symptoms (Haines et al., 2008), (Hirata et al., 1997), (Society, 2004), (D. Cheema, Coomarasamy, and El-Toukhy, 2007). No effect on endometrial thickness or on the level of estradiol or estrone[299] was found in a trial of dong quai alone. The study material was standardised for ferulic acid content (Hirata et al., 1997). In addition, Chinese traditional medicine does not recommend the use of dong quai alone, but rather in combination with other plant extracts (Society, 2004). The North American Menopause Society concludes that dong quai is no more effective than placebo and that data on oestrogenic activity are inconclusive (W. Tang and Eisenbrand, 1992).

Despite evidence that dong quai does not bind to oestrogen receptors, experiments have demonstrated the ability of A. sinensis extracts to stimulate breast cancer cells lines (MCF-7 and BT-20). Considering the lack of evidence for effect on menopausal vasomotor symptoms, dong quai should not be used by menopausal women with breast cancer (Kronenberg and Fugh-Berman, 2002b), (Haimov-Kochman, Brzezinski, and Hochner-Celnikier, 2008), (Haimov-Kochman and Hochner-Celnikier, 2005a), (C. B. Lau et al., 2005).

## Other effects

### Angiogenesis

In-vitro and in-vivo animal experiments suggest that Angelica sinensis possesses angiogenic[300] activity. Experiments on human periodontal and bone tissue have been conducted (Lam, H. C. Lin, and Lao, 2008), (H. Zhao et al., 2008), (Q. Yang et al., 2002). The clinical relevance of these findings has yet to be confirmed.

### Antiallergy

An aqueous extract of Angelica sinensis inhibited IgE-antibody production in a mouse model of atopic allergy. The extract was active orally and the activity was retained on dialysis, indicating that it was caused by high molecular weight components of the extract (C. Sung et al., 1982). The simple lactone ligustilide is thought to be a major bioactive principle of dong quai. Its antiasthmatic action was studied in guinea pigs (Tao, Ruan, and Mei, 1984).

[299] estrone is an oestrogenic hormone secreted by the ovary as well as adipose tissue

[300] of vascular origin

## Anti-inflammatory effects

Chemical constituents from related species have demonstrated anti-inflammatory effects in-vitro and in animal experiments (Kosuge, Yokota, and Sugiyama, 1985), (F. N. Ko et al., 1992), (Guh et al., 1996), (Y. Chen, H. Y. Tsai, and T. S. Wu, 1995), (J. Liu, Zschocke, et al., 1998). Histamine antagonism and analgesic properties have also been demonstrated (Y. Chen, H. Y. Tsai, and T. S. Wu, 1995), (Kimura and Okuda, 1997).

## Antioxidant

An in-vitro study demonstrated a protective effect of Angelica sinensis on hydrogen peroxide-induced endothelial cell damage (Hou et al., 2004).

## Anti-spasmodic

Ligustilide and the related butylidenephthalide and butylphthalide were found to have anti-spasmodic activity against rat uterine contractions and other smooth muscle systems. The compounds were characterised as nonspecific anti-spasmodics with a mechanism different from that of papaverine (W. C. Ko, 1980).

## Cancer

In in-vitro experiments, Angelica sinensis extracts have induced apoptosism activity against cervical and hepatocellular carcinoma and leukaemia cell lines, (Q. C. Chen, J. Lee, and W. Jin, 2007), (Chae, K. M. Park, and G. Y. Lee, 2004) and inhibitory actions against a number of tumours (W. H. Lee, T. S. Jin, and W. C. Tsai, 2006), (N. M. Tsai, S. Z. Lin, and C. C. Lee, 2005).

## CNS

The furocoumarin phellopterin has been characterized as a competitive partial agonist of central benzodiazepine receptors by gamma-aminobutyic acid (GABA) and TBPS shift assays, (Dekermendjian, Ai, and M. Nielsen, 1996) and to bind with high affinity to benzodiazepine receptors in-vitro; however, other closely related furocoumarins were weaker or inactive (Bergendorff, Dekermendjian, and M. Nielsen, 1997). The ligustilide and butylidenephthalide constituents of Japanese angelica root may exert central noradrenergic or GABA activity (K. Matsumoto, Kohno, and Ojima, 1998).

### Renal

Nephrotic syndrome has been traditionally treated with Angelica senensis and Astragalus mongholicus by Chinese practitioners. Animal models demonstrated an efficacy with these plant extracts similar to that of enalapril in preventing renal fibrosis and limiting the deterioration of renal function (H. Wang, J. Li, et al., 2004).

## Treatment

Dong quai is sometimes suggested for the following conditions -

### Menopausal symptoms

Some women say dong quai relieves symptoms such as hot flashes. Researchers are not sure whether dong quai acts like oestrogen or blocks oestrogen in the body. Studies are conflicting, and one study found that dong quai did not help to relieve menopausal symptoms (unknown, 2015d).

### Other

Dong quai has also been suggested for these conditions, although there is no good scientific evidence -

- **Amenorrhoea**
- **Heart disease** - One study suggested that a combination of dong quai, Asian ginseng (Panax ginseng), and astragalus (Astragalus membranaceus) decreased symptoms of chest pain in a small group of people with heart disease.
- **High blood pressure**
- **Premature ejaculation** - as one ingredient in a cream applied to the skin (unknown, 2015d).

## Medicinal Uses and Indications

It is considered in traditional Chinese medicine to have a warm nature and a sweet, acrid, and bitter taste. The main traditional use of dong quai is to regulate the female reproductive organs. The root is one ingredient of "four things soup", a traditionally used woman's tonic in China (Resource, 2015j).

Dong quai is used in combination with other plant extracts in Chinese traditional medicine as an analgesic for rheumatism, an allergy suppressant, and in the treatment of menstrual disorders. Dong quai and its chemical constituents possess antiasthmatic, anti-spasmodic, anti-inflammatory, and anti-coagulant properties. Clinical trials supporting traditional uses are limited. It has also been used to flavour liqueurs and confections (drugs.com, 2009g).

Few studies have investigated dong quai for use in humans. Some lab tests suggest that dong quai contains compounds that may help reduce pain, open blood vessels, and stimulate and relax the muscles of the uterus. More studies are needed to see whether dong quai works and is safe (unknown, 2015d).

Preliminary results from research conducted on animals suggests that dong quai may have strong tumour inhibitory and immune-enhancing effects. The polysaccharides found in the root might be able to increase the ability of the natural killer cells and other immune cells to destroy tumours. Researchers continue to study the potential of the herb as a treatment for cancer and HIV (AIDS).

There are indications that dong quai may also have an anti-allergic effect. Studies show that the herb could inhibit allergy-related antibodies (IgE) production.

It can hold back the development of fungi, viruses and bacteria. Pulverised roots for example been used successfully to treat shingles (herpes zoster). The herb has antibacterial effect and may be helpful to suppress the growth of various bacteria like haemolytic streptococcus, Bacillus typhi, Bacillus dysentricae and Bacillus choleraei.

There is some research on the use of dong quai for nerve pain (Resource, 2015j).

## How it works

Phytoestrogen modulate endogenous oestrogen effects; also contains coumarins (medscape, 2015e).

Dong quai root has been shown to affect oestrogen and other hormones in animals. It is not known if these same effects happen in humans.

## Contraindications

Relative contraindications in patients receiving warfarin, heparin, or other anti-coagulant/anti-platelet[301] therapy, in those with breast cancer, or in the first trimester of pregnancy (drugs.com, 2009g).

Breast cancer, endometriosis, hormone sensitive conditions, ovarian cancer, uterine cancer, uterine fibroids (medscape, 2015e).

## Adverse Reactions

Case reports exist of fever, gynaecomastia, and bleeding with concurrent warfarin use. A risk of photosensitization exists (drugs.com, 2009g).

[301] decrease platelet aggregation and inhibit thrombus formation

Furanocoumarins, such as bergapten and psoralen, have been widely studied for their photoactivated toxicity; however, only Angelica gigas (Korean angelica) has caused photodermatitis[302]. The risk of phototoxicity should be correlated with the content of specific toxic furocoumarins; in the case of Angelica sinensis, there appears to be little risk (Kronenberg and Fugh-Berman, 2002b), (Haimov-Kochman and Hochner-Celnikier, 2005a), (Hann et al., 1991).

Photodermatitis (especially A. archangelica), safrole, in essential oil, is carcinogenic, photosensitivity, potentially mutagenic (medscape, 2015e).

Fever was reported in a clinical trial (Page and Lawerence, 1999).

A case of gynaecomastia was reported, but causality is unclear (Goh and Loh, 2001). The possibility of dong quai tablet contamination has been raised (Fugh-Berman, 2003), (Kiong, 2001).

## Blood thinners (anti-coagulants and antiplatelets

Dong quai may raise the risk of bleeding, especially if you take blood thinners, such as warfarin (Coumadin), clopidogrel (Plavix), or aspirin. The same is true of using dong quai with many herbs and supplements. Talk to your doctor before taking dong quai. These are some of the herbs and supplements that may act like blood thinners -

- **Feverfew** (Tanacetum parthenium),
- **Fish oil and other omega-3 fatty acids**,
- **Garlic** (Allium sativum),
- **Ginger** (Zingiber officinale),
- **Ginkgo** (Ginkgo biloba),
- **Ginseng** (Panax ginseng),
- **Liquorice** (Glycyrrhiza glabra),
- **Chinese skullcap** (Scutellaria baicalensis),
- **Turmeric** (Curcuma longa) (unknown, 2015d).

## Hormone medications

There is not much research on using dong quai with hormone medications, such as oestrogens, progesterones, birth control pills, tamoxifen, or raloxifene (Evista). But, because dong quai may act like oestrogen in the body, you should not take it with hormone medications except under your doctor's supervision (unknown, 2015d).

[302] a form of allergic contact dermatitis in which the allergen must be activated by light to sensitise the allergic response, and to cause a rash or other systemic effects on subsequent exposure

### St. John's wort

Both Dong quai and St. John's wort can make you more sensitive to sunlight. Talk to your doctor before taking them together (unknown, 2015d).

## Side-effects

Dong quai has been associated with stomach upsets, nausea and vomiting with prolonged use. People with a known allergy to the Umbelliferae family (e.g. anise, caraway, celery, dill) should avoid it as it can cause skin rashes. It contains a group of compounds called psoralens which can increase **sensitivity in the sun**.

Dong quai contains osthole and ferulic acid which may inhibit platelet aggregation and thus should not be taken with anti-coagulants and drugs that increase the risk of bleeding. Pregnant and breast-feeding women should not take this herb (Resource, 2015j).

## Pregnancy/Lactation

Avoid use (F. J. Brinker, 1998d). Angelica sinensis, reported uterine stimulant and relaxant activity have been reported with, while a related species, Angelica archangelica L., was a reported abortifacient and affected the menstrual cycle (W. C. Ko, 1980), (drugs.com, 2009g).

DO NOT use dong quai during pregnancy. It may cause the uterus to contract and raise the risk of miscarriage. Nursing mothers should not take dong quai because no one knows if it is safe when you are breastfeeding (unknown, 2015d).

## Interactions

Warfarin, heparin, and other anti-platelet therapy due to anti-coagulant/anti-platelet action of A. sinensis (drugs.com, 2009g).

The coumarins of Angelica species have been associated with their bioactivity and toxicity; however, the low coumarin content of Angelica sinensis minimizes the significance in dong quai pharmacology. In other species of Angelica, coumarins clearly play an important role (Hoult and Payá, 1996).

Case reports of warfarin potentiation exist (Page and Lawerence, 1999); however, the mechanism for this interaction is unclear. Studies in rabbits demonstrated effects on clotting time (Page and Lawerence, 1999). Inhibition of platelet aggregation has been demonstrated in animal experiments (Page and Lawerence, 1999), (J. Liu, S. X. Xu, et al., 1989), while sodium ferulate exerted anti-platelet action in a trial of patients with ulcerative colitis (W. G. Dong, S. P. Liu, and H. H. Zhu, 2004).

The Angelica species has demonstrated photosensitization, and a theoretical interaction exists with other photosensitizers, such as St. John's wort or sulfa and quinolone antimicrobials (Scott and Elmer, 2002).

Dong quai, particularly at high doses, may make you more sensitive to sunlight and cause skin inflammation and rashes. Stay out of the sun or use sunscreen while taking dong quai (unknown, 2015d).

## Are there interactions with medications?

### Major

**Do not take this combination.**

- **Medications that slow blood clotting (anti-coagulant / anti-platelet drugs)** - Dong quai might slow blood clotting. Taking dong quai along with medications that also slow clotting might increase the chances of bruising and bleeding.
  Some medications that slow blood clotting include aspirin, clopidogrel(Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.
- **Warfarin (Coumadin)** Warfarin (Coumadin) is used to slow blood clotting. Dong quai can also slow blood clotting. Taking dong quai along with warfarin (Coumadin) can increase the chances of bruising and bleeding. Be sure to have your blood checked regularly. The dose of your warfarin (Coumadin) might need to be changed.

## Herbs and supplements that might slow blood clotting

Dong quai might slow blood clotting. Using dong quai along with other herbs that slow blood clotting might increase the risk of bleeding and bruising in some people. These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, panax ginseng, poplar, red clover, willow, and others.

## Are there interactions with foods?

There are no known interactions with foods.

## Precautions

You should not drink the essential oil of dong quai because it has a small amount of carcinogen[303].

[303] cancer causing

People who have chronic diarrhoea or abdominal bloating should not use dong quai.

People who are at risk of hormone-related cancers, including breast, ovarian, and uterine cancers, should not take dong quai because researchers are not sure if it acts like oestrogen in the body (unknown, 2015d).

## Efficacy

Controversial; apparently more effective in combination with other herbs (medscape, 2015e).

### How effective is it?

*Natural Medicines Comprehensive Database* rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

The effectiveness ratings for **Dong quai** are as follows -

#### Possibly effective for...

- **Premature ejaculation, when applied directly to the skin of the penis in combination with other herbs**. The other herbs are Panax ginseng root, Cistanches deserticola, Zanthoxyl species, Torlidis seed, clove flower, Asiasari root, cinnamon bark, and toad venom (SS Cream).

#### Possibly ineffective for...

- **Menopausal symptoms**

#### Insufficient evidence to rate effectiveness for...

- **Painful menstrual periods (dysmenorrhea)**
- **Premenstrual syndrome (PMS)**
- **High blood pressure**
- **Joint aches and pains**
- **Ulcers**
- **Anaemia**
- **Constipation**
- **Skin discolouration and psoriasis**
- **Allergies**
- **Other conditions**

More evidence is needed to rate the effectiveness of dong quai for these uses.

## Are there safety concerns?

Dong quai is possibly safe for adults when taken by mouth and when occasionally applied to the skin as an ingredient in a cream. More evidence is needed to determine its safety after prolonged or repeated use.

Dong quai can cause skin to become extra-sensitive to the sun. This might put you at greater risk for skin cancer. Wear sun block outside, especially if you are light-skinned.

Taking dong quai in large amounts for a long period of time is possibly unsafe. Dong quai contains chemicals that are considered to be a carcinogen.

## Special precautions & warnings

- **Pregnancy and breast-feeding** - Taking dong quai by mouth during pregnancy is possibly unsafe for the baby. Dong quai seems to affect the muscles of the uterus. There is also one report linking an herbal combination that contained dong quai with birth defects in a baby whose mother took the combination during the first three months of pregnancy. Don't use dong quai if you are pregnant.
  There isn't enough information about the safety of using dong quai during breast-feeding. Stay on the safe side and don't use it.
- **Hormone-sensitive conditions, e.g. breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** - Dong quai might act like oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use dong quai.
- **Protein S deficiency** - People with protein S deficiency have an increased risk of forming blood clots. There is some concern that dong quai might increase the risk of clot formation in these people because it has some of the effects of oestrogen. Don't use dong quai if you have protein S deficiency.
- **Surgery** - Dong quai can slow blood clotting. It might increase the risk of bleeding during and after surgery. Stop taking dong quai at least 2 weeks before a scheduled surgery.

## Dosage

Several forms of the plant exist and dosages vary widely: crude root extract by decoction ranges from 3 to 15 g/day; while in combination, preparations 75 mg to 500 mg may be taken up to 6 times a day; powdered root, 1 to 2 g 3 times a day; and tablets 500 mg up to 6 times a day (drugs.com, 2009g).

In a clinical trial investigating use in menopause, dong quai 4.5 g was administered daily for 24 weeks. In combination, dong quai 100 mg standardised to 1% ligustilide was similarly used daily (Burke, Olson, and Cusack, 2002), (Hirata et al., 1997), (Haimov-Kochman and Hochner-Celnikier, 2005a), (C. B. Lau et al., 2005).

- **Capsules and tablets** - 500–600 mg up to six times daily.
- **Tincture (1:5) to treat menstrual cramps** - 5–20 drops up to three times daily.
- **Tea in the form of extraction or decoction to treat anaemia and for poor blood circulation** - one cup 2 or 3 times daily (Resource, 2015j).

The following doses have been studied in scientific research -

## Applied To The Skin

- **For early orgasm in men (premature ejaculation)** - a multi-ingredient cream preparation containing Panax ginseng root, dong quai, Cistanches deserticola, Zanthoxyl species, Torlidis seed, clove flower, Asiasari root, cinnamon bark, and toad venom (SS Cream) was applied to the glans penis one hour before sex and washed off immediately before sex (MedlinePlus, 2012).

## Paediatric

You should not give dong quai to a child (unknown, 2015d).

## Adult

Researchers do not know what a safe dose is, so there is no recommended dose.

- **Dried herb (raw root)** - may be boiled or soaked in wine before consuming (unknown, 2015d).
- **Extract** - 1ml orally, three times a day or 1–2 g steeped in boiling water three times a day (medscape, 2015e).
- **Powdered herb (available in capsules)** - In one study for menopausal symptoms, people took 500 to 600 mg tablets or capsules up to 6 times daily (unknown, 2015d).
- **Tincture (1:5 w/v, 70% alcohol)** - 40 to 80 drops (equivalent to 2 to 4 mL, there are 5 mL in a tsp.), 3 times daily is one possible dosing schedule, however, individual doses will vary and it is unusual for Dong quai to be prescribed alone. It is usually part of a formula containing synergistic herbs (unknown, 2015d).
- **Menopausal symptoms** -
  - 4.5 g powder orally four times a day, OR
  - 3–4 g orally divided into three times a day with meals, OR
  - 520–1560 mg orally three times a day (medscape, 2015e).

## Toxicology

The oral LD-50 of concentrated dong quai extract has been estimated at 100 mg/kg. Intravenous administration of 1 mL/kg of the essential oil in rabbits resulted in hypotension and respiratory suppression. Phenol and certain furocoumarin groups found in dong quai have demonstrated cytotoxic properties (Q. Yang et al., 2002).

Data are limited. Chemical constituents have demonstrated cytotoxic properties (drugs.com, 2009g).

## Commentary

*There is insufficient evidence for Dong Quai to be administered as a herbal hormone, and on balance, it is better if it is not used for this purpose. However, it has a long-established recommendation for menopausal symptoms.*

## Definition

Radix Angelicae Sinensis consists of the dried roots of Angelica sinensis (C. Wong, 2015).

## Major chemical constituents

The characteristic components are the simple alkyl phthalides (ligustilide, (Z)- ligustilide, (Z)-6,7-epoxyligustilide, angelicide, (Z)-butylidenephthalide, butylphthalide, 2,4-dihydrophthalic anhydride), which are the major components of the essential oil fraction of the roots. Other characteristic components of the oil have been identified as terpenes ($\beta$-cadinene, carvacrol and cis-$\beta$-ocimene). The non-volatile constituents reported are phenylpropanoids ((E)-ferulic acid, coniferyl ferulate); benzenoids (valerophenone-o-carboxylic acid and vanillic acid); and coumarins (angelol G, angelicone and umbelliferone) (H. Y. Hsu, 1986), (D. P. Q. Zhu, 1987), (L. Z. Lin, 1998), (Terasawa, 1985). It has been shown by high-performance liquid chromatography that the major chemical constituent of the roots is ligustilide, which can account for over 5% (L. Z. Lin, 1998). Polysaccharide fractions of low relative molecular mass have also been reported (L. F. Ma, 1988), (Y. Wang and B. Zhu, 1996).

# Pharmacology

# Experimental pharmacology

## Smooth muscle contraction

Hot aqueous extracts of Radix Angelicae Sinensis stimulated smooth muscle contractions of the bladder, intestine and uterus when administered intravenously to dogs (10 g/kg body weight) (C. F. Schmidt, 1924). Intravenous administration of an aqueous or 95% ethanol extract of the roots to cats, rats and rabbits increased the strength of the contractions and tone of uterine smooth muscles (D. P. Q. Zhu, 1987). In-vitro assays demonstrated that a decoction of the roots stimulated the H[1] receptor of mouse uterus (Shi, L. Chang, and G. He, 1995). The active constituent responsible for this activity is an aqueous- and alcohol-soluble, non-volatile component, the structure of which is unknown (D. P. Q. Zhu, 1987). Conversely, ligustilide, a constituent of the essential oil of the roots, inhibited contractions of isolated uteri from various animal models (Mei, Tao, and B. Cui, 1991), (Pi, 1955). Intraperitoneal administration of ligustilide (0.14ml/kg body weight) to guinea-pigs inhibited asthmatic reactions induced by acetylcholine and histamine (Tao, 1984). Ligustilide (32.5-130.0 ţl/ml) inhibited smooth muscle contractions induced by barium sulfate, acetylcholine and histamine in isolated guinea-pig trachea (Tao, 1984).

## Antihepatotoxic activity

Intraperitoneal administration of a decoction of the roots (11ml/kg body weight) ameliorated galactosamine-induced hepatotoxicity in rats (Xiong, 1982). Ferulic acid, a constituent of the roots, protected rat liver mitochondria against damage induced by oxygen free radicals (Y. H. Lin, 1994). Intragastric pretreatment of mice with sodium ferulate (100 mg/kg body weight) daily for 10 days alleviated liver toxicity induced by paracetamol (H. Wang and Peng, 1994) and prednisolone (D. F. Wu, 1988), and bromobenzene induced liver injury (D. F. Wu and Peng, 1995).

## Cardiovascular activity

Cardiac haemodynamic studies demonstrated that intravenous administration of an aqueous root extract (2 g/kg body weight) to anaesthetized dogs increased coronary blood flow from 88 ml before administration to 128 ml (per 100g cardiac muscle/minute post-injection). Coronary vascular resistance and myocardial oxygen consumption also decreased, while the heart rate decreased or remained unchanged (Chou, 1979). An extract of the roots increased coronary blood flow in isolated guinea-pig hearts (Pen, 1981).

In animal models, both aqueous and ethanol extracts of the roots had an effect on arrhythmias induced by epinephrine, barium chloride and digitalis (Pen, 1981), (Cha, 1981). Intravenous administration of an ethanol extract of the roots (4g/kg body weight) antagonised chloroform- and epinephrine-induced arrhythmias in cats (Cha, C. C. Chien, and F. H. Lu, 1981). Ethanol extracts of the roots and ferulic acid restored normal sinus rhythm after ouabain-induced arrhythmia in isolated ventricular muscle from cats (Mei, Tao, and B. Cui, 1991). Aqueous extracts of the roots reduced the action potential amplitude and maximal upstroke velocity of the Q phase, and prolonged the effective refractory period and the duration of the action potential in guinea-pig myocardium (Z. M. Wei, 1985). Intravenous administration of an aqueous extract of the roots (50mg/kg body weight) to rabbits with ligation of the left anterior descending coronary artery provided protection against ischaemia- and reperfusion-induced myocardial dysfunction and injury (S. G. Chen, 1995). An aqueous extract of the roots bound to nitrendipine and diltiazem receptors, thereby demonstrating calcium channel blocking activity (Hon, 1990). A ligustilide dimer, isolated from the roots, inhibited [3H]nitrendipine binding to dihydropyridine-sensitive calcium channels (inhibitory concentration of 50% [IC[50]] 0.4 ţmol/l) (G. Q. Han, 1991). Since calcium channel blockers are known to have pronounced effects on the cardiovascular system, this activity may explain some of the reported effects of root extracts on the cardiovascular system.

## Antithrombotic activity

In-vitro and in-vivo studies have shown that extracts of the roots inhibit platelet aggregation and have antithrombotic activity (Mei, Tao, and B. Cui, 1991). Aqueous extracts of the roots (200 mg/ml) or ferulic acid (0.4 mg/ml) inhibited platelet aggregation induced by ADP or collagen in-vitro (Yin, 1980). A hot aqueous extract of the roots (500mg/ml) or ferulic acid (1 mg/ml) inhibited thrombin-induced platelet aggregation and release of [3H]5-hydroxytryptamine from labelled platelets in-vitro (Yin, 1980). An aqueous extract of the roots inhibited both ADP- and collagen-induced platelet aggregation when administered intravenously to rats (200 mg/ml) (Mei, Tao, and B. Cui, 1991), (Yin, 1980). The mechanism of action appears to be via inhibition of cyclooxygenase and throm-boxane A[2] synthase by ferulic acid, leading to decreased production of thromboxane A[2] (L. N. Xu, 1990). The antithrombotic activity of the drug is associated with inhibition of platelet aggregation, reduction in the concentration of plasma fibrinogen, changes in cell surface charge and a decrease in blood viscosity (Mei, Tao, and B. Cui, 1991).

Intraperitoneal administration of polysaccharides isolated from the roots increased haematopoiesis in mouse bone marrow, as determined by an increase in colony-forming units in the marrow cells (L. F. Ma, 1988), (Y. C. Chen and Gao, 1994). The polysaccharides promoted the proliferation and differentiation of haematopoietic progenitor cells in healthy and

anaemic mice (Y. Wang and B. Zhu, 1996). Results of this study indicated that the polysaccharides may enhance haematopoiesis by stimulating macrophages, fibroblasts and lymphocytes in haematopoietic and muscle tissue to secrete haematopoietic growth factor (Y. Wang and B. Zhu, 1996).

## Clinical pharmacology

### Menstrual disorders

Although there are a number of case reports concerning the clinical use of Radix Angelicae Sinensis in the treatment of amenorrhoea and dysmenorrhoea, these studies were published between 1899 and 1910 (Mueller, 1899), (Langes, 1901), (Palm, 1910), (P. Buck, 1899). Randomised, controlled clinical trials are needed to confirm these observations. In these early case studies, female patients were treated with 5 ml of a fluid extract of the roots three times daily before meals for 1 week before menstruation. The treatment relieved premenstrual pain and induced menstrual flow in most cases. No abortifacient activity was observed in two pregnant women treated with the same fluid extract (Mueller, 1899). In other studies, the fluid extract was used for the treatment of dysmenorrhoea in nulliparous women, and of severe bleeding in multiparous women. Administration of 5 ml of the fluid extract three times daily for 1 week before menstruation was effective in decreasing menstrual pain and chronic endometritis (Langes, 1901). Successful treatment of amenorrhoea and dysmenorrhoea in female patients was further reported after administration of the same fluid extract (5 ml, three times daily) (Palm, 1910), (P. Buck, 1899). In another report, 112 women with dysmenorrhoea were treated for 3–7 days with ligustilide dimer isolated from the roots. The efficacy rate was 77%. Minor side-effects were **nausea** and **dizziness**, which disappeared after the treatment stopped (unknown, 1996a).

### Smooth muscle contraction

Decoctions of the roots reportedly stimulated uterine smooth muscle in female patients, but the doses used and the conditions being treated were not stated (H. M. Chang and But, 1986). A decoction of the roots lowered whole blood viscosity after administration to six patients (Terasawa, 1985).

## Medicinal uses

- **Uses supported by clinical data** - None. Although Radix Angelicae Sinensis has been alleged to be useful for the treatment of menopausal symptoms, a randomised, placebo-controlled clinical trial concluded that 4.5 g of the root daily for 24 weeks did not alleviate menopausal symptoms, such as hot flushes (Hirata, 1997).

- **Uses described in pharmacopoeias and in traditional systems of medicine** - Treatment of menstrual disorders such as irregular menstruation, amenorrhoea and dysmenorrhoea (C. Wong, 2015), (H. Y. Hsu, 1986), (Mueller, 1899), (Langes, 1901), (Palm, 1910), (P. Buck, 1899), (H. M. Chang and But, 1986). As an analgesic for symptomatic treatment of rheumatic arthralgia, abdominal pain and in the management of postoperative pain (C. Wong, 2015), (Mei, Tao, and B. Cui, 1991). Treatment of constipation (C. Wong, 2015), anaemia (C. Wong, 2015), (Mei, Tao, and B. Cui, 1991), chronic hepatitis and cirrhosis of the liver (Mei, Tao, and B. Cui, 1991).
- **Uses described in folk medicine, not supported by experimental or clinical data** - Treatment of dehydration, lumbago, abnormal menstruation, menopausal symptoms (including hot flushes), hypertonia and nervous disorders (P. Buck, 1899), (J. A. Duke and Ayensu, 1985).

## Contraindications

Radix Angelicae Sinensis should not be administered to children or patients with diarrhoea, haemorrhagic diseases or hypermenorrhoea, and should not be used during pregnancy or lactation (D. P. Q. Zhu, 1987).

## Adverse reactions

No adverse reactions were reported in 40 people who received an aqueous root extract by intravenous administration (240 ml/person) for 30 days (H. M. Chang and But, 1986).

## Side-effects

Oral administration of Radix Angelicae Sinensis is generally regarded as having few side-effects; however, **headaches** may occur in sensitive individuals (Hirata, 1997), (H. M. Chang and But, 1986).

## Precautions

- **Pregnancy: teratogenic effects** - See Contraindications.
- **Pregnancy: non-teratogenic effects** - See Contraindications.
- **Nursing mothers** - See Contraindications.
- **Paediatric use** - See Contraindications.

## Interactions

Decreased prothrombin times were reported in rabbits that received both a single subcutaneous dose of warfarin (2 mg/kg body weight) and a repeated oral dose of Radix Angelicae Sinensis (2g/kg body weight twice daily for 3 days) (Lo, 1995). Therefore, patients receiving anti-coagulant therapy should be advised against taking Radix Angelicae Sinensis without medical supervision.

## Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; or carcinogenesis[304], mutagenesis and impairment of fertility.

## Dosage forms

Powdered crude drug and fluid extracts (D. P. Q. Zhu, 1987). Store in an airtight container in a cool, dry place protected from moisture (C. Wong, 2015).

## Dosage

(Unless otherwise indicated)

Daily dosage: 4.5–9 g crude drug (C. Wong, 2015), (WHO, 2004).

## Commentary

*There is no evidence to show the usage of Radix Angelicae Sinensis as a 'herbal hormone', so I would suggest saving your money.*

[304] the actual formation of a cancer, whereby normal cells are transformed into cancer cells

Chapter 8

# F's

## Fennel

### Common Names

Common fennel, sweet fennel, bitter fennel, carosella, Florence fennel, finocchio, garden fennel, large fennel, wild fennel. Arabic = bisbas, Chinese = hui xiang, French = fenouil, German = Fenchel, Italian = finocchio commune, Japanese = uiky, Portuguese = funcho, Spanish = hinojo, Welsh = ffennigl.

### Latin Name

*Foeniculum vulgare Mill*

Rich in phytoestrogens, Fennel is often used for colic, wind, irritable bowel, kidneys, spleen, liver, lungs, suppressing appetite, breast enlargement, promoting menstruation, improving digestive system, milk flow and increasing urine flow. Fennel is also commonly used to treat amenorrhoea, angina, asthma, anxiety, depression, heartburn, water retention, lower blood pressure, boost libido, respiratory congestion, coughs and has been indicated for high blood pressure and to boost sexual desire.

Fennel is also commonly used to treat amenorrhoea, angina, asthma, heartburn, high blood pressure and to boost sexual desire. Fennel is a mild appetite suppressant and is used to improve the kidneys, spleen, liver and lungs.

Fennel is an effective treatment for respiratory congestion and is a common ingredient in cough remedies.

It is also used for cancer patients after radiation and chemotherapy treatments to help rebuild the digestive system. Fennel relaxes the smooth muscle lining the digestive tract (making it an anti-spasmodic). It also helps expel wind.

It is a tested remedy for wind, acid stomach, gout, cramps, colic and spasms. Fennel seed ground and made into tea is believed to be good for snake bites, insect bites or food poisoning. Excellent for obesity. It increases the flow of urine. It is gargled for hoarseness and sore throats (herbwisdom, 2015i).

## Botany

Fennel (synonyms Foeniculum officinale All., Anethum foeniculum) is an herb native to southern Europe and Asia Minor. It is also cultivated in the United States, Great Britain, and temperate areas of Eurasia. All parts of the plant are aromatic. When cultivated, fennel stalks grow to a height of approximately 1 metre. Plants have finely divided leaves composed of many linear or awl-shaped segments. Grayish compound umbels bear small, yellowish flowers. The fruits or seeds are oblong ovals about 6 mm long and are greenish or yellowish brown in color with 5 prominent dorsal ridges. The seeds have a taste resembling that of anise. Besides F. vulgare, Foeniculum dulce (carosella) is grown for its stalks, while Foeniculum vulgare variety azoricum Thell. (finocchio) is grown for its bulbous stalk bases. A number of subspecies have been identified, adding to the potential confusion surrounding the terminology of these plants.

## History

According to Greek legend, man received knowledge from Mount Olympus in the form of a fiery coal enclosed in a stalk of fennel. The herb was known in the ancient Chinese, Indian, Egyptian, and Greek civilizations, and the Roman scholar Pliny (AD 61-113) recommended it for improving eyesight. The name foeniculum is from the Latin word for fragrant hay. During the Middle Ages, wealthy people routinely added the seed to fish and vegetable dishes, while the poor reserved its use for fasting days as an appetite suppressant. The plant was introduced to North America by Spanish priests, and the English brought it to their early settlements in Virginia (I. Dobelis, 1986). All parts of the plant have been used for flavourings, the stalks have been eaten as a vegetable, and the seeds have served as a traditional carminative. Fennel has been used to flavour candies, liqueurs, medicines, and food; its use is especially favoured for pastries, sweet pickles, and fish. The oil can be used to protect stored fruits and vegetables against growth of toxic fungi (J. Duke, 1985). Beekeepers have grown it as a honey plant (I. Dobelis, 1986). It is a purported antidote to poisonous herbs, mushrooms, and snakebites, (Loewenfeld and Back, 1974) and it is also thought to be useful in treating gastroenteritis and indigestion, in stimulating lactation, as an expectorant, and as an emmenagogue (J. E. Meyer, 1934). Tea made from crushed fennel seeds has been used as an eyewash (I. Dobelis, 1986). Powdered fennel is said to drive fleas away from kennels and stables (J. Duke, 1985).

## Properties

Warming, carminative, anti-spasmodic, antidepressant, promotes milk-flow in nursing mothers, stomachic, pectoral, diuretic, diaphoretic, aromatic, antimicrobial, analgesic, antipyretic (herbwisdom, 2015i).

## Chemistry

Fennel seeds contain between 3% and 6% of an essential oil and approximately 20% of a fixed oil composed of petroselinic acid, oleic acid, and tocopherols. The essential oils of sweet and bitter fennel contain up to 90% trans-anethole, up to 20% fenchone, and small amounts of limonene, camphor, alpha-pinene, and about 6 additional minor volatile compounds (B. M. Lawrence, 1979). Sweet fennel contains derivatives of caffeic acid and hydroxybenzoic acid (Schmidtlein and K. Herrmann, 1975). The fruit (seeds) and leaves contain a number of flavonoid compounds, including quercetin 3-glucuronide, isoquercetin, kaempferol 3-glucuronide, and kaempferol 3-arabinoside. Low concentrations of isorhamnetin glycosides are found in the leaves (Kunzemann and K. Herrmann, 1977).

## Uses and Pharmacology

Colic, wind, irritable bowel, increase urine flow, breast enlargement, promotes menstruation, improves digestive system, improves milk flow, anxiety, depression, arthritis, water retention, appetite suppressant, amenorrhoea, angina, asthma, heartburn, lower blood pressure, boost libido, respiratory congestion, coughs (herbwisdom, 2015i).

Fennel has been used as a flavouring agent, a scent, and an insect repellent, as well as an herbal remedy for poisoning and gastrointestinal conditions. It has also been used as a stimulant to promote lactation and menstruation. However, clinical evidence to support the use of fennel for any indication is lacking (drugs.com, 2014a).

Treatment of infants and nursing children suffering from colic and dyspeptic disease. Also used as a digestive aid, cough and sore throat, reduces dysmenorrhoea, increase milk secretion, promotes menstruation, facilitate birth, alleviate the male andropause[305] symptoms, and increases libido, anti-inflammatory, analgesic and antioxidant properties (medscape, 2015f).

[305] also colloquially known as the 'male menopause', and is thought to be the result of a gradual drop in testosterone

## Stimulant to promote lactation and menstruation

As an herbal medicine, fennel is reputed to increase milk secretion, promote menstruation, facilitate birth, ease the male andropause, and increase libido. These supposed effects led to research on fennel for the development of synthetic oestrogens during the 1930s. The principal oestrogenic component of fennel was originally thought to be anethole, but it is now believed to be a polymer of anethole, such as dianethole or photoanethole (Albert-Puleo, 1980a).

### Animal data

An acetone extract of Foeniculum vulgare seeds had oestrogenic effects on the genital organs of male and female rats (Malini et al., 1985).

### Clinical data

There are no clinical data regarding the use of fennel as a stimulant to promote lactation and menstruation.

## Acaricidal activity

### Animal data

Oil derived from Foeniculum vulgare fruit demonstrated acaricidal[306] activity against Dermatophagoides farinae and Dermatophagoides pteronyssinus (house dust mites). The median lethal dose LD-50 for the oil was 119 and 103 mg/m$^2$ for D. farinae and D. pteronyssinus , respectively.

Twelve volatile compounds were identified from the oil of Foeniculum fruits. The main constituents were trans-anethole (53.2%), anisaldehyde (0.7%), beta-asarone (0.9%), beta-caryophyllene (1.1%), p -cymene (3.1%), estragole (12.7%), (+) fenchone (14.2%), d -limonene (0.7%), 1,5,8- p -menthatriene (0.6%), alpha-pinene (0.8%), gamma-terpinene (0.7%), and thymol (1.4%). The compound most toxic against both species was p -anisaldehyde. Further research is needed to determine any safety issues for the use of F. vulgare in humans (H. S. Lee, 2004).

### Clinical data

There are no clinical data regarding the use of fennel for acaricidal activity.

[306] a pesticide that kills ticks and mites

## Repellent activity

### Animal data

The repellent activity of constituents identified in Foeniculum vulgare against hungry female Aedes aegypti mosquitoes was compared with N,N-diethyl-m-toluamide (DEET) using skin and patch tests. With patch testing, responses varied according to the compound and dose. Fenchone caused 94% and 82% repellency at 0.01 and 0.005 mg/cm$^2$. ( E )-9-octadecenoic acid gave 91% repellency at 0.01 mg/cm$^2$ and 73% repellency at 0.005 mg/cm$^2$. At a dose of 0.2 mg/cm$^2$, the repellent effects of a fenchone skin test were 100% and 32% with ( E )-9-octadecenoic acid. The efficacy for fenchone was only 30 minutes, compared with more than 1 hour with DEET (D. H. Kim et al., 2002).

### Clinical data

There are no clinical data regarding the use of fennel for mosquito repellent activity.

## Anti-inflammatory effects

### Animal data

In mice, a Foeniculum vulgare fruit methanol extract at a dose of 200 mg/kg caused inhibition of paw oedema (69%). Ear oedema was also reduced by 70%. These results suggest that Foeniculum vulgare fruit methanolic extract may act on the cyclooxygenase and lipoxygenase pathways (E. M. Choi and J. K. Hwang, 2004).

### Clinical data

A study compared the effect and potency of mefenamic acid and an extract of fennel (2% concentration) for the treatment of primary dysmenorrhoea in 30 women. Mefenamic acid was more potent than fennel on the second and third days of menstruation($P \leq 0.05$). However, on the other days, the difference was not significant. With the doses prescribed, no complications were reported in the mefenamic acid treatment cycles (250 mg every 6 hours). However, 5 participants (16.6%) withdrew from the study because of fennel's odour, and one subject reported a mild increase in the volume of her menstrual flow during the fennel treatment cycle (Namavar Jahromi, Tartifizadeh, and Khabnadideh, 2003).

## Enhancement of transdermal drug delivery

### Animal data

In animal studies, pretreatment of the skin with several essential oils increased the flux values of trazodone. Pretreatment with a solution containing 10% fennel oil in propylene glycol showed an enhancement ratio of 9.25 compared with the control. The incorporation of fennel in the transdermal device also produced an increase in the flux of trazodone but less of an increase than when the skin was pretreated (M. K. Das, Bhattacharya, and Ghosal, 2006).

### Clinical data

There are no clinical data regarding the use of fennel for enhancement of transdermal drug delivery.

## Other uses

In a randomised, placebo-controlled, single-blinded[307], cross-over study of 20 patients with chronic constipation, use of a tea containing Foeniculum vulgare, Sambucus nigra, Cassia augustifolia, and Pimpinella anisum was associated with improvements in colonic transit time as well as number of bowel evacuations, with the latter effects beginning during the second day of therapy (P. D. Picon, R. V. Picon, and A. F. Costa, 2010).

A systematic review suggests a potential role for fennel in the management of infantile colic symptoms (R. Perry, K. Hunt, and Ernst, 2011).

In a rabbit model, Foeniculum vulgare exerted oculohypotensive effects in both normotensive and glaucoma-induced models (R. Agarwal, S. K. Gupta, et al., 2008).

The chief component of fennel, anethole, had anti-carcinogenic[308] and anti-inflammatory effects through modulation tumour necrosis factor-induced cellular processes (Aggarwal et al., 2008). In a murine[309] model, the tumour incidence was lower in mice with skin and forestomach papillomagenesis treated with fennel, suggesting a chemopreventive effect (B. Singh and Kale, 2008).

[307] describes a study in which either the investigator or the participant, but not both of them, is unaware of the nature of the treatment the participant is receiving

[308] pertaining to a substance or device that neutralises the effects of a cancer-causing substance

[309] pertaining to or affecting mice or rats

In a murine model, fennel seed methanolic extract had anticancer effects against a breast cancer cell line (MCF7) and liver cancer cell line (HepG-2). Additionally, antitumour effects occurred through modulation of lipid peroxidation (Mohamad, El-Bastawesy, and Abdel-Monem, 2011).

The volatile oil of fennel increases the phasic contraction of ileal and tracheal smooth muscle in guinea pigs. The effect was generally greater with ileal muscle (Reiter and Brandt, 1985b). Administration of the volatile oil to rats has exacerbated experimentally induced liver damage (Gershbein, 1977b).

Oil extracted from Foeniculum vulgare has a protective effect against the toxicity induced by carbon tetrachloride in rat livers. Although the responsible compound has not been identified, d -limonene and beta-myrcene have previously been shown to affect the liver (Ozbek, Ugras, and Dülger, 2003).

Fennel has demonstrated inhibitory effects on the growth of Bacillus amyloliquefaciens (Ozcan, Sagdic, and Ozkan, 2006). Bacteriostatic effects against Escherichia coli, Staphylococcus epidermidis, and Saccharomyces cerevisiae have also been demonstrated (Schelz, Molnar, and Hohmann, 2006). In an in-vitro study, Foeniculum vulgare exerted anti-fungal effects against Candida albicans (Pai et al., 2010). Additionally, the essential oil and hexane extract of Florence fennel and anethole exerted antimicrobial effects against probiotic bacteria (Cetin, Ozer, and Cakir, 2010).

Fennel essential oil inhibited contraction of an isolated uterus that was induced by oxytocin and prostaglandin E [2]. The optimum dose of fennel essential oil was 100 mg/mL. Fennel essential oil may have a mechanism of action similar to that of diclofenac, although the exact mechanism of action of the oil is unknown (Ostad, Soodi, et al., 2001).

Foeniculum vulgare fruit methanolic extract may have immunosuppressive properties. Antiallergic activity (type IV) was tested using 2,3-dinitrofluoro-benzeneinduced contact hypersensitivity reactions. Foeniculum vulgare fruit methanolic extract showed an inhibitory effect (L. X. Xu, A. R. Liu, and X. Q. Zhang, 1987).

Fennel inhibited rat lens and human recombinant aldose reductase; therefore, it may have a potential role in the management of diabetic complications (Saraswat et al., 2008).

Fennel essential oil and anethole exerted antithrombotic effects in an experimental model in guinea pig plasma. Specifically, anti-platelet effects were found against arachidonic acid-, collagen-, ADP-, and U46619-induced aggregation. In rat aorta, fennel essential oil and anethole exerted nitric oxide-dependent vasorelaxation (Tognolini et al., 2007). Some data suggest a possible diuretic effect with fennel (C. I. Wright et al., 2007).

Fennel has been shown to be effective in the treatment of hirsutism in women (Javidnia et al., 2003).

## How it works

Oral administration (200 mg/kg) of fruit methonolic extract -

- significantly increase plasma superoxide dismutase and catalase activity and HDL cholesterol levels,
- inhibitory effect against acute and subacute[310] inflammatory diseases and type IV allergic reaction,
- showed central analgesic effect (medscape, 2015f).

- **Fennel seed oil** - reduces intestinal spasms and increases motility of small intestine,
- **Hepatoprotection** - inhibits hepatotoxicity by decreasing levels of aspartateaminotransferase (AST), alanineaminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin (medscape, 2015f).

## Efficacy

**Colic** - A clinical trial showed breast-fed infants with colic had decreased crying time.

Insufficient reliable information about effectiveness for other uses (medscape, 2015f).

## Contraindications

Hypersensitivity to carrots, celery or mugwort. Concomitant antibiotics (medscape, 2015f).

## Cautions

If you are pregnant or breastfeeding, then seek your doctors advice.

## Adverse Reactions

Fennel may cause photodermatitis, contact dermatitis, and cross reactions. The oil may induce reactions, such as hallucinations and seizures. Poison hemlock may be mistaken for fennel (drugs.com, 2014a).

Ingestion of fennel's volatile oil may induce nausea, pulmonary oedema, seizures, and vomiting (Marcus and Lichtenstein, 1979). One case report describes a 28-year-old woman with well-controlled epilepsy who experienced a generalised tonic-clonic seizure, remaining unconscious for 45 minutes, and involuntary diarrhoea (Skalli and Soulaymani Bencheikh, 2011). Laxative and cholagogic properties have also been described

[310] This means that the symptom or illness is not yet chronic but has passed the acute phase

(Cuzzolin, Zaffani, and Benoni, 2006). The oil's therapeutic use has occasionally induced epileptiform[311] madness and hallucinations (J. Duke, 1985). The principal hazards with fennel itself are photodermatitis and contact dermatitis. Some individuals exhibit cross-reactivity to several species of Apiaceae, characteristic of the "celery-carrot-mugwort-condiment" cross-reactivity syndrome (Wüthrich and Hofer, 1984). Rare allergic reactions have been reported following ingestion of fennel.

Four case reports suggest that fennel tea given to infants for prolonged periods of time resulted in premature thelarche[312] in girls. All 4 subjects had serum estradiol levels 15 to 20 times higher than normal values for their ages. After stopping the ingestion, the premature thelarche resolved within 3 to 6 months (Türkyilmaz et al., 2008). A survey of fennel samples in Italy found viable aerobic bacteria, including coliforms, faecal streptococci, and Salmonella species, suggesting the plant may serve as a vector of infectious gastrointestinal diseases (Ercolani, 1976).

Breathing problems, tightness of chest/throat, chest pain, nausea and vomiting, skin hives, rash, itchy or swollen skin, mild increase in menstrual flow, sun sensitivity, seizures (medscape, 2015f).

## Side-effects

Get emergency medical help if you have any of these signs of an allergic reaction - **hives**; **difficult breathing**; **swelling of face, lips, tongue, or throat**.

Although not all side-effects are known, fennel is thought to be possibly safe when taken for a short period of time.

Stop using fennel and call your doctor at once if you have - **severe skin redness**, **itching**, **swelling**, or **rash**.

**Mild rash**, **itching** (Drugs.com, 2014).

## Pregnancy/Lactation

There are documented adverse reactions and emmenagogue effects. Avoid use (F. J. Brinker, 1998e), (Arao et al., 1997).

[311] resembling epilepsy or its manifestations

[312] the onset of secondary (postnatal) breast development

## Interactions

One study suggests the constituent 5-methoxypsoralen contained in fennel has the ability to inhibit cytochrome P450 3A4 (Zaidi, Kadota, and Tezuka, 2007). Therefore, cautious use of concomitant medications that require this isoenzyme as substrates is warranted.

## Dosage

Fennel seed and fennel seed oil have been used as stimulant and carminative agents in doses of 5 to 7 g and 0.1 to 0.6 mL, respectively (L. X. Xu, A. R. Liu, and X. Q. Zhang, 1987).

### Daily dosage

0.1–0.6 ml, equivalent to 0.1–0.6 g of herb.

#### Equivalent preparations

- Fennel honey syrup with 0.5 g fennel oil/kg
- 10–20 g fennel syrup or honey,
- 5–7 g herb,
- 5–7.5 g compound fennel tincture (herbalgram, 1991a).

- **Tea** - 1–2 g crushed seed in 150 mL boiling water (medscape, 2015f).
- **Tincture** - 5–7.5 g/day orally (medscape, 2015f).
- **Oil** - 0.1–0.6 mL; for no longer than 2 weeks (medscape, 2015f).
- **Capsules** - Take 1–2 caps (480–960 mg) three times a day orally, preferably with food (medscape, 2015f).

### Mode of Administration

Essential oil and galenical preparations for internal use (herbalgram, 1991a).

### Duration of Administration

Unless otherwise advised by a physician or pharmacist, you should not consume fennel oil for an extended period (several weeks).

Note: Fennel syrup, fennel honey: Diabetics must consider sugar content of bread exchange units according to manufacturer's information (herbalgram, 1991a).

**Pregnancy** - do not use fennel preparations other than fennel honey and fennel seed infusions.

**Children** - use only fennel honey

Do not use Fennel for a long time or in large quantities (medscape, 2015f).

## Toxicology

Fennel oil was genotoxic in the Bacillus subtilis DNA-repair test (Sekizawa and Shibamoto, 1982b). Estragole, which is present in the volatile oil, caused tumours in animals. A serious hazard is that poison hemlock can easily be mistaken for fennel. Hemlock contains highly narcotic coniine, and a small amount of hemlock juice can cause vomiting, paralysis, and death (Loewenfeld and Back, 1974).

Animal studies have demonstrated toxic effects of fennel essential oil on fetal cells. However, no evidence of teratogenicity was seen (Ostad, Khakinegad, and Sabzevari, 2004).

No pathological toxicity was seen in the organs of dead animals, indicating that death may be caused by the effects of metabolite imbalance or nervous system toxicity. The LD-50 was 1,326 mg/kg (Ostad, Soodi, et al., 2001).

In a murine model, fennel seed methanolic extract at doses of 100mg/kg did not result in any deaths. However, doses up to 500 mg/kg were associated with adverse effects, including loss of appetite and piloerection; a higher mortality rate was noted at 1,000 mg (Mohamad, El-Bastawesy, and Abdel-Monem, 2011).

### Commentary

*Rather worryingly, Poison Hemlock is often mistaken for Fennel! Also the fact that Italian Fennel samples were contaminated with viable aerobic bacteria, as it suggests that the plant may serve as a carrier of infectious gastric diseases. Fennel is reputed to have oestrogenic properties but there is no clinical evidence that backs it up. Therefore, save your money!*

# Fenugreek

## Common names

Fenugreek seed, Alhova, Bird's Foot, Greek Clover, Greek Hay, Hu Lu Ba, Methi, Trigonella. Arabic = Hulbah, Chinese = Hu lu ban, French = Fenugrec, French = Foin grec, German = Bockshornklee, Italian = Fieno greco, Portuguese = Fenacho, Portuguese = Feno greco, Spanish = Alholva, Spanish = Fenogreco, Swedish = Bockhornsklover.

## Latin name

*Trigonella foenum-graecum*

## Indicated for

Fenugreek has a long history as a breast enlarger and contains diosgenin which is used to make synthetic oestrogen. It has been found to promote the growth of new breast cells and increase the size and fullness of the breasts. Of all the herbs used for breast enlargement fenugreek has the highest concentrations of the effective plant compounds. Diosgenin, a steroid sapogenin is the starting compound for over 60% of the total steroid production by the pharmaceutical industry. Other sapogenins found in fenugreek seed include yamogenin, gitogenin, tigogenin, and neotigogens.

While Fenugreek is considered the finest herb for enhancing feminine beauty it also aids in sexual stimulation, balances blood sugar levels, and contains choline which aids the thinking process. Fenugreek has been the focus of several studies concerning the treatment of diabetes and the prevention of breast cancer. Its ability to balance hormone levels aids in treating PMS and menopause. Its antioxidants slow ageing and help prevent disease.

The plant has also been employed against bronchitis, fevers, sore throats, wounds, swollen glands, skin irritations, diabetes, ulcers, and in the treatment of cancer. Fenugreek has been used to promote lactation and as an aphrodisiac.

Fenugreek contains an amino acid called 4-hydroxyisoleucine, which appears to increase the body's production of insulin when blood sugar levels are high.

Higher insulin production may decrease the amounts of sugar that stay in the blood for many individuals. In some studies of animals and humans with both diabetes and high cholesterol levels, fenugreek lowered cholesterol levels as well as blood sugar levels.

However, no blood-sugar lowering effect was seen in non-diabetic animals. Similarly individuals with normal cholesterol levels showed no significant reductions in cholesterol while taking fenugreek.

Some evidence suggests that fenugreek may also have other medical uses. It may reduce the amounts of calcium oxalate in the kidneys. Calcium oxalate often contributes to kidney stones. In animal studies, fenugreek also appeared to lessen the chance of developing colon cancer by blocking the action of certain enzymes.

Topically, the gelatinous texture of fenugreek seed may have some benefit for soothing skin that is irritated by eczema or other conditions. It has also been applied as a warm poultice to relieve muscle aches and gout pain (herbwisdom, 2015j).

Fevers, sore throats, wounds, swollen glands, skin irritations, ulcers, muscle aches and gout pain.

## Botany

A member of the bean family, fenugreek grows as an erect annual with long, slender stems reaching 30 to 60 cm in height. The plant bears grey-green, tripartite, toothed leaves. White or pale yellow flowers appear in summer and develop into long, slender, sword-shaped seed pods with a curved, beak-like tip. Each pod contains about 10 to 20 small, yellowish-brown, angular seeds. These are dried to form the commercial spice. The plant thrives in full sun on rich, well-drained soils and has a spicy odour that remains on the hands after contact.

## History

The herb has been used for centuries as a cooking spice in Europe and remains a popular ingredient in pickles, curry powders, and spice mixtures in India and Asia. In folk medicine, fenugreek has been used in the treatment of boils, cellulitis, and tuberculosis. It was a key ingredient in a 19th century patent medicine for dysmenorrheal and postmenopausal symptoms, "Lydia Pinkham's Vegetable Compound"; it also has been recommended for the promotion of lactation. Fenugreek seeds have been used as an oral insulin substitute, and seed extracts have been reported to lower blood glucose levels (Madar and A. H. Stark, 2002). The maple aroma and flavour of fenugreek has led to its use in imitation maple syrup.

The first recorded use of fenugreek is described on an ancient Egyptian papyrus dated to 1500 B.C. Historically, fenugreek was used for a variety of health conditions, including menopausal symptoms and digestive problems. It was also used for inducing childbirth, and the seed is commonly used in cooking (drugs.com, 2014b).

## Properties

Antioxidant, carminative, demulcent, expectorant, laxative, and stomachic.

## Chemistry

The leaves contain at least seven saponins, known as graecunins. These compounds are glycosides of diosgenin (Varchney and Jani, 1979). Seeds contain 0.1% to 0.9% diosgenin and are extracted on a commercial basis (Sauvaire and Baccou, 1978), (Elujoba and Hardman, 1987). Plant tissue cultures from seeds grown under optimal conditions have been found to produce as much as 2% diosgenin with smaller amounts of gitongenin and trigogenin. The seeds also contain the saponin fenugrin B (H. Gangrade,

Mishra, and Kanshal, 1979). Several coumarin compounds have been identified in fenugreek seeds as well as a number of alkaloids (eg, trigonelline, gentianine, carpaine). A large proportion of the trigonelline is degraded to nicotinic acid and related pyridines during roasting. These degradation products are, in part, responsible for the flavour of the seed. The seeds also yield as much as 8% of a fixed, foul-smelling oil.

The C-glycoside flavones vitexin, vitexin glycoside, and the arabinoside isoorientin have been isolated from the plant (Adamska and Lutomski, 1971). Three minor steroidal sapogenins also have been found in the seeds: smilagenin, sarsapogenin, and yuccagenin (R. K. Gupta, Jain, and Thakur, 1986).

The mucilages of the seeds of several plants, including fenugreek, have been determined and their hydrolysates analysed (Karawya et al., 1980). Fenugreek gel consists chiefly of galactomannans characterized by their high water-holding capacity. These galactomannans have a unique structure and may be responsible for some of the characteristic therapeutic properties attributed to fenugreek (Madar and A. H. Stark, 2002).

## Uses and Pharmacology

The use of fenugreek has been limited by its bitter taste and pungent odour. Isolation of the biologically active components or production of a debittered extract, which would allow greater use of the plant, have been investigated (Madar and A. H. Stark, 2002).

Clinical data from very small studies suggest the use of fenugreek for cholesterol lowering. It is used as a flavouring in Indian and Asian cookery, and in folk medicine for the treatment of boils, cellulitis, and tuberculosis, and for its anti-inflammatory and diuretic effects.

## Cholesterol-lowering effects

Faecal bile acid and cholesterol excretion are increased by fenugreek administration (Madar and A. H. Stark, 2002). This may be secondary to a reaction between the bile acids and fenugreek-derived saponins causing the formation of micelles too large for the digestive tract to absorb. Another hypothesis attributes the cholesterol-lowering activities to the fibre-rich gum portion of the seed that reduces the rate of hepatic synthesis of cholesterol. It is likely that both mechanisms contribute to the overall effect.

### Animal data

Studies have clearly demonstrated the cholesterol-lowering activity of fenugreek in animals (Valette et al., 1984), (Singhal, R. K. Gupta, and Joshi, 1982), (A. Stark and Madar, 1993), (Sauvaire, Ribes, et al., 1991). In a typical study, fractions of fenugreek seeds were added to the diets of diabetic

hypercholesterolemic and normal dogs. The defatted fraction, which contains about 54% fibre and about 5% steroidal saponins, lowered plasma cholesterol, blood glucose, and plasma glucagon levels from pretreatment values in both groups of dogs (Valette et al., 1984). The hypocholesterolemic effect has been reproduced in rats (Singhal, R. K. Gupta, and Joshi, 1982), (Yadav, Moorthy, and Baquer, 2004). Administration of the fibre-rich fraction of fenugreek to diabetic rats lowered total cholesterol, triglycerides, and LDL (Hannan, Rokeya, and Faruque, 2003). The level of HDL was increased.

### Clinical data

Serum triglycerides were reduced from baseline in patients with newly-diagnosed, mild, type-2 diabetes mellitus who received a hydroalcoholic extract of fenugreek seeds 1 g/day (A. Gupta, R. Gupta, and B. Lal, 2001). Total cholesterol and proportions of LDL and HDL fractions were not altered by treatment. A systematic review identified 5 other randomised clinical trials (N = 140) investigating the cholesterol-lowering effects of fenugreek seeds (Thompson Coon and Ernst, 2003). Reductions (15% to 33%) of serum cholesterol from baseline were reported in all the trials identified. One small study using an aqueous extract of fenugreek leaves in healthy volunteers showed cholesterol reductions compared with control subjects after a single dose. Dose-dependent hypocholesterolemic effects of germinated fenugreek seeds also have been demonstrated (Sowmya and Rajyalkshmi, 1999). Total serum cholesterol and LDL cholesterol were reduced, while HDL cholesterol remained unchanged.

## Glucose-lowering effects

The galactomannan-rich soluble fibre fraction of fenugreek may be responsible for the anti-diabetic activity of the seeds (Madar and A. H. Stark, 2002). Insulinotrophic and anti-diabetic properties also have been associated with the amino acid 4-hydroxyisoleucine that occurs in fenugreek at a concentration of about 0.55%. In-vitro studies have indicated that this amino acid causes direct pancreatic $\beta$-cell stimulation. Delayed gastric emptying and inhibition of glucose transport also have been postulated as possible mechanisms (A. Gupta, R. Gupta, and B. Lal, 2001).

### Animal data

Multiple studies have been undertaken to demonstrate the glucose-lowering effects of fenugreek (Hannan, Rokeya, and Faruque, 2003), (Khosla, D. D. Gupta, and Nagpal, 1995), (R. D. Sharma, Raghuram, and Rao, 1990), (Madar, Abel, et al., 1988), (Ajabnoor and Tilmisany, 1988), (Ribes, Sauvaire, Da Costa, et al., 1986). A typical study evaluated the

hypoglycaemic effects of the seeds in dogs. The defatted fraction of the seeds lowered blood glucose levels, plasma glucagons, and somatostatin levels; carbohydrate-induced hyperglycaemia also was reduced (Ribes, Sauvaire, and Baccou, 1984).

### Clinical data

Glycaemic control was improved in a small study of patients with mild type-2 diabetes mellitus (A. Gupta, R. Gupta, and B. Lal, 2001). A reduction in glycosylated haemoglobin (HbA [1c]) levels and increased insulin sensitivity were observed in fenugreek recipients. The preparation was well tolerated, with no patients withdrawing from the study because of adverse effects. Patients receiving the fenugreek preparation also were allowed to receive adjuvant anti-diabetic preparations if required; caution is advised in the interpretation of these results.

## Anti-inflammatory effects

### Animal data

Rats treated with a single dose of fenugreek extract 100 or 200 mg/kg showed a dose-related[313] response when treated with carrageenin. Inhibition of inflammatory swelling was 45% and 62% in the lower and higher dose groups, respectively, compared with 100% in untreated animals (Sur, M. Das, and Gomes, 2001).

### Clinical data

Research reveals no clinical data regarding the use of fenugreek as an anti-inflammatory agent.

## Antitumour activity

A French patent has been granted to a product purported to have antitumour activity, especially against fibromas. The product contains extracts of several herbal products, including fenugreek.

[313] If the effects change when the dose of the drug is changed, the effects are said to be dose-dependent

### Animal data

Pretreatment with a fenugreek extract was found to enhance macrophage cell counts in rats (Sur, M. Das, and Gomes, 2001). When these rats were subsequently inoculated with tumour cells, tumour cell growth was inhibited.

### Clinical data

Research reveals no clinical data regarding the use of fenugreek as an antitumour agent.

## Antioxidant effects

High levels of polyphenolic flavonoids (more than 100 mg per 100 g) have been isolated from fenugreek seeds. These have been associated with dose-dependent protection of erythrocytes from antioxidant damage in an in-vitro study (Kaviarasan, Vijayalakshmi, and Anuradha, 2004).

### Animal data

Simultaneous administration of an aqueous extract of fenugreek seeds with ethanol prevented the harmful effects of alcohol on lipid peroxidation and enzyme markers of hepatotoxicity (Thirunavukkarasu, Anuradha, and Viswanathan, 2003). Histopathological examination of liver and brain confirmed these findings, indicating that fenugreek could offer some protection against ethanol toxicity.

### Clinical data

Research reveals no clinical data regarding the use of fenugreek as an antioxidant.

## Other uses

The seeds are rich in protein, and the plant is grown as animal forage. Diosgenin, a precursor used in commercial steroid synthesis, is extracted from the seeds. The remaining residue is rich in nitrogen and potassium and is used as an agricultural fertiliser.

Because the seeds contain up to 50% of mucilaginous fibre, they have been used in the preparation of topical poultices and emollients; internally this ability to swell in volume has been utilised to relieve constipation and diarrhoea.

Reduction in cataract incidence has been demonstrated in diabetic rats receiving an extract of fenugreek seeds and leaves (Vats et al., 2004). After 115 days of treatment, cataracts were diagnosed in 25% of fenugreek recipients compared with 100% of diabetic controls. Oral administration of fenugreek seed fractions resulted in dose-dependent gastric protection against the effects of ethanol (a necrotizing agent) (Pandian, Anuradha, and Viswanathan, 2002). The seeds were as effective as omeprazole, a clinically-recognised antiulcer agent. Ulcer scores indicated that the soluble gel fraction was more effective than the aqueous extract or omeprazole.

Appetite stimulant, atherosclerosis, constipation, diabetes, dyspepsia/gastritis, fevers, kidney ailments, hyperlipidemia/hypertriglyceridemia, lactation promotion, local inflammation (topical) (medscape, 2015g).

Today, fenugreek is used as a folk or traditional remedy for diabetes and loss of appetite, and to stimulate milk production in breastfeeding women. It is also applied to the skin for inflammation.

The dried seeds are ground and taken by mouth or used to form a paste that is applied to the skin.

Fenugreek has been used orally for loss of appetite and stomach complaints. Fenugreek has also been used topically (on the skin) to treat inflammation, boils, wounds, and eczema (drugs.com, 2014b).

## Uses

Breast enhancement and health, increasing breast milk, sexual desire, PMS, blood sugar, antioxidant, menopause.

Diabetes. (Check with your doctor first).

## Contraindications

Contraindications have not yet been identified.

## Adverse Reactions

Allergic reaction, asthma, diarrhoea, flatulence, hypoglycaemia, wheezing, unusual body odour, loss of consciousness (medscape, 2015g).

When ingested in culinary quantities, fenugreek usually is devoid of adverse reactions. However, a case of hypersensitivity to curry powder has been linked to ingestion of the spice (Ohnuma, E. Yamaguchi, and Kawakami, 1998). Rechallenge with individual ingredients of the powder elicited bronchospasm and bowel symptoms with fenugreek and cardamom.

Patients receiving a hydroalcoholic extract of fenugreek seeds in clinical trials have reported dyspepsia and mild abdominal distention for the first few days of treatment (A. Gupta, R. Gupta, and B. Lal, 2001). These conditions subsided on continuation of therapy.

False diagnosis of maple syrup urine disease (see Pregnancy/Lactation) has been reported in several infants who were given fenugreek-containing herbal teas (Korman, E. Cohen, and Preminger, 2001), (Sewell, Mosandl, and Bohles, 1999), (Bartley et al., 1981).

Although uncommon, allergic reactions to fenugreek have been reported. Stop taking fenugreek and seek emergency medical attention if you experience symptoms of a serious allergic reaction including **difficulty breathing**, **throat closing**, **swelling of your lips, tongue, or face**, or **hives** (drugs.com, 2014b).

## Side Effects and Cautions

- Possible side effects of fenugreek when taken by mouth include **wind**, **bloating**, and **diarrhoea**. Fenugreek can cause **skin irritation**.
- Given its historical use for inducing childbirth, women should use caution when taking fenugreek during pregnancy.
- Tell all your health care providers about any complementary health practices you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care (NCCIH, 2012c).

## Pregnancy/Lactation

Fenugreek has documented uterine stimulant effects and has been used in traditional medicine to induce childbirth and hasten delivery by promoting uterine contractions therefore avoid use in pregnancy.

Maple syrup urine disease, a disorder of branched-chain amino acid catabolism that results in abnormal accumulations of the amino acids and their metabolites, was suspected in a healthy infant born to a mother who ingested a paste prepared from fenugreek seeds early in labour (Korman, E. Cohen, and Preminger, 2001). Fenugreek, maple syrup, and the urine of patients with the disease share a characteristic odour originating from a common ingredient, sotolone. The seeds have been used in traditional medicine to augment milk supply in nursing women. The extent of transmission of fenugreek-derived constituents into breast milk is unknown.

## Interactions

The effects of anti-coagulant drugs such as warfarin may be potentiated. Patients taking anti-coagulants should consult their health care provider before taking fenugreek; dosage adjustments may be necessary.

A 67-year-old woman taking warfarin 2 mg/day experienced an increase in anti-coagulant parameters after ingesting natural products containing boldo and fenugreek (Lambert and Cormier, 2001). Anti-coagulant activity returned to therapeutic range 1 week after discontinuation of the herbal products. The patient wished to continue with boldo and fenugreek; coagulation parameters were maintained in the normal range by decreasing the warfarin dose 15%.

## Dosage

Studies in patients with type-2 diabetes mellitus and hypercholesterolemia have used 5 g/day of seeds or 1 g/day of a hydroalcoholic extract of fenugreek (A. Gupta, R. Gupta, and B. Lal, 2001).

Unless otherwise prescribed -

**Internal** 6 g drug,

Equivalent preparations

**External** 50 g powdered drug with 1 litre of water (herbalgram, 1990e).

### Seed

1–2 g orally, three times a day, but, do not take more than 6g in a 24-hour period (medscape, 2015g).

### Tea

1 cup many times/day; To be made in 500 mg seed in 150 mL water (medscape, 2015g).

### Poultice

Apply to the skin as required (medscape, 2015g).

### Paste

50 g of powdered seed in 0.25 or 1 L hot water (medscape, 2015g).

### Diabetes Mellitus, Postprandial Glucose Control

10–15 g orally four times a day, or in divided doses with your meals,

OR

**Hydroalcoholic extract** 1 g orally four times a day,

OR

**Seed** 5 g a day orally (medscape, 2015g)

### Hyperlipidemia

0.6–2.5 g orally twice a day, to be taken with your meals (medscape, 2015g).

## Efficacy

### Diabetes

Reduces postprandial blood glucose in type 1 or 2 (medscape, 2015g).

### Hypercholesterolemia

Conflicting evidence on lowering cholesterol; more studies needed (medscape, 2015g).

### Hypertriglyceridemia

Preliminary clinical research suggests it may lower triglycerides in type 2 diabetics (medscape, 2015g).

## How it works

Foenugracein and other components decrease postprandial glucose, glucagon, somatostatin, insulin, total cholesterol, and triglycerides, while increasing HDL.

Fibre and mucilage slow gastrointestinal absorption of glucose and cholesterol.

Steroidal saponins inhibit gastrointestinal cholesterol absorption (medscape, 2015g).

## What the Science Says

- A few small studies have found that fenugreek may help lower blood sugar levels in people with diabetes.
- There is not enough scientific evidence to support the use of fenugreek for any other health condition.

## Toxicology

The acute toxicity from a large dose of fenugreek has not been characterised, but may result in hypoglycaemia. It is probable that toxicity is low; the LD-50 of fenugreek extract was more than 1 g/kg when administered intraperitonealy to rats (Sur, M. Das, and Gomes, 2001).

## Commentary

*Although it is reputed to be a breast enlarger, there are no studies that back this up. However, Fenugreek is a source of diosgenin, which is used to make pharmaceutical oestrogen, so there may be some truth in the claim. Fenugreek may possibly be useful as a herbal hormone, but I would like to see more clinical studies and trials first.*

Chapter 9

# Misc

## Hops

### Common Names

Hops, Chinese = She ma, French = Houblon, German = Hopfen, Italian = Bruscandolo, Italian = Luppolo, Italian = Volticella, Spanish = Lupulo, Swedish = Humle.

### Latin name

*Humulus lupulus*

### Botany

Hops is a perennial climbing vine extensively cultivated worldwide. Male and female flowers are located on separate plants; the cone-shaped fruits are known as strobiles, which are collected in the autumn and carefully dried.

### History

Hops have been used for centuries to flavour and preserve beer. The bitter, aromatic taste of beer is mostly due to the hops content. Hop extracts are also used for other flavouring purposes in the food industry. Medical uses of hops and lupulin include aiding digestion, mild sedation, diuresis, and treating menstrual problems. Hops pickers have reported sedation during harvest, and hops flowers have been added to pillows for relief of nervous conditions.

In the Middle Ages, beers tended to be of a very low alcohol content (small beer). In Europe, many villages had one or more small breweries with a barley field and a hop garden in close vicinity. Early documents include mention of a hop garden in the will of Charlemagne's father, Pepin III (M. Jackson, 1988), (unknown, 2009a). However, the first documented use of hops in beer is from the 9th century, though Hildegard of Bingen, 300 years later, is often cited as the earliest documented source (Hornsey, 2003). Before this period, brewers used a wide variety of bitter herbs and flowers, including dandelion, burdock root, marigold, horehound (the German name for horehound means "mountain hops"), ground ivy, and heather (Griffin, 2006).

Hops are used extensively in brewing for their antibacterial effect that favours the activity of brewer's yeast over less desirable microorganisms and for many purported benefits, including balancing the sweetness of the malt with bitterness, contributing a variety of desirable flavours and aromas. Historically, traditional herb combinations for beers were believed to have been abandoned when beers made with hops were noticed to be less prone to spoilage (Priest and I. Campbell, 2003)

Wild hops were used in brewing at least 3,000 years ago, but they were first cultivated in the 8th century in central Europe (Van Wyk, 2005). Their cultivation spread from there to the rest of the world. In England, hops were considered dangerous plants and banned until about 1600 (Van Wyk, 2005). The aroma and bitterness of hops contribute to the brewing of beer. It was used as a diuretic or sedative by the early herbalists and is said to improve digestion. Fuchs states,

> "It draws out both forms of bile; it checks abscesses; it draws out phlegm?" (F. G. Meyer, Trueblood, and Heller, 1999).

The first documented hop cultivation was in 736, in the Hallertau region of present-day Germany, although the first mention of the use of hops in brewing in that country was 1079 (Corran, 1975) However in a will of Pepin the Short, the father of Charlemagne, 768 hop gardens were left to the Cloister of Saint-Denis. Not until the 13th century did hops begin to start threatening the use of gruit[314] for flavouring. Gruit was used when taxes were levied by the nobility on hops. Whichever was taxed made the brewer then quickly switch to the other. In Britain, hopped beer was first imported from Holland around 1400, yet hops were condemned as late as 1519 as a "wicked and pernicious weed" (Unger, 2004). In 1471, Norwich, England, banned use of the plant in the brewing of ale ("beer" was the name for fermented malt liquors bittered with hops; only in recent times are the words often used as synonyms).

[314] a herb mixture used for bittering and flavouring beer

Hop used in England were imported from France, Holland and Germany with import duty paid for those; it was not until 1524 that hops were first grown in the southeast of England (Kent) when they were introduced as an agricultural crop by Dutch farmers. Therefore, in the hop industry there are many words which originally were Dutch words (like "oast-house"). Hops were then grown as far north as Aberdeen, near breweries for infrastructure convenience.

It was another century before hop cultivation began in the present-day United States - in 1629 by English and Dutch farmers (Bamforth, 1998). Before national alcohol prohibition, cultivation was mainly centered around New York, California, Oregon, and Washington. Problems with powdery mildew and downy mildew devastated New York's production by the 1920's, and California only produces hops on a small scale (Knight, 2015).

### World production

Hops production is concentrated in moist temperate climates, with much of the world's production occurring near the 48th parallel north. Hop plants prefer the same soils as potatoes. The leading potato-growing states in the United States are also major hops-producing areas. However, not all potato-growing areas can produce good hops naturally. Soils in the Maritime Provinces of Canada lack the boron that hops prefer, for example. Historically, hops were not grown in Ireland, but were imported from England. In 1752 more than 500 tons of English hops were imported through Dublin alone (unknown, 1752).

Important production centers today are the Hallertau in Germany which, in 2006, had more hop-growing area than any other country on Earth (Committee, 2006), the Yakima (Washington) and Willamette (Oregon) valleys, and western Canyon County, Idaho (including the communities of Parma, Wilder, Greenleaf, and Notus). The principal production centres in the UK are in Kent which produces Kent Goldings hops, Herefordshire and Worcestershire (Moss, 2013). Essentially all of the harvested hops are used in beer making.

## Folk Medicine

Dried strobili used medicinally as a bitter tonic, sedative, hypnotic. The decoction from the flower is said to remedy swellings and hardness of the uterus. A cataplasm of the leaf is said to remedy cold tumours. The dried fruit, used for poultices and formentations, is said to remedy painful tumours. The pomade, made from the lupulin, is said to remedy cancerous ulcerations[315] (Hartwell, 1967-1971). Reported to be

[315] a tumour growing under the skin breaks through the skins surface, and forms an ulcer or open sore

anaphrodisiac, anodyne[316], antiseptic, diuretic, hypnotic, nervine, sedative, soporific, stomachic, sudorific, tonic, and vermifuge. Hops are a folk remedy for boils, bruises, calculus, cancer, cramps, cough, cystitis, debility, delirium, diarrhoea, dyspepsia, fever, fits, hysteria, inflammation, insomnia, jaundice, nerves, neuralgia, rheumatism, and worms (J. A. Duke and Wain, 1981). Moerman (Moerman, 1982) gives interesting insight on American Indian uses of a plant alien to them originally. Delaware Indians heated a small bag of leaves to apply to earache or toothache. More interesting was the Delaware use of hops as a sedative, drinking hop tea several times a day to alleviate nervousness. Cherokee, Mohegan, and Fox also used the plant as a sedative. George III is said to have slept on a pillow stuffed with hops to alleviate some symptoms of his porphyria. The antibiotic principle lupulone is tuberculostatic (J. A. Duke, 1972).

## Chemistry

The most characteristic constituents of hops are the bitter principles, known as alpha- and beta-acids. In the plant the alpha-acids occur as humulone, cohumulone, and adhumulone (Hoek, Hermans-Lokkerbol, and Verpoorte, 2001), (Carson, 1951). During the brewing process, these compounds are isomerized to the iso-alpha-acid series of compounds, that possess the bitter taste (Carson, 1952). The beta-acid series of compounds include lupulone and congeners (Hoek, Hermans-Lokkerbol, and Verpoorte, 2001), (Carson, 1951); this series is destroyed during brewing. The relative proportions of the bitter acids affect the quality of the hops, and many methods have been developed for quantifying hop acids in different varieties, including nuclear magnetic resonance (NMR) (Hoek, Hermans-Lokkerbol, and Verpoorte, 2001), (Molyneux and Y. Wong, 1975) and high-pressure liquid chromatography (HPLC) (De Cooman, Everaert, and De Keukeleire, 1998), (Hampton et al., 2002). The complex profile of hop acids is dependent on genetics, cultivation, and storage conditions. Long-term storage of hops leads to major deterioration in quality.

The essential oils of hops are less characteristic but are still important to hop quality. Over 100 volatile compounds have been identified, with gas chromatography and gas chromatography-mass spectroscopy (GC-MS) being key techniques for analysis (Eri et al., 2000), (Steinhaus and Scheiberle, 2000). Caryophyllene, beta-myrcene, and humulene are the most abundant constituents of hops volatile oils.

A third group of hops constituents is the prenylflavonoids. Xanthohumol is the dominant prenylflavonoid of hops (Stevens, Ivancic, et al., 1997), with 8-prenylnaringenin also of importance (Tekel' et al., 1999). A GC-MS method has been developed for the latter (Tekel' et al., 1999), while liquid chromatography-tandem mass spectrometry (LC-MS) has been used to directly quantify prenylflavonoids and their isomerization products in

[316] a drug used to lessen pain through reducing the sensitivity of the brain or nervous system

beer and hops extracts (Stevens, A. W. Taylor, and Deinzer, 1999). The variation in prenylflavonoids between hops varieties has also been studied (Stevens, A. W. Taylor, and Nickerson, 2000). The fate of xanthohumol as hops is processed into beer has been studied; 20% to 30% is converted to isoxanthohumol (Stevens, A. W. Taylor, Clawson, et al., 1999). The metabolism of xanthohumol in rat and human liver microsomes has also been characterised (Yilmazer, Stevens, Deinzer, et al., 2001), (Yilmazer, Stevens, and Buhler, 2001).

According to the Wealth of India (CSIR, 1948–1976), hops contain 6–12% moisture, 11–21% resins (no tetrahydrocannabinols), 0.2–0.5% volatile oils, 2–4% tannins, 13–24% protein, 3–4% fructose and glucose, 12–14% pectins, and 7–10% ash. According to Leung (Kubo et al., 1975) hops contain 0.3 to 1% volatile oil; 3 to 12% resinous bitter principles composed of a-bitter acids (humulone, cohumulone, adhumulone, prehumulone, posthumulone, etc., and b-bitter acids (lupulone, colupulone, adlupulone, etc., in decreasing concentration); other resins, some of which are oxidation products of the a- and b-acids; xanthohumol (a chalcone); flavonoid glycosides (astragalin, quercitrin, isoquercitrin, rutin, kaempferol-3-rutinoside, etc.); phenolic acids; tannins; lipids; amino acids; oestrogenic substances; and many others. The volatile oil is made up mostly of humulene (a-caryophyllene), myrcene, b-caryophyllene, and farnesene, which together may account for over 90% of the oil. Other compounds number over 100, including germacratriene, a- and b-selinenes, selina-3,7(11)-diene, selina-4(14),7(11)-diene, a-copaene, a- and b-pinenes, limonene, p-cymene, linalool, nerol, geraniol, nerolidol, citral, methylnonyl ketone, other oxygenated compounds, 2,3,4-trithiapentane (present only in oil of unsulphured hops in ca 0.01%), S-methylthio-2-methylbutanoate, S-methylthio-4-methylpentanoate, and 4,5-epithiocaryophyllene (Kubo et al., 1975). Buttery and Ling (Buttery and L. C. Ling, 1967) compare 5 cvs for 76 of their volatile oil components. Countering claims that the "wonder cure" GLA is found only in mother's milk and evening primrose, I consulted the USDA lab at Peoria, and learned that GLA was also in hops and borage, to mention just a few of the other vegetable sources.

## Uses and Pharmacology

Anxiety, insomnia and other sleep disorders, restlessness, tension, excitability, ADHD, nervousness, and irritability (medscape, 2015h).

Hops have been used for flavouring; hops and lupulin have been used as a digestive aid, for mild sedation, diuresis, and treating menstrual problems, but no clinical studies are available to confirm these uses.

Hops contain humulone, isohumulone and humulene which are bitter-tasting compounds. It also contains the natural phenols xanthohumol, isoxanthohumol and the most oestrogenic phytoestrogen known, 8-prenylnaringenin (Nikolic et al., 2004).

## Sedative

The observation that hops pickers often experienced sedation prompted investigation of hops for sedative principles.

### Animal data

The compound 2-methyl-3-buten-2-ol was isolated and found to reduce the spontaneous movement of rats when given intraperitoneally (Wohlfart, Hänsel, and H. Schmidt, 1983). The small amounts found in hops (Eri et al., 2000) makes it unlikely that this compound completely explains hops sedation.

### Clinical data

Hops are often included in combination with valerian in sleep aids; studies of such products have found that valerian is more important to the pharmacologic activity than hops (Vonderheid-Guth et al., 2000), (Fussel, Wolf, and Brattsröm, 2000), (Müller et al., 2002).

## Phytoestrogenic

### Animal data

8-prenylnaringenin was found to be a potent oestrogen receptor agonist in oestrogen-responsive cells, while other hops phenolics were less active (isoxanthohumol, 6-prenylnaringenin) or had no activity (xanthohumol) (S. R. Milligan, J. C. Kalita, Heyerick, et al., 1999). The amounts present in beer were considered to be too small to cause oestrogenic effects. Oestrogenic effects in-vivo were observed in mice given isolated 8-prenylnaringenin in drinking water at 100 mcg/mL, using uterine vascular permeability as an endpoint (S. R. Milligan, J. C. Kalita, and Pocock, 2000).

### Clinical data

Oestrogenic effects were also observed in evaluation of hops extract for the treatment of menstrual symptoms (Coldham and Sauer, 2001). Use of hops in breast enhancement products was cause for concern (S. Milligan, J. Kalita, and Pocock, 2002), (J. Liu, Burdette, and H. Xu, 2001b).

## Cancer chemoprevention

Hops bitter acids have substantial effects on metabolic enzymes.

## Animal data

Colupulone adsorbed on brewers' yeast was found to induce cytochrome P-450 3A in mice, an enzyme capable of N-demethylation of ethylmorphine (Mannering, J. A. Shoeman, and Deloria, 1992), (Mannering, J. A. Shoeman, and D. W. Shoeman, 1994). However, short-term assays for aflatoxin or benzpyrene activation through colupulone induction of CYP450 did not find a change in mutagen activation (Shipp, Mehigh, and Helferich, 1994). While beer and other alcoholic beverages have been found to inhibit mutagenesis induced by carcinogens in an Ames test, the compounds responsible were not identified (Arimoto-Kobayashi et al., 1999). In a later study, several hops prenylflavonoids inhibited carcinogenic amine activation by CYP1A2 (Miranda, Y. Yang, and Henderson, 2000).

Humulone was identified as the active hops constituent that inhibited phorbol ester-induced inflammation in mice (Yasukawa, A. Yamaguchi, et al., 1993). The same group later demonstrated that humulone was active in blocking tumour promotion in the classical two-stage model of carcinogenesis (Yasukawa, Takeuchi, and Takido, 1995). Several different hops prenylflavonoids demonstrated antiproliferative and cytotoxic effects in breast, colon, and ovarian human cancer cell lines (Miranda, Stevens, and Helmrich, 1999). 8-prenylnaringenin was shown to upregulate[317] the cadherin and catenin genes in human breast cancer cells (Rong, Boterberg, and Maubach, 2001). A comprehensive evaluation of xanthohumol as a cancer chemopreventative agent found that it warranted clinical investigation because it had distinct activities at the initiation, promotion, and progression stages of carcinogenesis (Gerhauser, Alt, and Heiss, 2002).

## Clinical data

Research reveals no clinical data regarding the use of hops for cancer chemoprevention.

# Antibiotic and other

The hop bitter acids have antibacterial and anti-fungal activity important for the preservative function of hops in beer. When tested at the normal pH of beer (4.0), isohumulone inhibited bacterial growth at concentrations at which it is normally found in beer (Simpson and A. R. Smith, 1992). The prenylflavonoids of hops were shown to be more effective antioxidants than nonprenylated flavonoids (Rodriguez et al., 2001). Humulone potently suppressed COX-2 gene expression at the level of transcription (K. Yamamoto et al., 2000). Xanthohumols inhibited diacylglycerol acyltransferase, an effect of possible importance in lipid metabolism (Tabata et al., 1997). Polyphenolics of hops were shown to inhibit alpha-acid oxidase

[317] to increase the responsiveness of a cell or organ to a stimulus

activity, thereby providing an internal control over hops' acid metabolism (E. A. Williams and Menary, 1988). Hops proanthocyanidins were shown to inhibit neuronal nitric oxide synthetase and efficiently scavenge reactive nitrogen species (Stevens, Miranda, et al., 2002).

## How it works

2-methyl-3-butene-2-ol has sedative properties (medscape, 2015h).

## Efficacy

Possibly effective for mild sedation (medscape, 2015h).

## Adverse Reactions

Research reveals little or no information regarding adverse reactions with the use of hops.

Hops dermatitis has long been recognized. Not only hands and face, but legs have suffered purpuric eruptions due to hop picking. Although only 1 in 3,000 workers is estimated to be treated, one in 30 are believed to suffer dermatitis (J. A. Duke, 1983b).

Possibly **contact dermatitis** (medscape, 2015h).

## Pregnancy/Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking.

## Interactions

None well documented.

## Dosage

Hops has been used as a mild sedative or sleep aid, with the dried strobile given in doses of 1.5 to 2 g. An extract combination with valerian, Ze 91019 (Redormin , Ivel) has been studied at a hops dose of 60 mg for insomnia. (Fussel, Wolf, and Brattstrom, 2000).

### Insomnia

- **Dried strobile** - 1.5–2 g

- **Extract combined with valerian** - 60 mg (medscape, 2015h).

### Toxicology

As an historical food constituent, hops has "generally recognized as safe" (GRAS) status by the FDA, however; use of medicinal quantities of hops may pose more risk than common levels of exposure in food use. Dogs appear to be somewhat sensitive to hops compounds. A malignant hyperthermic reaction was observed in 5 dogs who consumed boiled hops residues used in home brewing (Duncan, Hare, and W. B. Buck, 1997). A subchronic[318] toxicity study of the hops alpha-acids was conducted in dogs; while high doses induced vomiting, the animals generally tolerated lower doses without ill effects. A wide safety margin for humans was extrapolated from this experiment (Chappel, S. Y. Smith, and Chagnon, 1998).

### Commentary

*Although it is stated that hops have oestrogenic properties, this doesn't appear to have been followed up so it isn't possible to state that hops are useful for their oestrogenic properties. There seems to be a lack of follow-through in major studies to give this information, so at the the moment, the jury is still out!*

## Kudzu

### Common names

Kudzu vine, Japanese arrowroot, kudzu bean, kakka, kakkon, ko-hemp, Japanese = Kakkonto, Chinese = Ge, Chinese = Ko t'eng, Japanese = Kuzu, Korean = Chilk, Spanish = Kudzu, Spanish = Kudzu comun, Vietnamese = Cu nang, Vietnamese = Cu san day

### Latin name

*Pueraria lobata*

[318] Of intermediate duration, usually used to describe studies or periods of exposure lasting between 5 and 90 days

## Botany

Kudzu is a fast-growing vine native to the subtropical regions of China and Japan. The leaves of the plant contain 3 broad oval leaflets with purple flowers and curling tendril spikes (USDA, 2008a), (Chevallier, 1996). Because kudzu produces stems that can grow to 20m in length with extensive roots, it has been used to control soil erosion. Since its introduction to the United States, kudzu has become well established and proliferates in moist southern regions, where it grows vigorously and is now considered an invasive pest.

## History

Kudzu was introduced to the United States in the late 1800s to control soil erosion (Lukas, D. Penetar, and Berko, 2005), and although widely recognized as a ground cover and fodder crop in the Western world, the plant has a long history of medicinal use in Asian cultures. Beginning in the 6th century BC, Chinese herbalists used the plant for prevention of intoxication, muscular pain, and treatment of measles (Chevallier, 1996), (B. J. Xu, Y. N. Zheng, and C. K. Sung, 2005). Kudzu is native to Japan, China, and Fiji (Penso, 1980), (Pharmacy, 1994).

## Chemistry

Numerous reports have identified chemical constituents in various plant parts of kudzu (Kurihara and Kiruchi, 1973), (Kurihara and Kiruchi, 1976), (M. H. Chen, 1985). Flavonoid, isoflavonoid, and isoflavone content (including puerarin) have been identified in kudzu roots and flowers (Saiad and Borysov, 1978), (Saiad and Borysov, 1979), (L. X. Xu, A. R. Liu, and X. Q. Zhang, 1987), (Ohshima et al., 1988), (Kubo et al., 1975), (Kurihara and Kikuchi, 1975), (S. P. Zhao and Y. Z. Zhang, 1985), (Z. Ma et al., 2005), (D. M. Penetar et al., 2006), (Boué, Wiese, and Nehls, 2003). Kudzu contains a high total isoflavone content compared with other isoflavone-containing herbs, with the dry root containing as much as 5.32 mg/g (Hayashino, 2005), (Cherdshewasart, Cheewasopit, and Picha, 2004a).

Oleanene triterpene glycosides, also known as kudzu saponins, have been isolated from the plant (Arao et al., 1995), (Arao et al., 1997). Analysis of isoflavonoid aglycones and their glycosides has been performed (Rong, De Keukeleire, et al., 1998). Robinin in kudzu leaf also has been reported (Saiad, Borysov, and Koval'ov, 1979). Other constituents evaluated include daidzin, daidzein, genistein, genestin (A. Lal et al., 2003), tectoridin (E. K. Park et al., 2006) kakkalide, (H. U. Lee, Bae, and D. H. Kim, 2005), formononetin, biochanin A, and plant sterols (Chevallier, 1996), (Pharmacy, 1994), (Keung and Vallee, 1993a), (Keung, 1993), (Bruneton, 1995b). In addition, morphological and anatomical identification studies of kudzu have been performed (Kartmazova et al., 1980).

## Uses and Pharmacology

## Alcoholism

### Animal data

Available animal studies have been reviewed (B. J. Xu, Y. N. Zheng, and C. K. Sung, 2005), (Rezvani et al., 2003), (Keung, 2003). Isoflavones daidzin, daidzein, and puerarin may account for the suppression of ethanol intake, and although the mechanism of action is not certain, inhibition of alcohol dehydrogenase is thought to be a major factor in kudzu's antidipsotropic[319] activity (Keung, 1993), (Keung, 2003), (Keung and Vallee, 1993b), (Keung and Vallee, 1998), (Xie, R. C. Lin, and Antony, 1994), (R. C. Lin and T. K. Li, 1998).

### Clinical data

Few clinical trials have been conducted, with conflicting results. Kudzu extract was found to have no effect on drinking patterns or cravings in a study of (R. C. Lin and T. K. Li, 1998) military veterans after 1 month of administration (Shebek and Rindone, 2000). Whereas, another small study (N = 14) conducted over a period of several weeks was able to demonstrate reduction in the number of beers and total volume consumed among heavy alcohol drinkers (Lukas, D. Penetar, and Berko, 2005), (unknown, 2005). The amount of isoflavone present in the extracts used in the 2 trials probably differed, thus accounting for the inconsistent results (Lukas, D. Penetar, and Berko, 2005).

## Oestrogenic activity

The high isoflavone content of kudzu has prompted several researchers to investigate the oestrogenic activity of extracts. In-vitro experiments suggest daidzein to be more potent than daidzin or puerarin (E. K. Park et al., 2006). Studies comparing kudzu with red clover, soybean, mung, and alfalfa sprouts found kudzu to be the most potent (Boué, Wiese, and Nehls, 2003), while another study suggested that the ethanol extract of P. lobata is less effective than P. mirifica or Mucana collettii (Cherdshewasart, Cheewasopit, and Picha, 2004a). One trial of 25 menopausal women found a decrease in the number of hot flushes per day when a multiple-ingredient preparation, including kudzu extract, was used (Lukaczer, Darland, and Tripp, 2005). However, a larger trial was unable to find positive effects of kudzu extract in treating menopause symptoms (Woo, E. Lau, and S. C. Ho, 2003).

[319] to reduce or prevent alcoholic drinking

## Other uses

- **Cancer** - A kudzu ethanolic extract has been evaluated for antiproliferative activity against breast, ovarian, and cervical cancer cell lines (G. C. Jeon et al., 2005a).
- **Cardiovascular** - Kuzdu has been examined for its effect on vascular smooth muscle tissue (L. Y. Wang, A. P. Zhao, and X. S. Chai, 1994), potential effects in arrhythmia, ischaemia, angina pectoris (Qicheng, 1980), (Lai and B. Tang, 1989), (Y. Zhou, X. Su, et al., 1995), and antioxidant activity (Sato et al., 1992). Clinical studies are lacking.
- **Hepatoprotection** - A few in-vitro experiments have been conducted on mice and human cells investigating the hepatoprotective effects of puerarin and saponins (Hayashino, 2005), (Arao, Udayama, Kinjo, Nohara, et al., 1997), (Arao, Udayama, Kinjo, and Nohara, 1998).
- **Hypolipidemia** - Biochanin A demonstrated potential hypolipidemic activity via activation of peroxisome proliferator-activated receptors in an in-vitro experiment (Shen et al., 2006).
- **Osteogenic activity** - Kudzu extract increased the synthesis of alkaline phosphatase in human osteoblast cells (Huh, H. R. Yang, and D. S. Park, 2006).

## Insufficient Evidence for

- **Alcoholism** - Early research suggests that heavy drinkers who take kudzu extract for 7 days consume less beer when given a chance to drink. But kudzu doesn't seem to decrease the craving for alcohol or improve sobriety in long-term alcoholics.
- **Chest pains** - Some early research suggests that puerarin, a chemical in kudzu, might improve signs and symptoms of chest pain when taken by mouth or injected intravenously (by intravenous (IV)). Some evidence suggests that using IV puerarin along with usual treatment might be more effective than usual treatment alone. However, studies on puerarin are generally of poor quality and might not be reliable. Puerarin injection products are not available in North America.
- Preventing chest pain during a procedure called percutaneous transluminal coronary angioplasty (PTCA). Early research suggests that injecting 200 mL of puerarin, a chemical in kudzu, intravenously (by IV) one week before and immediately prior to percutaneous transluminal coronary angioplasty (PTCA) might reduce episodes of chest pain. Puerarin injection products are not available in North America.
- **Coronary heart disease** **Coronary Heart Disease (CHD)** - Early research suggests that injecting 500 mL of puerarin, a chemical in kudzu, intravenously (by IV) once daily for 3 weeks might reduce "bad" LDL cholesterol, increase "good" HDL cholesterol, and reduce pre-meal insulin levels in people with CHD. Puerarin injection products are not available in North America.

- **Diabetes** - Early research suggests that taking puerarin, a chemical in kudzu, 750 mg daily orally along with the diabetes medication rosiglitazone (Avandia) reduces blood sugar in patients with type 2 diabetes. However, injecting puerarin intravenously (by IV) does not appear to reduce blood sugar. Puerarin injection products are not available in North America.
- **Kidney disease in people with diabetes (diabetic nephropathy)** - Early research suggests that taking puerarin, a chemical in kudzu, 750 mg daily orally along with the diabetes medication rosiglitazone (Avandia) improves kidney function in people with diabetic nephropathy.
- **Problems with the retina of the eye in people with diabetes (diabetic retinopathy)** - Some research suggests that injecting puerarin, a chemical in kudzu, intravenously (by IV) does not improve vision in people with diabetic retinopathy. Puerarin injection products are not available in North America.
- **Exercise performance** - Early research suggests that taking a combination supplement containing kudzu isoflavones along with other ingredients might improve exercise performance in some people.
- **Heart failure** - Early research suggests that taking puerarin, a chemical in kudzu, 400 mg/day orally for 10 days might improve heart function in people with heart failure.
- **Stroke** Some early research suggests that taking puerarin, a chemical in kudzu, alone or with aspirin, might improve brain function in some people after stroke. However, other research shows that injecting puerarin intravenously (by IV) does not reduce death or dependency after a stroke.
- **Low back pain** - Early research suggests that injections of puerarin, a chemical in kudzu, might reduce pain in some people with low back pain. Puerarin injection products are not available in North America.
- **Symptoms of menopause** - Research on kudzu for symptoms of menopause has been conflicting. Some research suggests that taking kudzu by mouth can reduce hot flashes and improve vaginal dryness in women going through menopause. Other research shows that taking kudzu does not affect sex hormone levels, blood fat levels, bone density, or other symptoms of menopause. However, it might have a positive effect on the mental abilities of postmenopausal women.
- **Heart attack (myocardial infarction)** - Early research suggests that injecting puerarin, a chemical in kudzu, intravenously (by IV) along with usual treatment might help some people after a heart attack. Puerarin injection products are not available in North America.
- **Weight loss** - Early research suggests that taking kudzu extract 300 mg orally daily for 12 weeks reduces body fat and body mass index (BMI) in people who are obese. However, taking kudzu extract 200 mg daily does not appear to have the same effects.
- Symptoms of alcohol hangover (headache, upset stomach, dizziness and vomiting).

- Muscle pain.
- Measles.
- Dysentery.
- Stomach inflammation (gastritis).
- Fever.
- Diarrhoea.
- Thirst.
- Cold.
- Flu.
- Neck stiffness.
- Promoting sweating (diaphoretic).
- High blood pressure.
- Abnormal heart rate and rhythm.
- Other conditions.

More evidence is needed to rate the effectiveness of kudzu for these uses (webmd, 2009).

## Adverse Reactions

Kudzu has been used as a medicinal herb for centuries with few reported toxic adverse reactions (Keung, 1993). There have been a small number of case reports of allergy, specifically maculopapular drug eruption and Stevens-Johnson syndrome-type reaction, to the kudzu-containing Kakkonto decoction (Akita et al., 2003).

Kudzu is possibly safe for most people when taken by mouth appropriately for up to 4 months or when injected intravenously (by IV) for up to 20 days.

No side-effects have been reported in clinical studies when kudzu is taken by mouth. There is, however, one case report of allergic reaction following use of a combination herbal product containing kudzu (Kakkonto). Another report suggests that taking kudzu root by mouth might cause liver damage.

When given by IV, the kudzu ingredient, puerarin, has been associated with itching and nausea. It has also caused red cells to break inside blood vessels (webmd, 2009).

## Special Precautions & Warnings

- **Pregnancy and breast-feeding** - There is not enough reliable information about the safety of taking kudzu if you are pregnant or breast feeding. Stay on the safe side and avoid use.
- **Bleeding or blood clotting disorders** - Kudzu might slow blood clotting. It might make bleeding and blood clotting disorders worse, and it might also interfere with medications used as treatment.

- **Cardiovascular (heart and blood vessel) conditions** - There is a concern that kudzu might interfere with cardiovascular treatments. Kudzu extracts seem to lower blood pressure and affect heart rhythm in animals.
- **Diabetes** - Kudzu might affect blood sugar levels in people with diabetes. Watch for signs of low blood sugar (hypoglycaemia) and monitor your blood sugar carefully if you have diabetes and use kudzu.
- **Hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** - Kudzu might act like oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use kudzu.
- **Liver disease** - There is some concern that taking kudzu might harm the liver. In theory, kudzu might make liver diseases, such as hepatitis, worse. People with liver disease or a history of liver disease should avoid kudzu.
- **Surgery** - Kudzu might affect blood sugar levels and might interfere with blood sugar control during and after surgery. Stop taking kudzu at least 2 weeks before a scheduled surgery (webmd, 2009).

## Interactions

### Moderate Interaction

Be cautious with this combination

- Birth control pills (Contraceptive drugs) interacts with Kudzu
  Some birth control pills contain oestrogen. Kudzu might have some of the same effects as oestrogen. But kudzu isn't as strong as the oestrogen in birth control pills. Taking kudzu along with birth control pills might decrease the effectiveness of birth control pills. If you take birth control pills along with kudzu, use an additional form of contraception such as a condom.
  Some birth control pills include ethinyl estradiol and levonorgestrel (Triphasil), ethinyl estradiol and norethindrone (Ortho-Novum 1/35, Ortho-Novum 7/7/7), and others.
- Oestrogens interacts with Kudzu
  The body breaks down caffeine (contained in kudzu) to get rid of it. Oestrogens can decrease how quickly the body breaks down caffeine. Decreasing the break-down of caffeine can cause jitteriness, headache, fast heartbeat, and other side effects. If you take oestrogens, limit your caffeine intake.
  Some oestrogen pills include conjugated equine oestrogens (Premarin), ethinyl estradiol, estradiol, and others.
- Medications that slow blood clotting (anti-coagulant / anti-platelet drugs) interacts with Kudzu

Kudzu might slow blood clotting. Taking kudzu along with medications that also slow clotting might increase the chances of bruising and bleeding.
Some medications that slow blood clotting include aspirin, clopidogrel (Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.

- Methotrexate (MTX, Rheumatrex) interacts with Kudzu
  Kudzu might decrease how fast the body gets rid of methotrexate (Rheumatrex). This might increase the risk of methotrexate side effects.
- Tamoxifen (Nolvadex) interacts with Kudzu
  Some types of cancer are affected by hormones in the body. Oestrogen-sensitive cancers are cancers that are affected by oestrogen levels in the body. Tamoxifen (Nolvadex) is used to help treat and prevent these types of cancer. Kudzu seems to also affect oestrogen levels in the body. By affecting oestrogen in the body, kudzu might decrease the effectiveness of tamoxifen (Nolvadex). Do not take kudzu if you are taking tamoxifen (Nolvadex) (webmd, 2009).

## Minor Interaction

Be watchful with this combination

- Medications for diabetes (Antidiabetes drugs) interacts with Kudzu
  Kudzu might decrease blood sugar. Diabetes medications are also used to lower blood sugar. Taking kudzu along with diabetes medications might cause your blood sugar to go too low. Monitor your blood sugar closely. The dose of your diabetes medication might need to be changed.
  Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others (webmd, 2009).

# Dosage

Kudzu extract 3 g daily with 25% isoflavone content has been studied in adult heavy drinkers (Lukas, D. Penetar, and Berko, 2005). In another study, 2.4 g kudzu root of unknown isoflavone content was given daily (Shebek and Rindone, 2000). A wide range of isoflavone content may exist in commercial kudzu preparations, with most containing less than 1% (Lukas,

D. Penetar, and Berko, 2005). Based on pharmacokinetic studies in healthy adults, a 3-times-daily dosing schedule is recommended. The isoflavone puerarin was rapidly absorbed after oral administration, reaching a peak in 2 hours (D. M. Penetar et al., 2006).

The appropriate dose of kudzu depends on several factors such as the user's age, health, and several other conditions. At this time there is not enough scientific information to determine an appropriate range of doses for kudzu. Keep in mind that natural products are not always necessarily safe and dosages can be important. Be sure to follow relevant directions on product labels and consult your pharmacist or physician or other healthcare professional before using (webmd, 2009).

### Toxicology

The safety profile of kudzu and its extracts has yet to be defined through systematic pharmacologic screens, although traditional Chinese medicine data indicate a lack of toxicity (Qicheng, 1980). Acute toxicity of four Pueraria species has been studied comparatively (Y. Zhou, X. Su, et al., 1995).

### Commentary

*Although it is stated that kudzu has oestrogenic properties, this doesn't appear to have been followed up so it isn't possible to state that kudzu is useful for its oestrogenic properties. There seems to be a lack of follow-through in major studies to give this information, so at the the moment, the jury is still out, again!*

## Liquorice

### Common names

Acide Glycyrrhizique, Acide Glycyrrhizinique, Alcacuz, Alcazuz, Bois Doux, Bois Sucré, Can Cao, Chinese Liquorice, Deglycyrrhized Liquorice, Gan Cao, Gan Zao, Glabra, Glycyrrhiza, Glycyrrhiza glabra, Glycyrrhiza glabra typica, Glycyrrhiza glabra violacea, Glycyrrhiza glabra glandulifera, Glycyrrhiza Radix, Glycyrrhiza uralensis, Glycyrrhizae, Glycyrrhizic Acid, Glycyrrhizinic Acid, Isoflavone, Jethi-Madh, Kanzo, Kan-ts'ao, Kuo-lao, Lakritze, Licorice, Licorice Root, Ling-t'ung, Liquorice Root, Liquiritiae Radix, Liquirizia, Mei-ts'ao, Mi-kan, Mi-ts'ao, Mulathi, Mulethi, Orozuz, Phytoestrogen, Phyto-strogène, Racine de Réglisse, Racine Douce, Radix Glycyrrhizae, Régalissse, Regaliz, Reglisse, Réglisse, Réglisse Déglycyrrhisée, Réglisse Espagnole, Réglisse Russe, Regliz, Russian Liquorice, Spanish Liquorice, Subholz, Sussholz, Sweet Root, Sweet Licorice, Sweet Wood, Yashtimadhu, Yashti-Madhu, Yashti-Madhuka, Yasti

Madhu, Zhi Gan Cao. Chinese = Fen zao, French = Réglisse, French = Glycyrrhize, German = Lakritzen-Staude, German = SüSSholz, Hindi = Mulhatti, Italian = Liquirizia, Korean = Mingamtscho, Russian = Solodka golaja, Sanskrit = Madhuka, Spanish = Orozuz, Spanish = Regalicia, French = Bois doux, Japanese = Kanzo, Danish = Lakrids, German = Lakritzenwurzel, Shao-yao-gan-cao-tang, Glycyrrhizae extractum crudum, Liquiriti radix, Succens liquiritiae, Licochalcone-A, Glycyrrhizae radix

## Latin names

*Glycyrrhiza glabra*

## Overview

Liquorice (Glycyrrhiza glabra) has been used in food and as medicine for thousands of years. Also known as "sweet root," Liquorice root contains a compound that is about 50 times sweeter than sugar. Liquorice root has been used in both Eastern and Western medicine to treat a variety of illnesses, ranging from the common cold to liver disease. It acts as a demulcent and an expectorant. It is still used today for several conditions, although not all of its uses are supported by scientific evidence.

Liquorice that has the active ingredient of glycyrrhiza can have serious side-effects. Another type of Liquorice, called DGL or deglycyrrhizinated Liquorice, doesn't seem to have the same side effects and is sometimes used to treat peptic ulcers, canker sores[320], and reflux (GERD). Whole Liquorice is still sometimes suggested for cough, asthma, and other breathing problems. Topical preparations are used for eczema and other skin problems (unknown, 2014i).

Liquorice root contains many anti-depressant compounds and is an excellent alternative to St. John's Wort. As a herbal medicine it has an impressive list of well documented uses and is probably one of the most over-looked of all herbal wonders. Liquorice is useful for many ailments including asthma, athlete's foot, baldness, body odour, bursitis, canker sores, chronic fatigue, depression, colds and flu, coughs, dandruff, emphysema, gingivitis and tooth decay, gout, heartburn, HIV, viral infections, fungal infections, ulcers, liver problems, Lyme disease, menopause, psoriasis, shingles, sore throat, tendinitis, tuberculosis, ulcers, yeast infections, prostate enlargement and arthritis.

Hundreds of potentially healing substances have been identified in liquorice as well, including compounds called flavonoids and various phytoestrogens. The herb's key therapeutic compound, glycyrrhizin (which is 50 times sweeter than sugar) exerts numerous beneficial effects on the

[320] small white or yellowish sores or ulcers that develop inside the mouth. They are painful, self-healing, and can recur

body, making liquorice a valuable herb for treating a host of ailments. It seems to prevent the breakdown of adrenal hormones such as cortisol (the body's primary stress-fighting adrenal hormone), making these hormones more available to the body.

It has a well-documented reputation for healing ulcers. It can lower stomach acid levels, relieve heartburn and indigestion and acts as a mild laxative.

It can also be used for irritation, inflammation and spasm in the digestive tract. Through its beneficial action on the liver, it increases bile flow and lowers cholesterol levels.

Liquorice also appears to enhance immunity by boosting levels of interferon, a key immune system chemical that fights off attacking viruses. It also contains powerful antioxidants as well as certain phytoestrogens that can perform some of the functions of the body's natural oestrogens; very helpful during the menopause. Glycyrrhizinic acid also seems to stop the growth of many bacteria and of viruses such as influenza A.

In the respiratory system it has a similarly soothing and healing action, reducing irritation and inflammation and has an expectorant effect, useful in irritating coughs, asthma and chest infections.

It has an aspirin-like action and is helpful in relieving fevers and soothing pain such as headaches. Its anti-allergenic effect is very useful for hay fever, allergic rhinitis, conjunctivitis and bronchial asthma. Possibly by its action on the adrenal glands, liquorice has the ability to improve resistance to stress. It should be thought of during times of both physical and emotional stress, after surgery or during convalescence, or when feeling tired and run down (herbwisdom, 2015k).

## Botany

G. glabra is a 1.5 m shrub that grows in subtropical climates in rich soil. The name glycyrrhiza is derived from Greek words meaning "sweet roots." The roots of the plant are harvested to produce liquorice. Most commercial liquorice is extracted from several varieties of G. glabra . The most common variety, G. glabra var. typica (Spanish or European licquorice), is characterised by blue flowers, while the variety G. glabra var. glandulifera (Russian liquorice) has violet blossoms. Turkey, Greece, Iran, and Iraq supply most commercial liquorice. The variety grown in the United States is G. glabra var. lepidota , while that grown in Iran and Iraq is var. violacea. Chinese liquorice is derived from the related species G. uralensis and G. pallidiflora (NRCS, 2007), (Isbrucker and Burdock, 2006).

## History

Therapeutic use of liquorice dates back to the Roman Empire. The Greek physician Hippocrates (460 BC) and botanist Theophratus (371 BC) extolled its uses, and Roman naturalist Pliny the Elder (23 AD) recommended it as an expectorant and carminative. Liquorice also figures prominently in Chinese herbal medicine. It is used in modern medicinals chiefly as a flavouring agent that masks bitter agents, such as quinine, and in cough and cold preparations for its expectorant activity. Most liquorice candy in the United States is actually flavoured with anise, not liquorice. A sample of liquorice from 756 AD was analysed and found to still contain detectable active principles after 1,200 years (Shibata, 1994).

## Properties

Anti-allergic, anti-arthritic, anti-inflammatory, demulcent, emollient[321], oestrogenic (mild), expectorant, laxative, pectoral (moderate), soothing (herbwisdom, 2015k).

## Indicated for

Addison's disease, allergic rhinitis, arthritis, athlete's foot, baldness, bronchitis, bursitis, canker sores, catarrh of the upper respiratory tract, chronic fatigue, colds, colitis and intestinal infections, conjunctivitis, constipation, coughs, dandruff, depression, duodenal-ulcers, emphysema, exhaustion, fibromyalgia, flu, fungal infections, gastritis, gingivitis and tooth decay, gout, hayfever, heartburn, hepatitis, inflamed gallbladder, liver disease, Lyme disease, menopause, prostate enlargement, psoriasis, shingles, sore throat, spleen disorders, tendinitis, throat problems, tuberculosis, ulcers, viral infections, yeast infections. Reducing stomach acid and relieving heartburn and indigestion. Increasing bile flow and lowering cholesterol. Improving resistance to physical and emotional stress.

Do not confuse with liquorice confectionery which contains very little, if any, liquorice and is in fact flavoured by anise.

Can cause water retention and raised blood pressure. Prolonged use should be avoided if you suffer from high blood pressure.

Can cause mild adrenal stimulation (herbwisdom, 2015k).

[321] a moisturising treatment applied directly to the skin

## Chemistry

Liquorice root contains a variety of compounds, including triterpenoids, polyphenols, and polysaccharides (starches, mannose, and sucrose). Polyphenols include certain phenolic acids, such as liquiritin, flavones and flavans; chalcones; and isoflavonoids, such as glabridin (Isbrucker and Burdock, 2006), (Z. Y. Wang and Nixon, 2001), (Chin, H. A. Jung, and Y. Liu, 2007). The bright yellow colour of the root is attributed to the flavonoid content, especially liquiritin and isoliquiritin. Plant gums, resins, and essential oils have been extracted; however, the root is cultivated for the principle active glycoside glycyrrhizin (Isbrucker and Burdock, 2006), (Raggi, Bugamelli, and Nobile, 1994). The amount of glycyrrhizin varies from 7% to 10% or more depending on growing conditions (Raggi, Bugamelli, and Nobile, 1994). Glycyrrhizin, glycyrrhizic acid, and glycyrrhizinate amount to 10% to 25% of the root extract (Isbrucker and Burdock, 2006). The ammoniated salt of glycyrrhizin is manufactured to specifications from liquorice extract and used as a flavouring agent (Isbrucker and Burdock, 2006). Carbenoxolone, a synthetic analog of glycyrrhetic acid, has been used as a pharmacological agent in the management of peptic ulcers (Isbrucker and Burdock, 2006). A process has been established to remove glycyrrhizic acid from liquorice to eliminate the adverse metabolic effects of liquorice. A high-pressure liquid chromotography method to compare the bioavailability of glycyrrhizic acid whether in liquorice root or in pure glycyrrhiza extract has been published. These can now be tested in blood, urine, and bile (Raggi, Bugamelli, and Nobile, 1994).

## Uses and Pharmacology

Used historically for gastrointestinal complaints, liquorice is primarily used as a flavouring agent in the tobacco and sweet industries and to some extent in the pharmaceutical and drinks industries today.

Liquorice is used for various digestive system complaints including stomach ulcers, heartburn, colic, and ongoing inflammation of the lining of the stomach (chronic gastritis).

Some people use liquorice for sore throat, bronchitis, cough, and infections caused by bacteria or viruses.

Liquorice is also used for osteoarthritis, SLE, liver disorders, malaria, tuberculosis, food poisoning, and chronic fatigue syndrome (CFS).

Liquorice is sometimes used along with the herbs Panax ginseng and Bupleurum falcatum to improve the function of the adrenal glands, especially in people who have taken steroid drugs long-term. Steroids tend to suppress the activity of the adrenal glands. The adrenal glands produce important hormones that regulate the bodys response to stress.

Liquorice is also used in an herbal form called Shakuyaku-kanzo-to to increase fertility in women with a hormonal disorder called polycystic ovary syndrome. In combination with other herbs, liquorice is also used to treat prostate cancer and the skin disorder known as eczema.

Some people use liquorice as a shampoo to reduce oiliness in their hair.

Many "liquorice" products manufactured in the U.S. actually don't contain any liquorice. Instead, they contain anise oil, which has the characteristic smell and taste of "black liquorice."

Liquorice interacts with many prescription medicines. Talk to your healthcare provider if you plan to start using liquorice.

## Also used for

Adrenocortical insufficiency.

Arthritis, bronchitis, dry cough, peptic ulcers, gastritis, infections (bacterial/viral), prostate cancer, sore throat, SLE, upper respiratory inflammation (herbwisdom, 2015k).

## Antiviral

Historically, liquorice and its extracts have been used in China and Japan to treat chronic viral hepatitis (Isbrucker and Burdock, 2006). In in-vitro experiments, glycyrrhizin inhibited certain pathogenic viruses by a mechanism that is unclear. Inhibition of viral binding to cell membranes and replication, as well as interference with cellular signal transduction have been suggested. Animal and human studies suggest a more complex mechanism involving induction of interferon production via effects of T-cell function (Isbrucker and Burdock, 2006).

Although the mechanism is unclear, glycyrrhizic acid inhibited the reactivation of latent Kaposi sarcoma-associated herpes virus, (Curreli, Friedman-Kien, and Flore, 2005), (J. I. Cohen, 2005) and showed efficacy against SARS-associated coronavirus (Cinatl, Morgenstern, and G. Bauer, 2003).

Increased survival times for mice have been demonstrated with glycyrrhizin administration for influenza virus A [2] herpes simplex (Isbrucker and Burdock, 2006).

In clinical trials in chronic hepatitis, Stronger Neo-Minophagen C (an intravenous [IV] glycyrrhizin solution produced in Japan) normalized serum transaminase levels and improved liver function but demonstrated no effect on hepatitis C RNA levels (Isbrucker and Burdock, 2006).

## Cancer

Interest in the potential for liquorice extracts in the prevention of cancer continues, but in-vitro and human clinical trials are lacking.

Chemical compounds including glabridin, liquiritin, isoliquiritin, glycyrrhizin, glycyrrhizinic acid, and carbenoxolone have been studied for their effects on mice, rat, and human cancer cell lines, with most studies indicating a dose-dependent action on cell/tumour proliferation and apoptosis. Prostate, breast, colon, liver, and lung cancer cell lines have been investigated (Isbrucker and Burdock, 2006), (Shibata, 1994), (Z. Y. Wang and Nixon, 2001), (J. I. Jung, Lim, and H. J. Choi, 2006), (S. Dong, Inoue, and Y. Zhu, 2007), (Adams et al., 2006), (C. K. Lee, 2007), (Chintharlapalli, Papineni, and Jutooru, 2007).

Various mechanisms of action have been suggested for liquorice compounds, including antioxidant activity, DNA-protective activity, suppressive action, cyclooxygenase inhibition, and phytoestrogenic and progesterone antagonist activity (Isbrucker and Burdock, 2006), (Shibata, 1994). In one experiment, glabridin demonstrated growth-promoting activity at low concentrations but inhibitory activity at higher concentrations (S. Dong, Inoue, and Y. Zhu, 2007). The authors suggest the various chemical compounds in liquorice extracts may act to modulate one another's effects. Another experiment compared activity of different esters of glycyrrhetinic acid indicating structure activity relationships for liquorice compounds (Chintharlapalli, Papineni, and Jutooru, 2007).

In a large retrospective study in Japan (N = 1,249), difference in progression to hepatocellular carcinoma was found in patients with chronic hepatitis C unresponsive to interferon treatment. After adjustment for many variables, those patients who received IV glycyrrhizinic acid 4 mg showed a decrease in the rate of progression to liver cancer, possibly irrespective of length of treatment (Ikeda, Arase, and Kobayashi, 2006). The same authors had earlier demonstrated a protective effect of long-term glycyrrhizin administration in hepatocellular cancer (Shibata, 1994).

## Gastro-intestinal

As a result of liquorice's extensive folk use for gastric irritation, multiple studies in the 1970s and 1980s explored the efficacy of liquorice, glycyrrhizinated compounds, deglycyrrhizinated liquorice, and carbenoxlone in gastric/peptic ulcers (Isbrucker and Burdock, 2006), (Kassir, 1985), (A. G. Morgan, McAdam, et al., 1982), (A. G. Morgan, Pacsoo, and McAdam, 1985). The studies largely showed inconclusive results and efficacy lower than other pharmaceutical agents, such as cimetidine. Due to insufficient evidence in the management of ulcers, liquorice is now largely limited to a flavouring ingredient in OTC preparations (Isbrucker and Burdock, 2006).

## Other effects

- **Anti-inflammatory** - Glycyrrhetic acid has shown anti-inflammatory and antiarthritic activity in animal studies, which may be caused by prostaglandin E [2] inhibitory qualities demonstrated by several glycyrrhizin analogs. Japanese researchers found that liquorice could aid in the clearance of excess immune complexes in mice with SLE (R. Chen and C. Yuan, 1991).
- **Cardiac** - Carbenoxolone and a traditional liquorice preparation Zhigancao may slow myocardial conduction (Kojodjojo et al., 2006), (T. Matsumoto et al., 1996).
- **Dental** - Glycyrrhizin may reduce the growth and acid production of oral bacteria, but results have varied. Other experiments suggest that inhibition of bacterial adherence and inhibition of the enzyme required for plaque formation may be alternative mechanisms for the anticariogenic action of liquorice (Isbrucker and Burdock, 2006).
- **Diabetes** - Carbenoxolone and glycyrrhizin have been investigated in animal experiments for use in diabetes. Results have varied and the mechanism by which they might act is unclear (Sandeep, Andrew, and Homer, 2005), (Tomlinson, Sherlock, and B. Hughes, 2007), (Andrews, Rooyackers, and B. R. Walker, 2003).
- **Hepatoprotection** - Animal experiments and studies in liver cancer suggest a protective role for liquorice in hepatotoxicity (Isbrucker and Burdock, 2006), (C. K. Lee, 2007).
- **Hormonal effects** - Reductions in serum testosterone have been demonstrated in several studies in healthy men consuming glycyrrhizin 0.5 g/day for 7 days. Another trial did not find a reduction; however, methodology between the 2 studies varied (Isbrucker and Burdock, 2006), (Arimanini, Mattarello, and Fiore, 2004).
  In women, liquorice has been used in conjunction with spironolactone in the treatment of polycystic ovary syndrome (Armanini, Castello, and Scaroni, 2007). The oestrogenic activity of liquorice, as well as compounds glabridin and glabrene, has been documented (Armanini, Castello, and Scaroni, 2007), (Oerter Klein et al., 2003).
- **Peptic ulcers** - deglycyrrhizinated liquorice (DGL) is often suggested as a treatment for stomach ulcers, although it's not clear whether it works. A few studies have found that DGL and antacids helped treat ulcers as well as some prescription drugs. However, since antacids were combined with DGL, it's not possible to know how much of the benefit came from DGL alone (unknown, 2014i).
  One animal study found that aspirin coated with liquorice reduced the number of ulcers in rats by 50%. (High doses of aspirin often cause ulcers in rats.) In one study, liquorice root fluid extract was used to treat 100 patients with stomach ulcers – 86 of whom had not improved with conventional medication – for 6 weeks. Ulcers disappeared in 22 people; 90% of participants got better. Other studies have found that DGL had no effect on peptic ulcers in humans (unknown, 2014i).

- **Apthous ulcers** - One small study found that people with apthous ulcers[322] who gargled 4 times per day with DGL dissolved in warm water found pain relief (unknown, 2014i).
- **Eczema** - In one study, Liquorice gel, applied to the skin, helped relieve symptoms of itching, swelling, and redness. A gel with 2% liquorice worked better than a gel with 1% liquorice (unknown, 2014i).
- **Dyspepsia (indigestion, GERD)** - Preliminary studies suggest that a specific herbal formula containing liquorice, called Iberogast or STW 5, may help relieve symptoms of indigestion or gastroesophageal reflux disease (GERD). This herbal formula also contains peppermint and chamomile, two herbs often used for indigestion (unknown, 2014i).
- **Upper respiratory infections (cold, cough)** - Liquorice is a traditional treatment for cough, asthma, and sore throat. One study found that gargling with liquorice before getting anesthesia cut the incidence of postoperative sore throat by half (unknown, 2014i).
- **Weight loss** - One study found that a preparation of liquorice may reduce body fat. Fifteen people of normal weight consumed 3.5 g of liquorice each day for 2 months. Body fat was measured before and after treatment. Liquorice appeared to reduce body fat mass and to suppress the hormone aldosterone; however, the people in the study retained more water.
  Another study found that a topical preparation of glycyrrhetinic acid (a component of liquorice) reduced the thickness of fat on the thigh in human subjects. A third study found that people who took 900 mg of liquorice flavonoid oil daily for 8 weeks experienced reductions in body fat, body weight, body mass index, and LDL cholesterol levels. More studies are needed to say if liquorice really helps reduce fat. In addition, taking liquorice long term has a number of health risks (unknown, 2014i).

Liquorice with glycyrrhizin may help to -

- **Control respiratory problems and sore throat** - Liquorice eases congestion and coughing by helping to loosen and thin mucus in airways; this makes a cough more "productive," bringing up phlegm and other mucus bits. Liquorice also helps to relax bronchial spasms. The herb also soothes soreness in the throat and fights viruses that cause respiratory illnesses and an overproduction of mucus (herbwisdom, 2015k).
- **Lessen symptoms of chronic fatigue syndrome & fibromyalgia** - By enhancing cortisol activity, glycyrrhizin helps to increase energy, ease stress and reduce the symptoms of ailments sensitive to cortisol levels, such as chronic fatigue syndrome and fibromylagia (herbwisdom, 2015k).

[322] ulcers in the mouth which typically last for 10-14 days and they heal without leaving a scar

- **Combat hepatitis** - Liquorice both protects the liver and promotes healing in this vital organ. The herb's anti-inflammatory properties help calm hepatitis-associated liver inflammation. Liquorice also fights the virus commonly responsible for hepatitis and supplies valuable antioxidant compounds that help maintain the overall health of the liver (herbwisdom, 2015k).
- **Treat PMS and menstrual problems** - The phytoestrogens in liquorice have a mild oestrogenic effect, making the herb potentially useful in easing certain symptoms of PMS, such as irritability, bloating and breast tenderness. Although the glycyrrhizin in liquorice actually inhibits the effect of the body's own oestrogens, the mild oestrogenic effect produced by liquorice's phytoestrogens manages to override this inhibiting action (herbwisdom, 2015k).
- **Prevent heart disease** - Recent studies have found that by limiting the damage from LDL cholesterol, liquorice may discourage artery-clogging plaque formation and contribute to the healthy functioning of the heart. Research indicates that modest doses of liquorice (100 mg a day) have this effect (herbwisdom, 2015k).
- **Other** - People who regularly take large amounts of liquorice – more than 20 g/day – may raise blood levels of the hormone aldosterone, which can cause serious side effects, including headache, high blood pressure, and heart problems. For people who already have high blood pressure or heart or kidney disease, as little as 5 g/day can cause these side effects. More research is needed (unknown, 2014i).

## How effective is it?

*Natural Medicines Comprehensive Database* rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

The effectiveness ratings for **Liquorice** are as follows -

### Possibly effective for...

- **Itchy and inflamed skin (eczema)** There is some evidence that applying liquorice to the skin can improve symptoms of eczema. Applying a gel containing liquorice three times daily for 2 weeks seems to reduce redness, swelling, and itching.
- **Heartburn (dyspepsia)** Research suggests that taking a specific product containing liquorice plus peppermint leaf, German chamomile, caraway, lemon balm, clown's mustard plant, celandine, angelica, and milk thistle (Iberogast, Medical Futures, Inc) three times daily for 4 weeks can improve symptoms of heartburn.

## Insufficient evidence to rate effectiveness for...

- **Bleeding** - Early research suggests that applying a specific product containing alpinia, liquorice, thyme, stinging nettle, and common grape vine to the skin reduces bleeding during surgery, but does not reduce time in surgery. Another early study suggests that applying the same product after dental surgery reduces bleeding.
- **Apthous ulcers** - Research suggests that applying a patch containing liquorice to the inside of the mouth for 16 hours daily for 8 days reduces the size of apthous ulcers but does not speed up healing time. Other research suggests that applying liquorice patches and gargling with warm water containing liquorice reduces pain in patients with apthous ulcers.
- **Dental plaque** - Early research suggests that using a toothpaste containing liquorice twice daily does not reduce plaque, gingivitis, or bleeding when compared to toothpaste without liquorice. Using mouthwash containing glycyrrhizin also does not seem to reduce plaque.
- **Recurrent fevers (Familial Mediterranean fever)** - Early research suggests that taking a specific product containing andrographis, Siberian ginseng, schisandra, and liquorice (ImmunoGuard, Inspired Nutritionals) reduces the duration, frequency, and severity of attacks of familial Mediterranean fever in children.
- **Hepatitis** - There is some evidence that certain components in liquorice might be effective in treating hepatitis B and hepatitis C when given intravenously (by IV). However, the studies involved too few patients to draw firm conclusions.
- **High cholesterol** - Early research suggests that taking liquorice root extract daily for 1 month reduces total cholesterol, LDL cholesterol, and triglyceride levels in people with high cholesterol.
- **High potassium levels** - Some research suggests that certain components in liquorice decrease potassium levels in people with diabetes or kidney problems.
- **Irritable bowel syndrome (IBS)** - Early research suggests that a product containing slippery elm bark, lactulose, oat bran, and liquorice root can improve bowel movements in people with constipation-related to IBS. Stomach pain and bloating might also be reduced.
- **Skin discolouration (melasma)** - Early research suggests that applying a cream containing liquorice, emblica, and belides (Clariderm Clear) twice daily for 60 days is effective for lightening skin in people with skin discolorations.
- **Muscle cramps** - Early research suggests that taking a specific product containing liquorice and peony (Shakuyaku-kanzo-to) might reduce muscle cramps in people with liver disease (hepatic cirrhosis) or in people undergoing treatment for kidney failure (hemodialysis).

- **Abnormal levels of a hormone in the blood (neuroleptic-induced hyperprolactinemia)** - Early evidence suggests that taking 45 grams of a specific product containing peony and liquorice (Peony-Glycyrrhiza Decoction, PGD) daily for 4 weeks reduces levels of a hormone called prolactin in women with high levels of prolactin, without affecting other hormone levels or mental symptoms. Other early research suggests that a product containing liquorice and peony (shakutaku-kanzo-to) reduces prolactin levels in men in the short-term, but not in the long-term.
- **Liver disease (nonalcoholic fatty liver disease)** - Early research suggests that taking 2 grams of liquorice root extract daily for 2 months reduces test markers of liver injury in patients with liver disease not caused by drinking alcohol.
- **Mouth sores (aral lichen planus)** - Early evidence suggests that administering a certain liquorice component intravenously (by IV) improves symptoms of mouth sores in people with hepatitis C.
- **Pain** Early research suggests that taking a combination of liquorice root and peony root with Taiwanese tonic vegetable soup containing lily bulb, lotus seed, and jujube fruit reduces pain in cancer patients.
- **Stomach ulcers** - There is some evidence that specially prepared liquorice will speed up the healing of stomach ulcers. However, other evidence suggests that similar liquorice preparations do not improve stomach ulcer symptoms.
- **Recovery after surgery** - There is early evidence that gargling with a solution containing liquorice for 30 seconds five minutes before receiving anesthesia and having a tube placed into the windpipe decreases cough and sore throat after surgery.
- **Psoriasis** - Early evidence suggests that applying a cream containing liquorice and milk to the skin for 4 weeks does not reduce the amount of standard therapy needed, but does seem to improve skin peeling in patients with psoriasis.
- **Weight loss** - There is conflicting information about the use of liquorice for weight loss. Liquorice seems to reduce body fat. However, it causes water retention that can offset any change in body weight.
- **Arthritis**,
- **Lupus**,
- **Infections**,
- **Infertility**,
- **Cough**,
- **Chronic fatigue syndrome (CFS)**,
- **Prostate cancer**,
- **Other conditions**.

More evidence is needed to rate the effectiveness of liquorice for these uses.

## How does it work?

The chemicals contained in liquorice are thought to decrease swelling, thin mucus secretions, decrease cough, and increase the chemicals in our body that heal ulcers.

## Contraindications

Breast cancer, cholestatic liver disorders, cirrhosis, Congestive Heart Failure (CHF), diabetes mellitus, endometriosis, hormone sensitive conditions, hypertonia, hypersensitivity to liquorice, hypertension, hypokalaemia[323], ovarian cancer, renal insufficiency (severe), uterine cancer, uterine fibroids (herbwisdom, 2015k).

## Adverse Reactions

At "usual" dosages or normal consumption levels, few adverse reactions are evident. Reports of adverse reactions in the literature are generally due to liquorice intoxication or chronic excessive intake, and these effects are described in Toxicology below.

Consumption of as little as 50 g/day can produce mineralocorticoid hypertension (Quinkler and Stewart, 2003). Caution is advised in elderly patients with hypertension due to the potential for mineralocorticoid hypokalaemiamic effects (Yasue et al., 2007).

Ocular effects have been described and may be due to the syslooxygenase-inhibitory effect of glabridin; however, large amounts of liquorice are required for this effect. Vasospasm of the optic nerve blood vessels resulting in visual disturbances mimicking ocular migraine (but with no headache) has been reported (Santaella and Fraunfelder, 2007).

Hypersensitivity reactions to glycyrrhiza-containing products have also been noted (Isbrucker and Burdock, 2006).

Amenorrhoea, CHF, decreased libido, oedema, erectile dysfunction, headache, hypertension, hypertensive encephalopathy, hypokalaemia, hypokalaemic myopathy, lethargy, lower extremity weakness, mineralocorticoid effects, myoglobinuria, pulmonary oedema, quadriplegia, rhabdomyolysis, fluid retention (herbwisdom, 2015k).

[323] low potassium in the blood

## Side-effects

Liquorice with glycyrrhizin may cause serious side effects. Too much glycyrrhizin causes a condition called pseudoaldosteronism, which can cause a person to become overly sensitive to a hormone in the adrenal cortex. This condition can lead to headaches, fatigue, high blood pressure, and even heart attacks. It may also cause water retention, which can lead to leg swelling and other problems.

Although the dangerous effects mostly happen with high doses of liquorice or glycyrrhizin, smaller amounts of liquorice may cause side effects. Some people have **muscle pain** or **numbness in the arms and legs**. To be safe, ask your health care provider to monitor your use of liquorice.

Liquorice is likely safe for most people when consumed in amounts found in foods. Liquorice is possibly safe when consumed in larger amounts for medicinal purposes and when applied to the skin for a short amount of time. However, it is possibly unsafe when used in large amounts for more than 4 weeks. Consuming liquorice daily for several weeks or longer can cause severe side effects including **high blood pressure**, **low potassium levels**, **weakness**, **paralysis**, and **occasionally brain damage** in otherwise healthy people. In people who eat a lot of salt or have heart disease, kidney disease, or high blood pressure, as little as 5 grams per day can cause these problems. Other side effects of liquorice use include **tiredness**, **absence of a menstrual period**, **headache**, **water and sodium retention**, and **decreased sexual interest and function** in men. People who chew tobacco flavoured with liquorice might develop high blood pressure and other serious side effects.

## Special precautions & warnings

- **Pregnancy and breast-feeding** - It is unsafe to take liquorice by mouth if you are pregnant. High consumption of liquorice during pregnancy, about 250 grams of liquorice per week, seems to increase the risk of early delivery. It might cause a miscarriage or early delivery. Not enough is known about the safety of liquorice during breast-feeding. Don't use liquorice if you are pregnant or breast-feeding (MedlinePlus, 2014d).
  Use during pregnancy should be avoided. Liquorice exhibits oestrogenic activity and has reputed abortifacient effects (C. A. Newall, L. A. Anderson, and Phillipson, 1996b), (Ernst, 2002a). Glycyrrhetic acid has been demonstrated to cross the placental barrier in rats (Isbrucker and Burdock, 2006). Research suggests a risk factor for preterm delivery when excessive liquorice is consumed; however, the data used to support this observation were heterogeneous and retrospectively gathered via questionnaire (Strandberg, Andersson, and Järvenpää, 2003).

Despite herbal texts suggesting the use of liquorice tea as a galactogogue, there is no clinical evidence to support this case.

- **High blood pressure** - Liquorice can raise blood pressure. Don't consume large amounts of it if you have high blood pressure.
- **Heart disease** - Liquorice can cause the body to store water, and this can make congestive heart failure worse. Liquorice can also increase the risk of irregular heartbeat. Don't consume liquorice if you have heart disease.
- **Hormone-sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** - Liquorice might act like oestrogen in the body. If you have any condition that might be made worse by exposure to oestrogen, don't use liquorice.
- **A muscle condition caused by nerve problems (hypertonia)** - Liquorice can cause the level of potassium to drop in the blood. This can make hypertonia worse. Avoid liquorice if you have hypertonia.
- **Low potassium levels in the blood (hypokalaemia)** - Liquorice can lower potassium in the blood. If your potassium is already low, liquorice might make it too low. Don't use liquorice if you have this condition.
- **Sexual problems in men** - Liquorice can lower a man's interest in sex and also worsen erectile dysfunction (ED) by lowering levels of testosterone.
- **Kidney disease** - Overuse of liquorice could make kidney disease worse. Don't use it.
- **Surgery** - Liquorice might interfere with blood pressure control during and after surgery. Stop taking liquorice at least 2 weeks before a scheduled surgery.
- **Other Information** - Use for no more than 4–6 weeks (herbwisdom, 2015k).

People with the following conditions should not take liquorice -

- Heart failure,
- Heart disease,
- Hormone-sensitive cancers, such as breast, ovarian, uterine, or prostate cancer,
- Fluid retention,
- High blood pressure (hypertension),
- Diabetes,
- Kidney disease,
- Liver disease,
- Low potassium (hypokalaemia),
- Erectile dysfunction

Pregnant or breastfeeding women should not take liquorice. Some studies suggest that taking liquorice during pregnancy can increase the risk of stillbirth.

Don't use any liquorice product for longer than 4 to 6 weeks.

## Interactions

### Digoxin

Congestive heart failure and digitalis toxicity occurred in an 84-year-old man during concurrent ingestion of digoxin 0.125 mg and an herbal laxative containing liquorice ( G. glabra ) (T. Harada et al., 2002). The mechanism for digitalis toxicity was attributed to possible electrolyte imbalance resulting from the mineralocorticoid activity of liquorice.

### Prednisolone

Glycyrrhizin may inhibit the metabolism of prednisolone, elevating prednisolone plasma concentrations and increasing the pharmacologic effects and adverse reactions. Ingestion of 3 different herbal products containing glycyrrhizin increased, decreased, or had no effect on prednisolone plasma levels, depending on which herbal preparation was ingested (Homma, Oka, and Ikeshima, 1995). In two studies of glycyrrhizin effects on the pharmacokinetics of IV prednisolone, pretreatment with glycyrrhizin 50 mg every 4 hours for 4 doses increased the area under the curve of total (M. F. Chen et al., 1991) and free prednisolone, decreased total plasma clearance, and prolonged the mean residence time of prednisolone (M. F. Chen et al., 1991), (M. F. Chen et al., 1990).

Liquorice may interfere with several medications, including the ones listed below. If you are taking any medication, ask your doctor before taking liquorice.

- **ACE inhibitors and diuretics** - If you are taking angiotensin converting enzyme (ACE) inhibitors or diuretics for high blood pressure, you should not use liquorice products. Liquorice could cause these medications to not work as well or could make side effects worse, including a build up of potassium in the body. ACE inhibitors include -
  - Captopril (Capoten),
  - Benazepril (Lotensin),
  - Enalapril (Vasotec),
  - Lisinopril (Prinivil, Zestril),
  - Gosinopril (Monopril),
  - Ramipril (Altace),
  - Perindopril (Aceon),
  - Quinapril (Accupril),
  - Moexipril (Univasc),
  - Trandolapril (Mavik).
- **Digoxin** – Because liquorice may dangerously increase the risk of toxic effects from digoxin, do not take this herb with this medication.
- **Corticosteroids** - Liquorice may increase the effects of corticosteroid medications. Talk to your doctor before using liquorice with any corticosteroids.

- **Insulin or drugs for diabetes** - Liquorice may have an effect on blood sugar levels.
- **Laxatives** - Liquorice may cause potassium loss in people taking stimulant laxatives.
- **MAO inhibitors** - Liquorice may make the effects of this class of antidepressant stronger.
- **Oral contraceptives** - There have been reports of women developing high blood pressure and low potassium levels when they took liquorice while on oral contraceptives.
- **Warfarin (Coumadin)** - Liquorice may decrease the levels of this blood thinner in the body, meaning it may not work as well.
- **Medications processed by the liver** - Liquorice may interfere with several medications processed by the liver, including celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), phenytoin (Dilantin), piroxicam (Feldene), phenobarbital, and secobarbital (Seconal).
- **Diuretics, hormonal medications, and many other medications interact with liquorice** (unknown, 2014i).

## Major

**Do not take this combination**

- **Warfarin (Coumadin)** - is used to slow blood clotting. The body breaks down warfarin (Coumadin) to get rid of it. Liquorice might increase the breakdown and decrease the effectiveness of warfarin (Coumadin). Decreasing the effectiveness of warfarin (Coumadin) might increase the risk of clotting. Be sure to have your blood checked regularly. The dose of your warfarin (Coumadin) might need to be changed.

## Moderate

**Be cautious with this combination**

- **Cisplatin (Platinol-AQ)** - Cisplatin (Platinol-AQ) is used to treat cancer. There is some concern that liquorice might decrease how well cisplatin (Platinol-AQ) works for cancer.
- **Digoxin (Lanoxin)** - Large amounts of liquorice can decrease potassium levels in the body. Low potassium levels can increase the side effects of digoxin (Lanoxin).
- **Oestrogens** - Liquorice seems to change hormone levels in the body. Taking liquorice along with oestrogen pills might decrease the effects of oestrogen pills.
  Some oestrogen pills include conjugated equine oestrogens (Premarin), ethinylestradiol, estradiol, and others.

- **Ethacrynic acid (Edecrin)** - Liquorice can cause the body to get rid of potassium. Ethacrynic acid (Edecrin) can also cause the body to get rid of potassium. Taking liquorice and ethacrynic acid (Edecrin) together might cause potassium to become too low.
- **Furosemide (Lasix)** - Liquorice can cause the body to get rid of potassium. Furosemide (Lasix) can also cause the body to get rid of potassium. Taking liquorice and furosemide together might cause the potassium levels in your body to go too low.
- **Medications changed by the liver (Cytochrome P450 2B6 (CYP2B6) substrates)** - Some medications are changed and broken down by the liver. Liquorice might decrease how quickly the liver breaks down some medications. Taking liquorice along with some medications that are broken down by the liver can increase the effects and side effects of some medications. Before taking liquorice, talk to your healthcare provider if you take any medications that are changed by the liver.
  Some of these medications changed by the liver include ketamine (Ketalar), phenobarbital, orphenadrine (Norflex), secobarbital (Seconal), dexamethasone (Decadron), and others.
- **Medications changed by the liver (Cytochrome P450 2C9 (CYP2C9) substrates)** - Some medications are changed and broken down by the liver. Liquorice might change how the liver breaks down some medications. Taking liquorice along with medications that are broken down by the liver might increase or decrease the effects of these medications. Before taking liquorice, talk to your healthcare provider if you are taking any medications that are changed by the liver.
  Some medications changed by the liver include celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), and warfarin (Coumadin).
- **Medications changed by the liver (Cytochrome P450 3A4 (CYP3A4) substrates)** - Some medications are changed and broken down by the liver. Liquorice might change how the liver breaks down some medications. Taking liquorice along with medications that are broken down by the liver might increase or decrease the effects of some medications. Before taking liquorice, talk to your healthcare provider if you are taking any medications that are changed by the liver.
  Some medications changed by the liver include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and many others.
- **Medications for high blood pressure (Antihypertensive drugs)** - Large amounts of liquorice seem to increase blood pressure. By increasing blood pressure, liquorice might decrease the effectiveness of medications for high blood pressure.

Some medications for high blood pressure include captopril (Capoten), enalapril (Vasotec), losartan (Cozaar), valsartan (Diovan), diltiazem (Cardizem), amlodipine (Norvasc), hydrochlorothiazide (HydroDIURIL), furosemide (Lasix), and many others.

- **Medications for inflammation (Corticosteroids)** - Some medications for inflammation can decrease potassium in the body. Liquorice might also decrease potassium in the body. Taking liquorice along with some medications for inflammation might decrease potassium in the body too much.
  Some medications for inflammation include dexamethasone (Decadron), hydrocortisone (Cortef), methylprednisolone (Medrol), prednisone (Deltasone), and others.
- **Midazolam (Versed, others)** - Midazolam (Versed) is changed and broken down by the body. Liquorice might increase how quickly this medication is broken down by the body. Liquorice should be used cautiously if you are taking midazolam (Versed).
- **Water pills (diuretic drugs)** - Large amounts of liquorice can decrease potassium levels in the body. "Water pills" can also decrease potassium in the body. Taking liquorice along with "water pills" might decrease potassium in the body too much.
  Some "water pills" that can deplete potassium include chlorothiazide (Diuril), chlorthalidone (Thalitone), furosemide (Lasix), hydrochlorothiazide (HCTZ, HydroDIURIL, Microzide), and others.

## Are there interactions with herbs and supplements?

- **Herbs that affect the heart** - Using too much liquorice can decrease potassium in the body. This can damage the heart. Using liquorice with herbs that can damage the heart might make this effect worse. Herbs that might damage the heart include digitalis, lily-of-the-valley, pheasant's eye, and squill.
- **Stimulant laxative herbs** - Using too much liquorice can decrease potassium in the body. Herbs that have a stimulant laxative effect can also lower potassium in the body. Using liquorice along with these herbs can increase the risk of lowering potassium levels too much. Stimulant laxative herbs include aloe vera, alder buckthorn, European buckthorn, cascara sagrada, castor oil, rhubarb, and senna.

## Are there interactions with foods?

- **Grapefruit juice** - Drinking grapefruit juice when taking liquorice might increase liquorice's ability to cause potassium depletion.
- **Salt** - Liquorice use can increase sodium and water retention and increase blood pressure. Also, eating a lot of salt can make the side effects of liquorice even worse.

## Available Forms

Liquorice products are made from peeled and unpeeled, dried root. There are powdered and finely cut root preparations made for teas, tablets, and capsules, as well as liquid extracts. Some liquorice extracts do not contain glycyrrhizin. These extracts are known as deglycyrrhizinated liquorice (DGL), and do not seem to have the undesired side effects of other forms of liquorice. Some studies suggest DGL may be better for stomach or duodenal ulcers. DGL may offer protection against ulcer formation when taken with aspirin (unknown, 2014i).

## Dosage

Liquorice has a poor oral bioavailability, requiring 10 hours to reach maximum glycyrrhizic acid concentrations in healthy volunteers from the ammoniated salt and 12 hours for liquorice extract. The lipophilic components of liquorice extract have been shown to reduce the gastric emptying rate and absorption of glycyrrhizic acid, and neither glycyrrhizin nor the acid accumulate in tissues. Extensive saturable albumin binding has been demonstrated in humans. Plasma clearance is decreased in patients with chronic hepatitis C and liver cirrhosis (Isbrucker and Burdock, 2006).

Liquorice root has been used in daily doses from 2 to 15 g for ulcer and gastritis. Higher doses given for extended periods may pose a risk of hyperkalaemia. Deglycyrrhizinated liquorice extracts are available (Kassir, 1985), (A. G. Morgan, McAdam, et al., 1982), (A. G. Morgan, Pacsoo, and McAdam, 1985).

A No-Observed Effects Level[324] has been proposed as purified glycyrrhizin 2 mg/kg/day, and the Acceptable Daily Intake for glycyrrhizin is suggested at 0.2 mg/kg/day (Isbrucker and Burdock, 2006).

The following doses have been studied in scientific research -

### By mouth

- **For upset stomach** - A specific combination product containing liquorice (Iberogast, Medical Futures, Inc) and several other herbs has been used in a dose of 1 mL three times daily (MedlinePlus, 2014d).

[324] An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control

## Paediatric

Older children who have a sore throat can chew a piece of liquorice root or drink liquorice tea. Ask your doctor to help you determine the right dose for your child. Don't give a child liquorice tea for more than a day without talking to your doctor. Never give liquorice tea to an infant or toddler (unknown, 2014i).

## Adult

Your health care provider should determine the dose of liquorice that's right for you. Typical forms and dosages include -

- **Dried root** - 1 to 5 g as an infusion or decoction (boiled), 3 times daily.
- **Liquorice 1:5 tincture** - 2 to 5 mL, 3 times daily.
- **Standardised extract** - 250 to 500 mg, 3 times daily, standardised to contain 20% glycyrrhizinic acid.
- **DGL extract** - 0.4 to 1.6 g, 3 times daily, for peptic ulcer.
- **DGL extract 4:1** - chew 300 to 400 mg, 3 times daily 20 minutes before meals, for peptic ulcer.
- **Mouthwash** - Mix 1/2 teaspoon liquorice extract with 1/4 cup water, swish, gargle, and expel the mouthwash 4 times daily for apthous ulcers (unknown, 2014i).

Don't use these doses of liquorice for longer than a week without talking to your doctor due to the risk of potentially dangerous side effects (unknown, 2014i).

- **Root** - 1–4 g orally, three times a day,
- **Tea** - 1 cup orally, three times a day, mixed in the proportions of 1–4 g powdered root in 150 ml water,
- **Ulcer** - 760–1520 mg DGL orally, must be mixed with saliva; For 8–16 weeks,
- **Cough** - 0.5–1 g orally of powdered root either three times a day or four times a day (herbwisdom, 2015k).

# Toxicology

Many case reports of hypokalaemic paralysis, pseudoaldosteronism, and cardiac myopathy due to hypokalaemia are found in the literature. Symptoms including severe hypokalaemia, mineralocorticoid hypertension, cardiac arrhythmias, paralysis of the extremities, metabolic alkalosis, hypoxemia, and hypercapnea[325] have been reported. Several authors suggest that liquorice intoxication might be a more commonplace cause for

[325] abnormally elevated carbon dioxide (CO2) levels in the blood

these states considering the widespread availability of liquorice-containing traditional and herbal medicines (Sigurjonsdottir et al., 1995), (Bielenberg, 1989), (Farese et al., 1991), (Y. J. Hsu, Y. F. Lin, and Chau, 2003), (linav and Chajek-Shaul, 2003), (Schapera, 2003), (S. H. Lin et al., 2003).

The mechanism by which the glycyrrhizinates exert their effect on the renin-angiotensin-aldosterone system has been elucidated (Isbrucker and Burdock, 2006), (Quinkler and Stewart, 2003), (Yasue et al., 2007), (linav and Chajek-Shaul, 2003). Competitive (and reversible) inhibition of the enzyme 11-beta-hydroxysteroid dehydrogenase results in the suppression of cortisol conversion to inactive cortisone. Consequent suppression of plasma renin activity and aldosterone levels is evident. Exchangeable sodium levels increase and cortisol occupation of mineralocorticoid receptors in the distal kidney tubules is enhanced. The condition responds to administration of spironolactone, potassium supplementation, and discontinuation of liquorice.

The majority of mutagenicity studies in animals show no genotoxic effects for liquorice or glycyrrhizinates (Isbrucker and Burdock, 2006). Teratogenicity studies in mice, rats, hamsters, and rabbits at a range of doses show no treatment-related effects (Isbrucker and Burdock, 2006). A study on foetal rat lung development explored the effect of glycyrrhizinates on 11-beta-hydroxysteroid dehydrogenase, because it is involved in surfactant synthesis. In the highest dose group, a reduction in the enzyme was observed but with no increase in foetal malformation or foetal death rate (Isbrucker and Burdock, 2006).

## Commentary

*Although Liquorice has oestrogenic possibilities, it can have some terrible side-effects, and you shouldn't take it for longer than a week, so really, its not viable as a herbal hormone for long-term usage.*

Chapter 10

# M's

## Marijuana

### Common Names

Anashca, Banji, Bhang, Blunt, Bud, Cannabis, Cannabis sativa, Charas, Dope, Esrar, Gaga, Ganga, Grass, Haschisch, Hash, Hashish, Herbe, Huo Ma Ren, Indian hemp, Joint, Kif, Mariguana, Marihuana, Marijuana, Mary Jane, Pot, Sawi, Sinsemilla, Weed, German = Haschisch, German = Indischer Hanf, Hindi = Ganjé-kaper, Italian = Canapa indiana, Russian = Konoplja indijskaja, Spanish = Cáñamo índico, Spanish = Hachís, Spanish = Marihuana, Mexican = Grifa, Mexican = María Juana, Mexican = Mota, Moroccan = Kif.

A variety of common names have been attributed to the plant. There are, however, specific terms for the various plant parts and extracts. These include: anascha and kif (resinous material and flowering tops mixed with the leaves); banji, hemp, cannabis, shesha, dimba, dagga, suma, vingory, and machona (entire plant); bhang and sawi (dried mature leaves); charas (resinous material); ganga (flowering tops); hashish and esrar (resinous material with flowering tops); and marijuana or marihuana (leaves and flowering tops). Commercial preparations include dronabinol (Marinol), an FDA schedule III drug; THC[326] plus cannabidiol (Cannador), not approved in the United States; Sativex (Cannabis extracts) spray, recently approved (2010) in the United Kingdom; and nabilone (Cesamet), an FDA schedule III drug.

### Latin name

*Cannabis sativa*

[326] tetrahydrocannabinol, see THC - Tetrahydrocannabinol for further specific information

## Overview

Marijuana is an herb. It contains chemicals called cannabinoids that affect the central nervous system. Cannabinoids are found in the highest concentration in the leaves and flowers, the parts that are used to make medicine.

Some people use marijuana recreationally to create a sense of well being or to alter the senses. It is either taken by mouth or smoked (inhaled).

Marijuana is also taken by mouth for medicinal purposes. A cannabinoid from marijuana, tetrahydrocannabinol THC, is used in the prescription-only, FDA-approved product dronabinol (Marinol) for the treatment of weight loss or appetite loss due to AIDS and for nausea and vomiting caused by cancer chemotherapy. Cannabinoids are at least as effective as some conventional medications for nausea, including prochlorperazine (Compazine), metoclopramide (Reglan), chlorpromazine (Compazine), and thiethylperazine (Torecan).

Cannabinoids from marijuana also appear to be similar to codeine for treatment of pain. However, extreme sleepiness and other CNS effects make cannabinoids undesirable as painkillers.

Other cannabinoids from marijuana have also been used by mouth to treat symptoms of multiple sclerosis (MS).

Some people inhale marijuana for medicinal purposes. Marijuana is smoked for nausea, glaucoma, appetite stimulation, mucous membrane inflammation, leprosy, fever, dandruff, haemorrhoids, obesity, asthma, UTIs, cough, anorexia associated with weight loss in AIDS patients, pain, and multiple sclerosis. It is also inhaled to weaken the immune system after kidney transplant to lessen the chance of transplant rejection.

Avoid confusion with hemp, a distinct variety of Cannabis sativa cultivated for its fibre and seeds, which contains less than 1% THC.

In the U.S., marijuana is classified as a Schedule I controlled substance, making possession illegal. Some states, such as California, Washington, Oregon, Arizona, and others, have legalized or decriminalized the use of medical marijuana, despite objections from the federal government. Some countries such as Canada also permit the use of medical marijuana (WMD, 2009c).

A multiple-use plant, furnishing fibre, oil, medicine, and narcotics. Fibres are best produced from male plants. In the temperate zone, oil is produced from females which have been left to stand after the fibre-producing males have been harvested. Leaves are added to soups in southeast Asia. Varnish is made from the pressed seeds. Three types of narcotics are produced: hashish (bhang), the dried leaves and flowers of male and female shoots; ganja, dried unfertilised inflorescences of special female plants; and charas, the crude resin, which is probably the strongest. Modern medicine uses cannabis in glaucoma and alleviating the pains of cancer and chemotherapy. More resin is produced in tropical than

in temperate climates. Lewis lung adenocarcinonoma growth has been retarded by oral administration of delta-9-tetrahydrocannabinol, delta-8-tetrahydrocannabinol and cannabinol, but not by cannabidiol. The delta-9 also inhibits the replication of Herpes simplex virus (J. A. Duke, 1983a).

## Botany

Cannabis is a leafy annual, with some varieties attaining heights of more than 3 m. The stalk may grow 7.6 to 10 cm thick, is square and hollow, and has ridges running along its length. Each leaf has 5 to 11 soft-textured leaflets, 18 to 25 cm long, radiating from the top of the stalk. The leaflets are narrow and lance-shaped with regular sawblade-like dentation. The plant is dioecious, having male or female flowers on different plants. The female plants have heavy foliage, while the male plants are more sparse. The resin mixture is found in the glandular hairs of the leaflets and floral bracts and is called hashish. Cannabis is cultivated worldwide for fibre, seed oil, and hashish (NRCS, 2010a), (P. J. Cohen, 2009a).

Annual herb, usually erect; stems variable, up to 5 m tall, with resinous pubescence, angular, sometimes hollow, especially above the first pairs of true leaves; basal leaves opposite, the upper leaves alternate, stipulate, long petiolate, palmate, with 3-11, rarely single, lanceolate, serrate, acuminate leaflets up to 10 cm long, 1.5 cm broad; flowers monoecious or dioecious, the male in axillary and terminal panicles, apetalous, with 5 yellowish petals and 5 poricidal stamens; the female flowers germinate in the axils and terminally, with one 1-ovulate ovary; fruit a brown, shining achene, variously marked or plain, tightly embracing the seed with its fleshy endosperm and curved embryo. Fl. summer; fr. late summer to early fall; year round in tropics. Seeds weigh 1.5-2.5 gm/100 seeds. (J. A. Duke, 1983a).

## History

The use of cannabis dates back more than 4,000 years in central Asia. It has been used for the treatment of catarrh, leprosy, fever, dandruff, haemorrhoids, obesity, asthma, UTIs, loss of appetite, inflammatory conditions, and cough. It has also been used as a source of fibre for ropes and clothing. The plant's sedative effects were recognised by the ancient Chinese, but the widespread use of the plant for its psychoactive effects began in the past century (J. Duke, 1985), (Fehr, 1983).

Cannabis as marijuana is a schedule 1 controlled substance in the United States, with synthetic cannabinoids registered for specific indications as Marinol (THC as dronabinol), indicated as an anti-emetic for chemotherapy-induced nausea and vomiting and the treatment of AIDS-related wasting

syndrome, and Cesamet (nabilone), used as an anti-emetic in cancer patients. The orobuccal spray Sativex is approved for multiple sclerosis spasticity in Canada and use was recently approved in the United Kingdom (Seamon, 2006), (Wilkins, 2006), (unknown, 2003a).

## Folk Medicine

Medicinally, plants are tonic, intoxicant, stomachic, anti-spasmodic, analgesic, narcotic, sedative and anodyne. Seeds and leaves are used to treat old cancer and scirrhous[327] tumours. The seed, either as a paste or as an unguent[328], is said to be a folk remedy for tumours and cancerous ulcers. The decoction of the root is said help remedy hard tumours and knots in the joints. The leaf, prepared in various manners, is said to alleviate cancerous sores, scirrhous tumours, cold tumours, and white tumours. The plant is also used for mammary tumours and corns (CSIR, 1948–1976). Europeans are said to use the dregs from Cannabis pipes in "cancer cures" (Watt and Breyer-Brandwijk, 1962). Few plants have a greater array of folk medicine uses: alcohol withdrawal, anthrax, asthma, blood poisoning, bronchitis, burns, catarrh, childbirth, convulsions, coughs, cystitis, delirium, depression, diarrhoea, dysentery, dysmenorrhoea, epilepsy, fever, gonorrhoea, gout, inflammation, insomnia, jaundice, lockjaw, malaria, mania, mennorhagia, migraine, morphine withdrawal, neuralgia, palsy, rheumatism, scalds, snakebite, swellings, tetany, toothache, uteral prolapse, and whooping cough. Seeds ground and mixed with porridge given to weaning children (J. A. Duke, 1983a).

## Chemistry

More than 420 different compounds have been isolated from cannabis and reported in chemical literature. The most commonly described compounds are the cannabinoids (THC, cannabidiol, cannabiniol, and 60 other related compounds). In addition, marijuana contains alkaloids, steroidal compounds, and mixtures of volatile components (Seamon, 2006), (Wilkins, 2006), (Baker, Pryce, et al., 2003). Synthetic cannabinoids include nabilone, ajulemic acid, HU-210, and WIN 55,212-2, some of which are nonpsychotropic agonists of cannabinoid receptors (Burstein et al., 2004), (Di Marzo and Petrocellis, 2006).

[327] a hard slow-growing malignant tumour having a preponderance of fibrous tissue

[328] a soothing preparation spread on wounds, etc

The concentration of THC varies in different parts of the plant, being higher in the bracts, flowers, and leaves and lower in the stems, seeds, and roots. THC concentration varies from insignificant amounts in hemp varieties to 3% to 6% in smoked marijuana and more than 6% in the resinous, compressed paste obtained from the dried flowers. Different cultivation methods and varieties contribute to variations in potency (Seamon, 2006), (P. J. Cohen, 2009b).

Analysis of cannabis includes methods such as gas chromatography, high-performance liquid chromatography, random amplification of polymorphic DNA, and thin layer chromatography. These methods are useful in sample differentiation, forensic analysis, and other applications (Lerckher et al., 1992), (Debruyne et al., 1994), (Petri et al., 1995), (Gillan et al., 1995). Radioimmunoassay of hair for marijuana presence in the body has also been performed (Hindin et al., 1994).

Most varieties contain cannabinol and cannabinin; Egyptian variety contains cannabidine, cannabol and cannabinol, their biological activity being due to the alcohols and phenolic compounds. Resin contains crystalline compound cannin. Alcoholic extracts of American variety vary considerably in physiological activity. Per 100 g, the seed is reported to contain 8.8 g $H^2O$, 21.5 g protein, 30.4 g fat, 34.7 g total carbohydrate, 18.8 g fibre, and 4.6 g ash. In Asia, per 100 g, the seed is reported to contain 421 calories, 13.6 g $H^2O$, 27.1 g protein, 25.6 g fat, 27.6 g total carbohydrate, 20.3 g fibre, 6.1 g ash, 120 mg Ca, 970 mg P, 12.0 mg Fe, 5 mg beta-carotene equivalent, 0.32 mg thiamine, 0.17 mg riboflavin, and 2.1 mg niacin. A crystalline globulin has been isolated from defatted meal. It contains 3.8% glycocol, 3.6 alanine, 20.9 valine and leucine, 2.4 phenylalanine, 2.1 tyrosine, 0.3 serine, 0.2 cystine, 4.1 proline, 2.0 oxyproline, 4.5 aspartic acid, 18.7 glutamic acid, 14.4 tryptophane and arginine, 1.7 lysine, and 2.4% histidine. Oil from the seeds contains 15% oleic, 70% linoleic, and 15% linolenic and isolinolenic acids. The seed cake contains 10.8% water, 10.2% fat, 30.8% protein, 40.6% N-free extract, and 7.7% ash (20.3% K2O; 0.8% Na2O; 23.6% CaO, 5.7% MgO, 1.0% Fe2O3, 36.5% P2O5, 0.2% SO3; 11.9% SiO2, 0.1% Cl and a trace of Mn2O3). Trigonelline occurs in the seed. Cannabis also contains choline, eugenol, guaiacol, nicotine, and piperidine (CSIR, 1948–1976), all listed as toxins by the National Institute of Occupational Safety and Health. A beta-resercyclic acid derivative has antibiotic and sedative properties; with a murine LD-50 of 500 mg/kg, it has some aritiviral effect and inhibits the growth of mouse mammary tumour in egg embryo (Watt and Breyer-Brandwijk, 1962).

## Uses and Pharmacology

Decrease intraocular pressure, analgesia, anti-emetic effects, appetite stimulant (medscape, 2015i).

Both exogenous and endogenous cannabinoids act on 2 receptors: CB1 receptors are found primarily in the CNS but also in lung, reproductive, and vascular endothelial tissue; CB2 receptors are found mainly in peripheral and immune-related tissue, but also in retinal and microglia cells (Seamon, 2006), (Baker, Pryce, et al., 2003), (Bari et al., 2006). Due to the illegality of marijuana possession and use in many jurisdictions, data from clinical trials is limited and much of the relevant documentation is based on retrospective data[329] or case studies (Association, 2010).

- **Absorption** - 10–20% inhaled; 1–10% orally,
- **Onset of action** - 6–12 minutes when inhaled; 30–120 minutes orally,
- **Peak effect** - 20–30 minutes when inhaled; 2–3 hours orally,
- **Toxic dose (THC)** - 15 mg/kg,
- **Lethal dose** 30 mg/kg,
- **Duration of effect** - 2–6 hours,
- **Protein Bound** - 97–99%,
- **Metabolism** - Hepatic hydroxylation to active and inactive metabolites, then further metabolised by alcohol dehydrogenase or alternatively, metabolites can be further oxidised to more polar compounds and glucuronide conjugates,
- **Excretion** - Faeces 30–50%; 10–16% excreted in the urine as metabolites,
- **Half-life** - 28 hours (56 hours with chronic use) (medscape, 2015i).

## Appetite stimulant

Dronabinol is indicated for use as an appetite stimulant in HIV patients, although limited data exist. Self-reported increases in appetite (data obtained from surveys) have not been demonstrated in prospective, blind, and randomised clinical trials, with no improvements in quality of life measures found and no weight gain over placebo (Di Marzo and Petrocellis, 2006), (Strasser et al., 2006).

## Cancer/chemotherapy-induced nausea and vomiting

### Animal data

Cannabinoids, including THC, have been studied in rodents for their potential in inhibiting tumour growth via the induction of apoptosis and inhibition of angiogenesis (Blázquez, Carracedo, and Salazar, 2008).

[329] the investigator collects data from past records and does not follow the patients up

## Clinical data

Synthetic cannabinoid analogs dronabinol and nabilone have been approved by the FDA for the treatment of recalcitrant chemotherapy-induced nausea and vomiting; however, clinical data on efficacy of THC and medicinal cannabis is equivocal and the incidence of adverse events is higher than that of standard neuroleptics (Di Marzo and Petrocellis, 2006), (Strasser et al., 2006), (Machado Rocha et al., 2008), (Engels et al., 2007), (Di Carlo and Izzo, 2003). Some studies suggest greater efficacy in specific age groups (ie, children) with causative chemotherapeutic agents and with different delivery methods (Di Marzo and Petrocellis, 2006), (Machado Rocha et al., 2008), (Engels et al., 2007).

# Glaucoma

## Animal data

Studies in rats and rabbits suggest cannabinoids act via various mechanisms in the eye. Suppression of dopamine and presynaptic transmitter release from cones and bipolar retinal cells has been demonstrated (Yazulla, 2008), as well as mydriasis due in part to action via sympathomimetic pathways (Korczyn and Eshel, 1982). Reduced intraocular pressure has also been demonstrated in rabbits possibly through cyclooxygenase pathways (Green, Kearse, and McIntyre, 2001).

## Clinical data

Clinical trials are generally lacking or of very small sample size. An early study achieved reductions in intraocular pressure at 1 hour after 2 g of marijuana was smoked via a water pipe (Hepler and Frank, 1971), with case reports suggesting similar findings (Trittibach, Frueh, and Goldblum, 2005), (Zhan et al., 2005). An open-label study conducted by ophthalmologists found an initial reduction in intraocular pressure in 9 subjects with glaucoma unresponsive to standard therapy. However, the effect was not sustained at the end of the 9-month study and all participants elected to discontinue the therapy. Oral THC up to a maximum of 20 mg 4 times a day was used (Flach, 2002). In another small study (N = 8), a single topical application of THC was effective in reducing the intraocular pressure after 30 minutes to a maximum effect at 60 minutes (Porcella et al., 2001). A randomised, double-blind, cross-over study (N = 6) evaluating oromucosal delivery of THC and cannabidiol found THC to have some effect, but not cannabidiol. Intraocular pressure returned to baseline at 4 hours (Tomida et al., 2006).

## Multiple sclerosis

### Animal data

Studies from in-vitro and animal experiments support the effectiveness of cannabinoids in multiple sclerosis, including the reduction of oligodendrocyte and neuronal cell death, influence on inflammation and microglial migration, and enhancement of remyelination (Teare and J. Zajicek, 2005), (Baker and Pryce, 2003a). Experimentally, it has been demonstrated that antagonism of CB1 receptors (but not CB2 receptors) inhibits spasticity, but can sometimes transiently worsen it (Baker, Pryce, et al., 2003).

### Clinical data

A number of small studies on marijuana use in multiple sclerosis have been published, as well as a large (N = 667) multicentre trial[330] conducted in the United Kingdom (Teare and J. Zajicek, 2005), (Wade et al., 2004), (Vaney, Heinzel-Gutenbrunner, and Jobin, 2004), (Hosking and J. P. Zajicek, 2008), (J. P. Zajicek, Sanders, and D. E. Wright, 2005). Despite availability of clinical data from these trials, a definitive role for the use of cannabis extracts or its analogs in multiple sclerosis is still lacking. This is due in part to difficulty in obtaining objective clinical measures of reductions in spasticity, as most trials use self-reporting as the primary outcome measure (Baker, Pryce, et al., 2003), (Teare and J. Zajicek, 2005), (Baker and Pryce, 2003b). The multicentre Cannabinoids in Multiple Sclerosis (CAMS) study found no effect on the primary outcome of muscle spasticity at 15 weeks; however, at 12 months a small improvement was found over baseline (Hosking and J. P. Zajicek, 2008), (J. P. Zajicek, Sanders, and D. E. Wright, 2005), (J. Zajicek et al., 2003). Improvements in self-reported outcomes of pain, spasticity, and spasms, and quality of sleep were recorded. No functional improvement in tremor was found in a short-term trial (Fox et al., 2004).

Improvements in urge incontinence were demonstrated in the CAMS study and other open-label trials (Baker, Pryce, et al., 2003), (Teare and J. Zajicek, 2005), (R. M. Freeman et al., 2006). Decreased incontinence episode rate was observed in both treatment arms of the study as well as in the placebo arm, but improvement was greater with cannabinoids compared with placebo (R. M. Freeman et al., 2006).

[330] controlled studies which are planned and carried out by several cooperating institutions to assess certain variables and outcomes in specific patient populations

## Pain

Surveys reveal widespread usage of cannabis to manage pain among patients with HIV, multiple sclerosis, rheumatoid arthritis, and cancer (M. A. Ware, Doyle, et al., 2003), (Woolridge et al., 2005), (S. Wright, M. Ware, and G. Guy, 2006). THC has been shown to affect brain-derived neurotrophic factor involved in the health of neurons and modulate neuroplasticity, which may be relevant in processes underlying learning and memory (D'Souza et al., 2009).

### Animal data

Results from experiments conducted in animals provide support for a therapeutic role in the management of pain (B. Costa et al., 2007), (F. Comelli et al., 2008). Experiments are focusing on finding cannabinoid derivatives devoid of psychoactive properties, such as ajulemic acid (Burstein et al., 2004).

### Clinical data

Clinical trials investigating the efficacy of cannabis and derivatives have been conducted on acute postoperative pain, induced pain in volunteers, and chronic pain, including neuropathic pain and pain due to cancer (Karst and Wippermann, 2009). Studies evaluating efficacy in postoperative pain have produced mixed results, with some reporting no difference compared with placebo (single dose of 5 mg of THC) and others showing a dose-dependent effect (Karst and Wippermann, 2009), (Buggy et al., 2003), (Holdcroft et al., 2006). In volunteers, no effect on experimental pain (eg, pressure, heat, cold, electrical) was found with a single dose of 20 mg THC (Naef et al., 2003). Similarly, no effect on the pain threshold was found in one study, while a modest analgesic effect was found in another (Kraft, Frickey, and Kaufmann, 2008), (Wallace, Schulteis, and J. H. Atkinson, 2007).

In systematic reviews of clinical trials in chronic and neuropathic pain, including multiple sclerosis, HIV, and diabetic neuropathies, low to moderate decreases in pain have been demonstrated, with estimates of relative efficacy for THC compared with codeine for pain as 10 mg THC to 60 mg codeine (Baker, Pryce, et al., 2003), (Karst and Wippermann, 2009), (Iskedjian et al., 2007), (Martín-Sánchez et al., 2009). The value of these results is moderated by a simultaneous increase in adverse events, with number-needed-for-harm estimates between 5 and 8 on visual analog scales for cognitive and motor function adverse events (Martín-Sánchez et al., 2009). Clinical trials conducted after these reviews produced mixed results, with some (Wilsey, Marcotte, and Tsodikov, 2008), (Ellis, Toperoff, and Vaida, 2009), but not all (Centonze, Mori, and Koch, 2009), (Selvarajah et al., 2010), demonstrating greater pain reduction with THC than with placebo.

## Other effects

- **Central Nervous System** - Limited studies have evaluated the efficacy of cannabinoids in sleep disorders (J. S. Berman, Symonds, and Birch, 2004), (M. A. Ware, Fitzcharles, et al., 2010), (E. B. Russo, G. W. Guy, and Robson, 2007), anxiety (Bhattacharyya, Fusar-Poli, and Borgwardt, 2009), (Phan et al., 2008), dyskinesia (C. B. Carroll, Bain, and Teare, 2004), and Tourette syndrome (Müller-Vahl, U. Schneider, and Prevedel, 2003), (Müller-Vahl, Prevedel, et al., 2003) with mixed results.
- **Lipids** - Hempseed oil has shown no benefit with regard to changes in the lipid profile, plasma glucose, or insulin (Kaul, Kreml, and Austria, 2008), (Schwab et al., 2006).
- **Glaucoma** - Doses of 25 to 50 mcg topical THC (Porcella et al., 2001), and 5 mg oromucosal THC (Tomida et al., 2006) reduced the intraocular pressure in studies in patients with resistant glaucoma. Delivery site and preparations may influence ophthalmic effects (Green, Kearse, and McIntyre, 2001).
- **Multiple sclerosis** - A large, multicentre trial used initial doses of 5 mg oral THC daily, self-titrated up to 25 mg THC daily for up to 52 weeks (J. P. Zajicek, Sanders, and D. E. Wright, 2005).
- **Pain** - Estimates of relative efficacy for THC compared with codeine for pain are 10 mg THC to 60 mg codeine (Karst and Wippermann, 2009). THC is distributed rapidly throughout the body, especially to tissues with high lipid content. Approximately 80% to 90% of an IV dose of THC is excreted in urine and the remainder is excreted in faeces via the bile (Mason and McBay, 1985).

## Uses & Effectiveness

### Possibly Effective for

- **Glaucoma** Smoking marijuana seems to reduce pressure inside the eye in people with glaucoma. However, it also seems to decrease blood flow to the optic nerve. So far, it is not known if marijuana can improve sight.
- **HIV/AIDS-related weight loss** Smoking marijuana seems to stimulate the appetite of people with AIDS. Marijuana cigarettes can also cause weight gain in people with HIV who are also taking indinavir (Crixivan) or nelfinavir (Viracept).
- **Multiple sclerosis (MS)** When smoked or when used as a mouth spray, marijuana seems to be effective for the treatment of muscle tightness and shakiness in people with MS. However, taking marijuana extract by mouth does not seem to consistently reduce shakiness in patients with MS.
- **Nerve pain** Early research shows that smoking marijuana three times a day might reduce nerve pain caused by HIV and other conditions.

- **Pain** Research shows that taking marijuana or certain marijuana components, called cannabinoids, by mouth can decrease pain in people experiencing long-term pain.

### Insufficient Evidence for

- Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). Early research shows that patients with ALS who use marijuana might have improvements in some symptoms, including depression, appetite, spasms, and drooling.
- Weight loss in people with advanced cancer (cachexia). Early research shows that taking marijuana extract by mouth does not improve appetite in people with cachexia.
- Rheumatoid arthritis (RA). Some research suggests that using a specific mouth spray containing marijuana extract (Sativex) can decrease morning pain and improve sleep in people with RA. However, it does not seem to improve joint stiffness in the morning or overall pain severity.
- Dandruff.
- Haemorrhoids.
- Obesity.
- Asthma.
- Urinary infections.
- Leprosy.
- Preventing organ rejection after kidney transplants.
- Other conditions.

More evidence is needed to rate marijuana for these uses (WMD, 2009c).

## How it works

THC, a component of marijuana, acts both centrally and peripherally on endogenous cannabinoid receptors; activation of cannabinoid receptors affects serotonin release, increases catecholamines, inhibits parasympathetic activity, and inhibits prostaglandin biosynthesis (medscape, 2015i).

## Contraindications

Hypersensitivity, coadministration with dronabinol (a Cannabis derivative) (medscape, 2015i).

## Adverse Reactions

Medical marijuana or its analogs are regarded as having a relatively positive safety profile, but supportive studies are limited (Wilkins, 2006). High doses are rarely fatal; however, a narrow dosing index exists between desired medicinal benefit and undesirable adverse reactions. Study dropouts are commonly recorded, due mainly to the impairment of cognitive ability (eg, attention, working memory) and gastrointestinal disturbances (Wilkins, 2006), (Roser et al., 2008), (T. Wang et al., 2008). Nonserious adverse events due to medicinal cannabinoid use were found to be 1.86 times higher than those seen with placebo in a systematic review of clinical studies (T. Wang et al., 2008). White lesions in the mouth similar to chemical burns have been reported with the use of oromucosal cannabinoids (Scully, 2007). Increases in plasma cortisol due to administered THC have been demonstrated (Ranganathan, Braley, and Pittman, 2009), and increases in heart rate and both transient hypotension and increased systolic blood pressure have also been recorded (P. J. Cohen, 2009a). An increased risk of cardiovascular events, such as acute myocardial infarction, has been suggested (W. Hall and Degenhardt, 2003).

No serious adverse events were reported in a 12-month study of cannabis use in multiple sclerosis patients (J. P. Zajicek, Sanders, and D. E. Wright, 2005). A systematic review of studies using medicinal cannabinoids, but not nabilone, found no difference in serious adverse events and no difference in death versus placebo (T. Wang et al., 2008). A study evaluating the use of oral Cannador in postoperative pain was terminated due to a vasovagal event in one patient (Holdcroft et al., 2006).

Tolerance, psychological or physical dependence, withdrawal symptoms, altered sensorium, dizziness, somnolence, fatigue, reduced coordination, cognitive impairment, impaired balance, euphoria, paranoia, hallucinations, mood alterations, panic, anxiety, hypotension, hypertension, tachycardia, flushing, syncope, xerostomia, nausea, vomiting, dysgeusia, tooth discolouration, anorexia, increased appetite, oral candidiasis, diarrhoea, constipation, urinary retention, skin rash, dry eyes, blurred vision, allergy, cough, pharyngitis (medscape, 2015i).

## Side Effects & Safety

The cannabinoid, dronabinol, which is found in marijuana, is likely safe when taken by mouth appropriately as a prescription medication. Dronabinol (Marinol) is an FDA-approved prescription product.

Marijuana is possibly safe when used as a standardised mouth spray (Sativex).

Marijuana is possibly unsafe when smoked or taken by mouth as a plant or plant extract. It is classified as an illegal substance on the federal government level.

Use of marijuana can cause

- **dry mouth**,
- **nausea**,
- **vomiting**,
- **dry or red eyes**,
- **heart and blood pressure problems**,
- **lung problems**,
- **impaired mental functioning**,
- **headache**,
- **dizziness**,
- **numbness**,
- **panic attacks**,
- **hallucinations**,
- **flashbacks**,
- **depression**, and
- **sexual problems**.

## Special Precautions & Warnings

- **Pregnancy** - Marijuana is unsafe when taken by mouth or smoked during pregnancy. Marijuana passes through the placenta and can slow the growth of the fetus. Marijuana use during pregnancy is also associated with childhood leukaemia and abnormalities in the foetus (WMD, 2009c).
  Information regarding safety and efficacy of medicinal marijuana in pregnancy and lactation is lacking. Avoid use. In retrospective studies, marijuana use has had a modest effect on feotal growth. Some mild developmental abnormalities have been associated with maternal use of the drug during pregnancy, but were not sustained in the long term (at 3 years of age), and no apparent differences in IQ were noted. Data, however, are inconsistent (W. Hall and Degenhardt, 2003), (Davies and Bledsoe, 2005), (Reece, 2009). THC crosses the placental barrier and is excreted in breast milk (Davies and Bledsoe, 2005). Lower baseline plasma prolactin levels have been demonstrated with frequent cannabis use (Ranganathan, Braley, and Pittman, 2009).
  FDA pregnancy category not available; insufficient data regarding safety to foetus, avoid use.
  Case-control study reported maternal use and childhood acute nonlymphoblastic leukaemia (ANLL[331]); Children's Cancer Study Group report 10-fold increase of ANLL with maternal use.

[331] An aggressive (fast-growing) disease in which too many myeloblasts (immature white blood cells that are not lym- phoblasts) are found in the bone marrow and blood

Some sources found increased risk for low birth weight with maternal use (medscape, 2015i).

- **Breast-feeding** - Using marijuana, either by mouth or by inhalation is likely unsafe during breast-feeding. The dronabinol (THC) in marijuana passes into breast milk and extensive marijuana use during breast-feeding may result in slowed development in the baby.
  THC found in Marijuana is reported to be concentrated and secreted into breast milk (medscape, 2015i).
- **Heart disease** - Marijuana might cause rapid heartbeat, short-term high blood pressure. It might also increase the risk of a having heart attack.
- **A weakened immune system** - Cannabinoids in marijuana can weaken the immune system, which might make it more difficult for the body to fight infections.
- **Lung diseases** - Long-term use of marijuana can make lung problems worse. Regular, long-term marijuana use has been associated with lung cancer and also with several cases of an unusual type of emphysema, a lung disease.
- **Seizure disorders** - Marijuana might make seizure disorders worse in some people; in other people it might help to control seizures.
- **Surgery** - Marijuana affects the CNS. It might slow the CNS too much when combined with anaesthesia and other medications during and after surgery. Stop using marijuana at least 2 weeks before a scheduled surgery (WMD, 2009c).

## Interactions

None well documented. Potentiation of analgesic medicines can be expected (M. E. Lynch and Clark, 2003). A study conducted in rats found that cannabis inhibited the CYP-450 pathway (F. Comelli et al., 2008).

- May potentiate CNS depression with concomitant use with CNS depressants (eg, barbiturates, ethanol, anxiolytics, sedatives, and hypnotics, sedating H1-blockers, SSRIs, TCAs),
- Use of marijuana with sedating anticholinergics may result in additive tachycardia and drowsiness,
- Other: cocaine, disulfiram, ethanol, protease inhibitors, sildenafil, theophylline, cyclophosphamide, doxorubicin,
- Cannabidiol, an inactive constituent of cannabis, may weakly inhibit cytochrome P450 enzymes (CYP1A2, 2C19, 2D6, and 3A4)
- Cannabis is also a minor substrate for CYP2C9, 2C19, 2D6, 3A4 (medscape, 2015i).

### Major Interaction

Do not take this combination

- Sedative medications (Barbiturates) interacts with Marijuana.

- Marijuana might cause sleepiness and drowsiness. Medications that cause sleepiness are called sedatives. Taking marijuana along with sedative medications might cause too much sleepiness.
- Sedative medications (CNS depressants) interacts with Marijuana.
- Some sedative medications include clonazepam (Klonopin), lorazepam (Ativan), phenobarbital (Donnatal), zolpidem (Ambien), and others.
- Theophylline interacts with Marijuana.
- Taking marijuana might decrease the effects of theophylline. But there isn't enough information to know if this is a big concern.

### Moderate Interaction

Be cautious with this combination

- Disulfiram (Antabuse) interacts with Marijuana
- Disulfiram (Antabuse) might interact with marijuana. Taking marijuana along with Disulfiram can cause agitation, trouble sleeping, and irritability.
- Fluoxetine (Prozac) interacts with Marijuana.
- Taking marijuana with fluoxetine (Prozac) might cause you to feel irritated, nervous, jittery, and excited. Doctors call this hypomania.

### Minor Interaction

Be watchful with this combination

- Warfarin (Coumadin) interacts with Marijuana.
- Using marijuana might increase the effects of warfarin (Coumadin). Smoking marijuana while taking warfarin (Coumadin) might increase the chance of bruising and bleeding (WMD, 2009c).

## Availability

The United States (US) Drug Enforcement Administration (DEA) classifies marijuana as a Schedule 1 substance under the Controlled Substances Act (CSA). Schedule I drugs are recognized as having a high potential for abuse with insufficient evidence for safety and efficacy with no currently accepted medical use for treatment in the US.

Marijuana is not approved by the US FDA for medical use in the US and remains classified as an illicit drug by the DEA. However, several states have adopted individual State Medical Marijuana Laws including: Alaska, California, Colorado, Hawaii, Maine, Maryland, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Washington, and Vermont.

In October of 2009 the US Justice Department announced that it will no longer enforce federal drug laws on persons who use marijuana for medicinal purposes or their sanctioned suppliers, as long as state laws are followed (medscape, 2015i).

## Dosage

Clinical studies use a wide range of preparations and usually allow dosage titration for effect, making standard dosage recommendations difficult. A large, multicentre trial used initial doses of 5 mg of oral delta-9-tetrahydrocannabinol (THC) daily, self-titrated up to 25 mg THC daily for up to 52 weeks in multiple sclerosis. Estimates of relative efficacy for THC compared with codeine for pain are 10 mg THC to 60 mg codeine.

The following doses have been studied in scientific research -

### Orally

- The prescription product dronabinol (Marinol), which is one chemical in marijuana, is used in doses of 5 to 15 mg/m2 every 2 for 4 hours for nausea and vomiting due to cancer chemotherapy, and 2.5 to 10 mg twice daily for improving appetite in people with AIDS.
  However, current scientific information indicates that smoking or inhaling marijuana might not be safe. Talk with your healthcare provider before using this product (WMD, 2009c).

### Analgesia, Anti-emetic, Appetite Stimulant, Glaucoma

Dosing of marijuana preparations is highly dependent on a variety of factors (eg, growing and harvesting conditions, plant parts isolated).

No standard guidelines exist for dosage ranges.

### Oral

- **Tincture** - 5–15 drops or 1–3 drops of fluid extract,
- **Marinol** - 5–15 mg/sq metre twice a day, 4 hourly as required or 2.5–10 mg orally twice a day (medscape, 2015i).

### Inhalation

- 1–3 grains (65–195mg) cannabis for smoking,
- Potency highly variable,
- Drug deteriorates rapidly (medscape, 2015i).

### Wasting Syndrome

Treatment of HIV-associated wasting syndrome (medscape, 2015i).

## Cautions

History of substance abuse or mental illness, hepatic disease, cardiovascular disease, seizure disorders, non-pharmaceutical preparations contaminated with the fungus which may be hazardous to patients with compromised immune systems, elderly patients, operating machinery or driving (medscape, 2015i).

## THC - Tetrahydrocannabinol

THC is the active chemical in cannabis and is one of the oldest hallucinogenic drugs known. There is evidence that cannabis extracts were used by the Chinese as a herbal remedy since the first century AD.

Cannabis contains approximately 60 different psychoactive chemicals called cannabinoids, of which the most important one is tetrahydrocannabinol (THC). The mode of action of THC is still not properly understood.

The cannabinoids are basically non-polar molecules, with low solubility in water, so they are normally self-administered by smoking. The volatilised fractions are inhaled as a vapour and give rise to a number of physiological effects. These effects depend very much upon the expectations and mood of the user, the quantity taken, and the possible presence of other drugs (such as alcohol) in the body. Generally people experience a pleasurable state of relaxation, with heightened sensory experiences of taste, sound and colour. Repeated experiments have failed to show any short term dangers, although it hasn't been proven to be 'safe' in the pharmacological sense either. THC is non-addictive and there are no withdrawal symptoms. However, one of the side-effects of its use is to make the user drowsy, with reduced concentration and short term memory. As a result, it was made illegal in the UK for recreational use in 1928, although it is still legal in a number of other countries.

Apart from the recreational uses and abuses, THC does have some medical uses. Its anti-emetic properties (inhibits vomiting) are particularly useful in the treatment of cancer patients on chemotherapy. Also, as THC increases the appetite and reduces the vomit response, it is starting to be used in the treatment of anorexia and other eating disorders (unknown, 2015f).

## Toxicology

No consensus exists on the risk of lung cancer from smoked medical marijuana, despite a plausible biological rationale and epidemiological data. The risks of medical marijuana should be considered in the context of applications in intractable diseases (W. Hall and Degenhardt, 2003), (Mehra et al., 2006). Likewise, the potential for addiction and risk of inducing mental illness is debated (Degenhardt and W. D. Hall, 2008). A systematic review found an increased risk of psychotic outcomes with the use of cannabis (odds ratio 1.41; 95% CI 1.20 to 1.65) (Moore, Zammit, and Lingford-Hughes, 2007).

A systematic review of long-term toxicity due to nonmedical (recreational) cannabis use found increased risks for psychotic, respiratory, and cardiovascular events, as well as for cancers of the lung, head and neck, brain, cervix, prostate, and testis (Reece, 2009). Heavy cannabis use is also associated with bone loss (Reece, 2009).

Marijuana has a strong potential for abuse and is classified as a schedule drug. No consensus exists as to the risk of lung cancer from smoked medical marijuana, or the risk of psychotic events from oral cannabinoid consumption. All risk factors should be considered in the context of applications for medical marijuana in intractable diseases. Long-term toxicity due to nonmedical (recreational) cannabis includes increased risk of psychotic, respiratory, and cardiovascular events, as well as cancer.

Non-users may suffer muscular incoordination (9 of 22 persons), dizziness (8), difficulty concentrating (8), confusion (7), difficulty walking (7), dysarthria (7), dry mouth (7), dysphagia (5), blurred vision (5), and vomiting (1), following oral ingestion of THC disguised in cookies. People working with the plant or the fibre may develop dermatitis. In larger doses, hemp drugs may induce catalepsy, followed by coma and DEATH from cardiac failure (CSIR, 1948–1976).

## Commentary

*With the potential for addiction and risk of inducing mental illness it is extremely debatable as to whether this should be used as a herbal hormone. I would suggest that, on balance, it shouldn't.*

# Milk Thistle

## Common names

Mary thistle, holy thistle. Milk thistle is sometimes called silymarin, which is actually a mixture of the herbs active components, including silybinin (also called silibinin or silybin). Blessed thistle, bull thistle, Carduus marianus, fructus cardui mariae, fructus silybi mariae, Lady's milk,

Lady's thistle, Mariana mariana, marian thistle, mild marian thistle, pternix, Silberdistil, silibinin, silybe, silybon, silybum, St. Mary's thistle, thistle of the Blessed Virgin, Blessed milk thistle, Carduus marianum, Legalon, Mediterranean milk thistle, Our Lady's Thistle, Silimarina, Silybin, Wild Artichoke, variegated thistle and Scotch thistle, Artichaut Sauvage, Cardo Lechoso, Cardui Mariae Fructus, Cardui Mariae Herba, Chardon de Notre-Dame, Chardon Marbré, Chardon-Marie, Épine Blanche, Mariendistel, Shui Fei Ji, Silybe de Marie, Silybin, Silymarin, Silymarine, St. Mary Thistle, St. Marys Thistle, French = Chardon argent, French = Chardon de Marie, French = Lait de Notre Dame, German = Mariendistel, Russian = Ostropestro, Russian = Rastoropsa pjatnistaja, Swedish = Mariatistel

## Latin name

*Silybum marianum*

## Overview

Milk thistle (Silybum marianum) has been used for 2,000 years as an herbal remedy for a variety of ailments, particularly liver, kidney, and gall bladder problems. Several scientific studies suggest that substances in milk thistle (especially a flavonoid called silymarin) protect the liver from toxins, including certain drugs, such as acetaminophen (Tylenol), which can cause liver damage in high doses. Silymarin has antioxidant and anti-inflammatory properties. And it may help the liver repair itself by growing new cells.

Although a number of animal studies demonstrate that milk thistle can be helpful in protecting the liver, results in human studies are mixed (unknown, 2014j).

- Milk thistle is a plant whose fruit and seeds have been used for more than 2,000 years as a treatment for liver and biliary disorders.
- The active substance in milk thistle, silymarin, is a complex mixture of flavonolignans, primarily consisting of the following isomers: silybin (consisting of silybins A and B), isosilybin (consisting of isosilybins A and B), silychristin (also known as silichristin), and silydianin (also known as silidianin). In the literature, silybin is often referred to as silibinin.
- Laboratory studies demonstrate that silymarin functions as an antioxidant, stabilises cellular membranes, stimulates detoxification pathways, stimulates regeneration of liver tissue, inhibits the growth of certain cancer cell lines, exerts direct cytotoxic activity toward certain cancer cell lines, and may increase the efficacy of certain chemotherapy agents.
- Human clinical trials have investigated milk thistle or silymarin primarily in individuals with hepatitis or cirrhosis.

- Few adverse effects have been reported for milk thistle, but little information about interactions with anticancer medications or other drugs is available. Milk thistle is available in the United States as a dietary supplement (MedlinePlus, 2014e).

## General Information

The plant is indigenous to Europe but can also be found in the United States and South America. Traditionally, the leaves have been used in salads, and the fruit of the flower has been roasted as a coffee substitute. The seeds of milk thistle are the medicinal parts of the plant (Magula, Galisova, and Iliev, 1996a). The primary active constituent of milk thistle is silymarin, which is composed of the following isomers: silybin (consisting of silybins A and B), isosilybin (consisting of isosilybins A and B), silychristin, and silydianin. Most supplements are standardised according to their silybin content. Silybin and isosilybin are both mixtures of two diastereomers, silybins A and B and isosilybins A and B, respectively (Palasciano, Portincasa, and Palmieri, 1994a), (Saba, Galeone, and Salvadorini, 1976a). Special formulations of silybin have been developed to enhance the bioavailability of the herbal product; these forms are sold under the names Legalon, silipide, and Siliphos. Because of milk thistles lipophilic nature, it is usually administered in capsule or tablet form rather than as an herbal tea. In Europe, silybin is administered intravenously as the only effective antidote for Amanita phalloides (Fr.) Link toxin (Fintelmann and Albert, 1980a). Humans exposed to this mushroom toxin develop serious liver failure that ultimately progresses to death.

Several companies distribute milk thistle as a dietary supplement. In the United States, dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the FDA are not required unless specific disease prevention or treatment claims are made. Because dietary supplements are not formally reviewed for manufacturing consistency, ingredients may vary considerably from lot to lot; in addition, there is no guarantee that ingredients identified on product labels are present at all or are present in the specified amounts. It is important to note that the FDA has not approved the use of milk thistle as a treatment for cancer patients or patients with any other medical condition.

Despite milk thistle's long history of being used to treat liver and biliary complaints, it was not until 1968 that silymarin was isolated from the seeds of the plant, and it was proposed that silymarin might be the active ingredient (Moscarella, Giusti, and Marra, 1993a). Silymarin was later determined to be a flavonolignan that is composed of four structurally similar compounds: silybin, isosilybin, silydianin, and silychristin (Palasciano, Portincasa, and Palmieri, 1994a). Researchers have

investigated the role that silibinin may play in the treatment of hepatitis and cirrhosis. Most studies have investigated the isolated compound silymarin or its most active isomer silybin, rather than the herbal plant in its whole form.

Silymarin is most well known for its purported effects on the liver. In laboratory studies, silymarin has been found to stabilise cell membranes, thus preventing toxic chemicals from entering the cell (Fintelmann and Albert, 1980a), (Lirussi, Nassuato, and Orlando, 1995a), (Trinchet, Coste, and V. Levy, 1989a), (Moscarella, Giusti, and Marra, 1993a), (Fintelmann, 1970a). Laboratory studies have also demonstrated that silymarin stimulates synthesis and activity of enzymes responsible for detoxification pathways and exhibits antioxidant properties (Fintelmann, 1970a), (Trinchet, Coste, and V. Levy, 1989a), (Leng-Peschlow and Strenge-Hesse, 1991a), (Sonnenbichler and Zetl, 1987a), (Skakun and Moseichuk, 1988a), (Campos, Garrido, and Guerra, 1989a), (Mullen and Dasarathy, 1998a), (Muzes, Deak, and Lang, 1990a), (Mira, M. S. Azevedo, and Manso, 1987a), (R. J. Andrade, Lucena, and De la Cruz, 1998a), (Anon, 1999), (Studlar, 1985). Specifically, silymarin has been shown to stimulate the glutathione S-transferase pathway and alter the intracellular concentration of glutathione (a potent antioxidant). Silymarin has also been shown to neutralise a wide range of free radicals.

Laboratory experiments conducted using cancer cell lines have suggested that silibinin enhances the efficacy of cisplatin and doxorubicin against ovarian and breast cancer cells (Schuppan, Strosser, and Burkard, 1998a). Silybin appears to have direct anticancer effects against prostate, breast, and ectocervical tumour cells (Albrecht, H. Frerick, and Kuhn, 1992a). Silybin may also affect the cell cycle in cancer cells by slowing down cell growth, as demonstrated with prostate cancer cell lines (F. Frerick, Kuhn, and Strenge-Hesse, 1990a). Laboratory studies using leukemia cell lines found that silybin did not stimulate growth of leukemia cells (Grungreiff, Albrecht, and Strenge-Hesse, 1995a).

No human clinical trials on milk thistle or silymarin as a cancer treatment or as an adjunctive therapy in individuals with cancer have been published. Most clinical trials have investigated silymarin's effectiveness in the treatment of patients with hepatitis, cirrhosis, or biliary disorders (Marena and Lampertico, 1991a), (Hruby, Caomos, and Thaler, 1984a), (Vailati, Aristia, and Sozze, 1993a), (Marcelli, Bizzoni, and Conte, 1992a), (Held, 1993a), (Velussi, Cernigoi, and Viezzoli, 1993a), (Cavalieri, 1974a), (Saba and Mignani, 1979), (Mironets, Krasovskaia, and Polishchuk, 1990a), (Fallah Huseini et al., 2004a). These studies have employed a wide range of doses (120–560 mg /day) and have yielded conflicting results. Many of the well-designed, large-scale trials have reported a beneficial effect rather than no effect. The most commonly reported adverse effects are a mild laxative effect and gastrointestinal upset.

## Botany

Milk thistle is indigenous to Europe and Asia but has been naturalised in North and South America. The plant grows 1.5 to 3 m in height and has large, prickly leaves. When broken, the leaves and stems exude a milky sap. The reddish-purple flowers are ridged with sharp spines. The part used as the drug includes the shiny, mottled, black- or grey-toned fruits that often are referred to as seeds. These make up the thistle portion, along with its silvery pappus, which readily falls away and is not part of the extract preparation (NRCS, 2010b), (WHO, 1999a).

## History

Milk thistle has been used for more than 2,000 years, primarily as a treatment for liver dysfunction. The oldest reported use of milk thistle was by Dioscorides, who recommended the herb as a treatment for serpent bites (Magula, Galisova, and Iliev, 1996a). Pliny the Elder (A.D. 23–79) reported that the juice of the plant mixed with honey is indicated for "carrying off bile" (Magula, Galisova, and Iliev, 1996a), (Palasciano, Portincasa, and Palmieri, 1994a). In the Middle Ages, milk thistle was revered as an antidote for liver toxins (Magula, Galisova, and Iliev, 1996a), (Palasciano, Portincasa, and Palmieri, 1994a). The British herbalist Culpepper reported it to be effective for relieving obstructions of the liver (Magula, Galisova, and Iliev, 1996a), (Palasciano, Portincasa, and Palmieri, 1994a). In 1898, eclectic physicians Felter and Lloyd stated the herb was good for congestion of the liver, spleen, and kidney (Magula, Galisova, and Iliev, 1996a), (Palasciano, Portincasa, and Palmieri, 1994a). Native Americans use milk thistle to treat boils and other skin diseases. Homeopathic practitioners used preparations from the seeds to treat jaundice, gallstones, peritonitis, haemorrhage, bronchitis, and varicose veins (Palasciano, Portincasa, and Palmieri, 1994a). The German Commission E recommends milk thistle use for dyspeptic complaints, toxin-induced liver damage, hepatic cirrhosis, and as a supportive therapy for chronic inflammatory liver conditions (Saba, Galeone, and Salvadorini, 1976a).

Milk thistle has been used medicinally since the 4th century BC. Its use in treating hepatobiliary diseases dates back to the 1700s, and its use as a liver protectant can be traced back to Greek references. Pliny the Elder, a 1st century Roman writer (AD 23–79), noted that the plant's juice was excellent for "carrying off bile." The 17th century English herbalist Nicholas Culpepper wrote that milk thistle was beneficial in treating jaundice and for removing liver and spleen obstructions. The Eclectic medical system (19th to 20th century) used milk thistle to treat varicose veins, menstrual difficulty, and congestion in the liver, spleen, and kidneys. The fruit, stem, and seeds are all considered to have medicinal value.

Early colonists introduced milk thistle to North America. The plant was grown in Europe and the de-spined leaves were used in salads and eaten as a vegetable; the stalks and root parts also were consumed. The flower portion was eaten "artichoke-style." The roasted seeds were used as a coffee substitute (WHO, 1999a), (S. Foster, 1991), (Schauenberg and Paris, 1990).

## Properties

Antioxidant, anti-inflammatory, anti-carcinogenic, hepatoprotective, immunostimulating, possibly oestrogenic (herbwisdom, 2015l).

## Indicated for

Alcoholic hepatitis, alcoholic fatty liver, cirrhosis, liver poisoning and viral hepatitis. It can benefit adrenal disorders and inflammatory bowel syndrome. Psoriasis. Lowering cholesterol. Protecting the liver when taking strong drugs or medicine. Candida. Food allergies.

Women with hormone-dependent conditions such as endometriosis, uterine fibroids, and cancers of the breast, ovaries, or uterus should not take or use milk thistle plant extract due to its possible oestrogenic effects.

Men who have prostate cancer should not take milk thistle without the approval of a doctor (herbwisdom, 2015l).

Milk Thistle is unique in its ability to protect the liver and has no equivalent in the pharmaceutical drug world. In fact, in cases of poisoning with Amanita mushrooms, which destroy the liver, milk thistle is the only treatment option. It has been so dramatically effective that the treatment has never been disputed, even by the traditional medical community. This species is an annual or biennial plant of the Asteraceae family.

Milk thistle acts in a similar fashion to detoxify other synthetic chemicals that find their way into our bodies, from acetaminophen and alcohol to heavy metals and radiation.

Milk thistle was approved in 1986 as a treatment for liver disease and it is widely used to treat alcoholic hepatitis, alcoholic fatty liver, cirrhosis, liver poisoning and viral hepatitis. It has also been shown to protect the liver against medications such as acetaminophen, a non-aspirin pain reliever.

The active ingredient, or liver-protecting compound in milk thistle is known as silymarin. This substance, which actually consists of a group of compounds called flavonolignans, helps repair liver cells damaged by alcohol and other toxic substances by stimulating protein synthesis. By changing the outside layer of liver cells, it also prevents certain toxins from getting inside. Silymarin also seems to encourage liver cell growth. It can reduce inflammation (important for people with liver inflammation or hepatitis), and has potent antioxidant effects. Antioxidants are thought to protect body cells from damage caused by a chemical process called

oxidation. Our Milk Thistle is not standardised to an exact amount (as it is made from pure dried natural herbs. Milk Thistle naturally contains about 70–80% Silymarin (and many other constituents thought to work in harmony).

This herb benefits adrenal disorders and inflammatory bowel syndrome, and is used to treat psoriasis (increases bile flow).

Milk thistle has some oestrogen-like effects that may stimulate the flow of breast milk in women who are breast-feeding infants. It may also be used to start late menstrual periods. Milk thistle's oestrogen-like effect may also have some usefulness for men with prostate cancer.

In animal studies and one small study in humans, milk thistle produced modest reductions in total cholesterol. However, these results have not been demonstrated in larger human studies.

This herb is a must for cleansing and for anyone with any sort of liver dysfunction or exposure to toxins (herbwisdom, 2015l).

Milk thistle is a flowering herb native to the Mediterranean region. It has been used for thousands of years as a remedy for a variety of ailments, and historically was thought to have protective effects on the liver and improve its function. Today, its primary folk uses include liver disorders such as cirrhosis and chronic hepatitis, and gallbladder disorders. Other folk uses include lowering cholesterol levels, reducing insulin resistance in people who have both type 2 diabetes and cirrhosis, and reducing the growth of breast, cervical, and prostate cancer cells.

Silymarin, which can be extracted from the seeds (fruit) of the milk thistle plant, is believed to be the biologically active part of the herb. The seeds are used to prepare capsules, extracts, powders, and tinctures (NCCIH, 2012e).

Milk thistle is a plant. The above ground parts and seeds are used to make medicine. The seeds are more commonly used.

Milk thistle is used most often for liver disorders, including liver damage caused by chemicals, Amanita phalloides mushroom poisoning, jaundice, chronic inflammatory liver disease, cirrhosis of the liver, and chronic hepatitis. Nevertheless, researchers have not yet concluded with certainty that milk thistle is effective for any of these uses.

Milk thistle is also used for loss of appetite, heartburn (dyspepsia), and gallbladder complaints.

Some people use milk thistle for diabetes, hangover, diseases of the spleen, prostate cancer, malaria, depression, uterine complaints, increasing breast milk flow, allergy symptoms, and starting menstrual flow.

In foods, milk thistle leaves and flowers are eaten as a vegetable for salads and a substitute for spinach. The seeds are roasted for use as a coffee substitute.

Milk thistle gets its name from the milky sap that comes out of the leaves when they are broken. The leaves also have unique white markings that, according to legend, were the Virgin Mary's milk. Dont confuse milk thistle with blessed thistle (Cnicus benedictus).

## Chemistry

Milk thistle extract is composed of 65% to 80% silymarin. The remainder consists of polyphenolics and fatty acids, such as linoleic acid. Silymarin is a complex of at least 7 flavolignans, including silibinin, silychristin (silichristin), and silidianin (silidianin) and the flavonoid taxifolin. Silybin A and B, diastereoisomers of silibinin, are considered the most biologically active components, although isosilibinin may be more potent. Other flavonolignans have been described, and various methods for chemical constituent identification have been detailed (WHO, 1999a), (Kroll, Shaw, and Oberlies, 2007), (Kren and Walterová, 2005), (Gazák, Walterová, and Kren, 2007), (Halbach and Görler, 1971), (Khafagy, Salam, and Hamid, 1981), (Varma, Talwar, and Garg, 1980).

## Uses and Pharmacology

Alcoholic liver disease, appetite stimulant, gallbladder problems, hepatic cirrhosis, chronic hepatitis, hepatotoxicity (chemical/drug-induced), jaundice, pleurisy, prostate cancer, spleen diseases (medscape, 2015j).

Most studies evaluating the mechanism of action of milk thistle have used silymarin and silibinin. Antioxidant properties have been demonstrated in various models using human cells, such as platelets. A reduction in drug-induced hepatotoxic ischaemic damage and iron-overload oxidative stress has also been shown. Silymarin stabilised hepatocyte and other cell membranes, as well as stimulated macromolecular and protein synthesis. Additionally, anti-inflammatory action was demonstrated with inhibition of neutrophil-mediated histamine release, lipoxygenase and prostaglandin synthetase, and leukotriene synthesis (WHO, 1999a), (Pradhan and Girish, 2006), (Post-White, Ladas, and Kelly, 2007), (Gharagozloo, Moayedi, and Zakerinia, 2009).

## Other pharmacological effects

Silybin and silymarin have been studied in the treatment of aging skin and rosacea, and in skin cancer prevention (Berardesca et al., 2008), (R. P. Singh and R. Agarwal, 2009), (R. P. Singh and R. Agarwal, 2005). In older studies, silybin has been evaluated in patients with cholestasis[332] (Schandalik, Gatti, and Perucca, 1992), (Schandalik and Perucca, 1994), (Rumyantseva, 1991). Silybin possesses antibacterial activity against gram-positive bacteria but

[332] a condition where bile cannot flow from the liver to the duodenum

shows no activity against gram-negative bacteria or fungi (D. G. Lee, H. K. Kim, and Y. Park, 2003). Milk thistle extract demonstrates neuroprotective effects in animal studies (Pradhan and Girish, 2006), (M. J. Wang, W. W. Lin, and H. L. Chen, 2002), (Kittur, Wilasrusmee, and Pedersen, 2002), (Katiyar, 2005).

The active ingredient – the one that protects the liver – in milk thistle is known as silymarin, a chemical extracted from the seeds. Silymarin is actually a group of flavonoids (silibinin, silidianin, and silicristin), which are thought to help repair liver cells damaged by alcohol and other toxic substances. Silymarin also protects new liver cells from being destroyed by these same toxins. It reduces inflammation (which is why it is often suggested for people with liver inflammation or hepatitis) and is a strong antioxidant.

Most milk thistle products are standardised preparations made from the seeds of the plant, to contain 70 to 80% of silymarin (unknown, 2014j).

## Cancer

In-vitro experiments and limited animal studies investigated the potential of silymarin and silibinin in a variety of cancer cell lines, including bladder, breast, cervical, hepatocellular, and prostate cancer. A variety of molecular mechanisms have been proposed, including antioxidant, anti-angiogenic action, apoptosis via cell cycle arrest, inhibition of transcription factors, and modulation of hormone receptors and cell signaling (Gazák, Walterová, and Kren, 2007), (R. Agarwal, C. Agarwal, et al., 2006), (Meeran and Katiyar, 2008), (Sagar, 2007), (Ramasamy and R. Agarwal, 2008), (M. C. Comelli et al., 2007), (Deep and R. Agarwal, 2007).

### Clinical trials

Clinical trials are lacking, and use of milk thistle preparations in cancer is not recommended outside of the trial setting (Ramasamy and R. Agarwal, 2008). A small phase one trial evaluating the tolerability of silibinin (commercial preparation Siliphos) in prostate cancer patients has been completed, and phase two trials are being planned (NIH, n.d.), (Flaig, Gustafson, and L. J. Su, 2007). Additionally, silibinin was administered to patients with colorectal adenocarcinoma over 7 days to evaluate the tissue concentrations of silibinin in the colorectal mucosa (Ramasamy and R. Agarwal, 2008). A clinical trial included silymarin combined with soy, isoflavones, lycopene, and antioxidants in patients with prostate cancer; therefore, outcomes cannot be attributed to any single ingredient alone (Schröder, Roobol, and Boevé, 2005). Use as an adjunct to chemotherapy to prevent drug-related hepatotoxicity has also been studied in limited

trials, including one in which children with acute lymphoblastic leukemia administered silibinin (as Siliphos) for 28 days achieved greater reduction in total bilirubin at day 28 compared with placebo (NIH, n.d.), (Greenlee et al., 2007).

## Diabetes

### In-vitro and animal experiments

In-vitro and animal experiments suggest milk thistle may exert hypoglycaemic effects (McCarty, 2005), (J. Q. Zhang, Mao, and Y. P. Zhou, 1993).

### Clinical trials

Limited clinical trials have been conducted in type 2 diabetes, insulin-dependent diabetes, and diabetes with comorbid conditions, such as alcoholic liver disease (NIH, n.d.), (Greenlee et al., 2007), (Hussain, 2007), (Huseini, Larijani, and Heshmat, 2006). Most trials record decreases in fasting and postprandial serum glucose, and coincidentally note improvements in the lipid profile; however, because the trials are of varying quality (unblinded and small numbers of participants), no conclusions can safely be made.

## Hepatitis

### Animal studies

A number of clinical trials in hepatitis have been undertaken, making the findings from animal experiments largely irrelevant.

### Clinical trials

A number of meta-analyses have been conducted on the efficacy of milk thistle in alcohol-induced and viral hepatitis (Rambaldi, B. P. Jacobs, and Gluud, 2007), (J. Liu, Manheimer, et al., 2003), (Saller, Brignoli, et al., 2008), (Rambaldi, B. P. Jacobs, Iaquinto, et al., 2005), (Saller, Meier, and Brignoli, 2001), (Verma and Thuluvath, 2007). No effect on all-cause mortality has been found, and no effect on complications of liver disease or on liver histology could be established (Rambaldi, B. P. Jacobs, and Gluud, 2007), (J. Liu, Manheimer, et al., 2003). Although a decrease in liver-related mortality could be demonstrated, when only high-quality trials were included, no effect on mortality was found (relative risk, 0.57; 95% confidence interval, 0.28 to 1.19) (Rambaldi, B. P. Jacobs, and Gluud, 2007), (Saller, Brignoli, et al., 2008). In some trials, a reduction in serum transaminases was demonstrated, but with no effect on liver histology or

clinical progression (Saller, Brignoli, et al., 2008), (K. E. Mayer, Myers, and S. S. Lee, 2005), (Ferenci, Scherzer, and Kerschner, 2008). A quicker resolution of those symptoms related to biliary retention has been shown in one subsequent trial, but with no effect on quality of life measures (El-Kamary, Shardell, and Abdel-Hamid, 2009). One small, open-label study in viral hepatitis demonstrated a reduction in viral load[333] with high-dose intravenous administration of silibinin (Ferenci, Scherzer, and Kerschner, 2008).

Considering the low-toxicity profile of milk thistle, clinical reviewers suggest use of milk thistle preparations in treating alcoholic-related cirrhosis (J. Liu, Manheimer, et al., 2003), (Saller, Brignoli, et al., 2008); however, its use in viral hepatitis outside of clinical trials is not supported by current data (Rambaldi, B. P. Jacobs, and Gluud, 2007), (Saller, Brignoli, et al., 2008), (Verma and Thuluvath, 2007), (Pradhan and Girish, 2006), (Tanamly, Tadros, and Labeeb, 2004). The use of silymarin in the treatment of toxicity due to Amanita mushroom poisoning is also supported, based on retrospective analysis of data. Prospective clinical trial data are not available (Pradhan and Girish, 2006), (NIH, n.d.), (Saller, Brignoli, et al., 2008), (Rainone, 2005).

- **Liver disease from alcohol** - Milk thistle is often suggested as a treatment for alcoholic hepatitis and alcoholic cirrhosis. But scientific studies show mixed results. Most studies show milk thistle improves liver function and increases survival in people with cirrhosis or chronic hepatitis. But problems in the design of the studies (such as small numbers of participants and differences in dosing and duration of milk thistle therapy) make it hard to draw any firm conclusions (unknown, 2014j).
  A comprehensive review by the U.S. Agency for Healthcare Research and Quality (AHRQ) recently identified 16 scientific studies on the use of milk thistle for the treatment of various forms of liver disease. A European standardised extract of milk thistle was used in most of the trials. Problems in study design (such as small numbers of participants, variations in the causes of liver disease, and differences in dosing and duration of milk thistle therapy) made it difficult to draw any definitive conclusions. However, five of seven studies evaluating milk thistle for alcoholic liver disease found significant improvements in liver function. Those with the mildest form of the disease appeared to improve the most. Milk thistle was less effective for those with severe liver disease such as cirrhosis. Cirrhosis is characterized by scarring and permanent, non-reversible damage to the liver. It is often referred to as end-stage liver disease (herbwisdom, 2015l).

[333] the term used to describe the amount of virus in a body fluid

- **High cholesterol** - One animal study found that silymarin (an active compound in milk thistle) worked as effectively as the cholesterol-lowering drug probucol, with the additional benefit of substantially increasing HDL ("good") cholesterol. Further studies in people are needed (herbwisdom, 2015l).
- **Viral hepatitis** - Milk thistle is widely used in the treatment of viral hepatitis (particularly hepatitis C). However, studies show mixed results. Some studies found improvements in liver function, while others did not. In one study of 16 patients who didn't respond to interferon and ribavirin therapy, milk thistle significantly reduced the viral load of hepatitis C. In 7 of the subjects the virus decreased to undetectable levels after 14 days of therapy (unknown, 2014j).
  Despite the fact that milk thistle is widely used in the treatment of hepatitis (particularly hepatitis C), results from four viral hepatitis studies were contradictory. Some found improvements in liver enzyme activity while others failed to detect these benefits. None of the studies compared milk thistle with interferon or other medications for viral hepatitis (herbwisdom, 2015l).
- **Mushroom poisoning** - Based on traditional use, milk thistle has been used as an emergency antidote for poisoning by death cap mushroom (Amanita phalloides). Animal studies have found that milk thistle extract completely counteracts the toxic effects of the mushroom when given within 10 minutes of ingestion. If given within 24 hours, it significantly reduces the risk of liver damage and death (unknown, 2014j).
- **Cancer** - Early laboratory studies suggest that silymarin and other active substances in milk thistle may have anti-cancer effects. These substances appear to -
  - Stop cancer cells from dividing and reproducing,
  - Shorten the lifespan of cancer cells,
  - Reduce blood supply to tumours (unknown, 2014j).

  Some studies suggest silymarin may favourably supplement sunscreen protection and may help reduce the risk of skin cancer. Other studies suggest milk thistle acts synergistically with chemotherapy. More studies are needed to show whether milk thistle has any effects in the body (not just in test tubes) (unknown, 2014j).
  Preliminary laboratory studies also suggest that active substances in milk thistle may have anti-cancer effects. One active substance known as silymarin has strong antioxidant properties and has been shown to inhibit the growth of human prostate, breast, and cervical cancer cells in test tubes. Further studies are needed to determine whether milk thistle is safe or effective for people with these forms of cancer (herbwisdom, 2015l).

## What the Science Says

- Previous laboratory studies suggested that milk thistle may benefit the liver by protecting and promoting the growth of liver cells, fighting oxidation, and inhibiting inflammation. However, results from small clinical trials of milk thistle for liver diseases have been mixed, and two rigorously designed studies found no benefit.
- A 2012 clinical trial, cofunded by NCCIH and the National Institute of Diabetes and Digestive and Kidney Diseases, showed that two higher-than-usual doses of silymarin were no better than placebo for chronic hepatitis C in people who had not responded to standard antiviral treatment.
- The 2008 Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) study, sponsored by the National Institutes of Health (NIH), found that hepatitis C patients who used silymarin had fewer and milder symptoms of liver disease and somewhat better quality of life but no change in virus activity or liver inflammation.

## Laboratory/Animal/Preclinical Studies

Research studies conducted in the laboratory have investigated the properties of silymarin or its isomer silybin using cell lines and animal models. Other substances in milk thistle have not been extensively studied.

Several research studies have investigated the effects of silymarin or silybin in a noncancer context. These studies have tested silymarin or silybin -

- In healthy animal liver and kidney cells.
- As a prophylaxis against toxic chemicals.
- In stimulating detoxification pathways (enzyme concentrations and activity).
- For antioxidant properties.

Silymarin or silybin has also been investigated in cancer models. The effects of silymarin and/or silybin have been investigated in prostate (DU 145, LNCaP, PC-3), (Magula, Galisova, and Iliev, 1996b), (Palasciano, Portincasa, and Palmieri, 1994b), (Saba, Galeone, and Salvadorini, 1976b), (Fintelmann and Albert, 1980b), (Moscarella, Giusti, and Marra, 1993b), (Lirussi, Nassuato, and Orlando, 1995b) breast (MDA-MB 468, MCF-7), (Fintelmann, 1970b), (Trinchet, Coste, and V. Levy, 1989b), (Leng-Peschlow and Strenge-Hesse, 1991b) hepatic (HepG2), (Sonnenbichler and Zetl, 1987b), (Skakun and Moseichuk, 1988b) epidermoid (A431), (Skakun and Moseichuk, 1988b) colon (Caco-2), (Campos, Garrido, and Guerra, 1989b) ovarian (OVCA 433, A2780), (Mullen and Dasarathy, 1998b) histiocytic lymphoma (U-937), (Muzes, Deak, and Lang, 1990b) and leukemia (HL-60) (Mira, M. S. Azevedo, and Manso, 1987b), (R. J. Andrade, Lucena, and De la Cruz, 1998b) cells. In animal tumour models, tongue cancer, (unknown, 1999) skin cancer, (Stuunknown., 1985), (Schuppan, Strosser, and Burkard, 1998b), (Albrecht, H. Frerick, and Kuhn, 1992b), (F. Frerick, Kuhn, and Strenge-Hesse, 1990b), (Grungreiff, Albrecht, and Strenge-Hesse,

1995b), (Marena and Lampertico, 1991b) bladder cancer, (Hruby, Caomos, and Thaler, 1984b) and adenocarcinoma of the colon (Vailati, Aristia, and Sozze, 1993b), (Marcelli, Bizzoni, and Conte, 1992b) and small intestine (Marcelli, Bizzoni, and Conte, 1992b) have been investigated. These studies have tested the ability of silymarin or silibinin to -

- Mitigate the toxicity associated with chemotherapy agents.
- Enhance the efficacy of chemotherapy agents.
- Inhibit the growth of cancer cell lines and inhibit tumour initiation or tumour promotion.

Although many of these studies have produced encouraging results, none of the findings have been replicated in human clinical trials.

Laboratory data suggest that silymarin and silybin protect the liver from damage induced by toxic chemicals. Animal studies have found that liver cells treated with silybin and then exposed to toxins do not incur cell damage or death at the same rate as liver cells that are not treated with silybin. This finding suggests that silybin can prevent toxins from entering the cell or effectively exports toxins out of the cell before damage ensues (Skakun and Moseichuk, 1988b), (Held, 1993b), (Velussi, Cernigoi, and Viezzoli, 1993b), (Cavalieri, 1974b), (Saba, Mignani, and Pagliai, 1979), (Mironets, Krasovskaia, and Polishchuk, 1990b). Alternatively, this may be related to the effect of silymarin on detoxification systems. In-vitro data have shown silybin to stimulate and/or inhibit phase I detoxification pathways in silybin-treated human liver cells. However, this effect was found to be dose-dependent, and these levels are not physiologically attainable with the current manufacturer dose recommendations (Fallah Huseini et al., 2004b), (V. Lawrence, B. Jacobs, and Dennehy, 2000).

Silymarin has been shown to stimulate phase II detoxification pathways in mice. Administration of silymarin (100 or 200 mg /kg body weight/day) to SENCAR mice for 3 days significantly increased glutathione S-transferase activity in the liver ($P < .01.001$), lung ($P < .05.01$), stomach ($P < .05$), small bowel ($P < .01$), and skin ($P < .01$). This effect appeared to be dose-dependent (Lahiri-Chatterjee et al., 1999). Administration of silymarin to rats challenged with a toxin (50 mg/kg body weight) resulted in higher levels of glutathione in liver cells, decreased levels of oxidative stress (measured by malondialdehyde concentrations), and less elevated liver function tests (measured by levels of aspartate aminotransferase AST and alanine aminotransferase ALT) (Mironets, Krasovskaia, and Polishchuk, 1990b). Silymarin and silybin have also been found to accelerate cell regeneration in the liver through stimulation of precursors to DNA synthesis and enhancement of production of the cellular enzymes required for synthesis of DNA (Savio, Harrasser, and Basso, 1998), (Skottova and Krecman, 1998), (Soto et al., 1998), (Zima et al., 1998), (Zi, Grasso, et al., 1998), (Zi, Feyes, and R. Agarwal, 1998). Laboratory studies have also shown silymarin and silybin to be potent antioxidants (Velussi, Cernigoi, and Viezzoli, 1993b), (Cavalieri, 1974b), (Locher et al., 1998), (Bialecka,

1997), (Ramellini and Meldolesi, 1976), (Schonfeld, Weisbrod, and Muller, 1997), (Flisiak and Prokopowicz, 1997), (Zi, Mukhtar, and R. Agarwal, 1997), (Kiesewetter, Leodolter, and Thaler, 1977), (Katiyar et al., 1997). Silymarin has been shown to mitigate oxidative stress in cells treated with pro-oxidant compounds.

A number of laboratory studies have investigated the effect of silymarin or silybin on the efficacy and toxicity of chemotherapy agents or have measured their direct cytotoxic activity. In an investigation of the effect of a variety of flavonoids on the formation of DNA damage, silymarin did not induce DNA damage in colon (Caco-2) cells, hepatoma (HepG2) cells, and human lymphocytes (Campos, Garrido, and Guerra, 1989b). At higher concentrations of silymarin (4001,000 µmol/L) DNA damage was induced in an epithelial cell line (HeLa cells). At higher concentrations (1,000 µmol/L) DNA damage was observed in human lymphocytes. Cell growth was inhibited as the flavonoid concentration was increased in human lymphocytes and HeLa cells. Only at very high concentrations was cell viability affected by silymarin in HepG2 cells. Although this study demonstrated that the flavonolignans of Silybum marianum (L.) are capable of inhibiting cellular proliferation and inducing DNA strand breaks, the results were obtained at very high concentrations that may be difficult to achieve in humans. This study also showed that silymarin does not stimulate cell growth in the HeLa, Burkitt lymphoma, and human hepatoma cell lines.

Silymarin has also been investigated as a possible adjunctive agent in mitigating some of the toxicity associated with chemotherapy agents. Silybin and silychristin exerted a protective effect on monkey kidney cells exposed to vincristine and especially cisplatin chemotherapy (Scambia et al., 1996). Silybin (200 mg/kg body weight) administration with cisplatin in rats resulted in statistically significant reductions in measures of kidney toxicity (Basaga et al., 1997). Significant decreases in weight loss, faster recovery of urinary osmolality measures, and depressions in the increase in activity of urinary alanine aminopeptidase ([AAP], a marker of kidney toxicity) were observed. Silybin had no effect on magnesium excretion or glomerular function. Silybin (2 g /kg body weight) administration in rats receiving cisplatin prevented reductions in creatinine clearance, increases in urea plasma levels, and large increases in urinary AAP (Bokemeyer et al., 1996). No effect on magnesium excretion was observed. Silybin did not interfere with the antineoplastic effects of cisplatin or ifosfamide in germ cell tumours. In experiments with ovarian and breast cancer cell lines, silybin potentiated the effect of cisplatin and doxorubicin (Mullen and Dasarathy, 1998b). IdB 1,016, a form of silybin bound to a phospholipid complex, was found to enhance the activity of cisplatin against A2780 ovarian cancer cells but had no effect on its own (Wenzel, Stolte, and Soose, 1996). Silybin increased the chemosensitivity of DU 145 prostate cancer cells resistant to chemotherapy (Carducci et al., 1996).

Studies have also investigated the effect of silymarin on tumour initiation and promotion. Silymarin appears to have a chemopreventive effect through perturbations in the cell cycle, altering cell signaling that induces cellular proliferation, affecting angiogenesis, or through its anti-inflammatory properties (Magula, Galisova, and Iliev, 1996b), (Fintelmann, 1970b), (Mullen and Dasarathy, 1998b), (Schuppan, Strosser, and Burkard, 1998b), (Shear et al., 1995). These findings have been supported in human prostate, breast, ectocervical, ovarian, hepatic, leukemia, and epidermoid cell lines (Fintelmann and Albert, 1980b), (Fintelmann, 1970b), (Leng-Peschlow and Strenge-Hesse, 1991b), (Sonnenbichler and Zetl, 1987b), (Mira, M. S. Azevedo, and Manso, 1987b), (Dehmlow, Erhard, and Groot, 1996). An investigation of the effect of silymarin on ultraviolet B radiation-induced nonmelanoma skin cancer in mice found that silymarin treatment significantly reduced tumour incidence ($P < .003$), tumor multiplicity ($P < .0001$), and tumour volume ($P < .0001$) (Schuppan, Strosser, and Burkard, 1998b). These findings suggest that silymarin plays a prominent role in the reduction of cancer cells and in preventing the formation of cancer cells. A number of studies have investigated the mechanism through, which silymarin may affect tumour promotion in mouse skin tumour models. Studies have found that silymarin reduces transcription of markers of tumour promotion and activity (Schuppan, Strosser, and Burkard, 1998b), inhibits transcription of tumour promoters (Gaedeke et al., 1996), stimulates antioxidant activities (Schuppan, Strosser, and Burkard, 1998b), (Marena and Lampertico, 1991b), interferes with cell signaling (Dehmlow, Erhard, and Groot, 1996), inhibits inflammatory actions (Schuppan, Strosser, and Burkard, 1998b), and modulates cell-cycle regulation (Dehmlow, Murawski, and Groot, 1996).

In prostate cancer cell lines, silybin has been shown to inhibit growth factors and stimulate cell growth, (Magula, Galisova, and Iliev, 1996b), (Palasciano, Portincasa, and Palmieri, 1994b), (Saba, Galeone, and Salvadorini, 1976b), (Moscarella, Giusti, and Marra, 1993b) promote cell cycle arrest, (Magula, Galisova, and Iliev, 1996b), (Fintelmann and Albert, 1980b) and inhibit antiapoptotic activity (Carducci et al., 1996). In rats with azoxymethane -induced colon cancer, dietary silymarin resulted in a reduction in the incidence and multiplicity of adenocarcinoma of the colon in a dose-dependent manner (Vailati, Aristia, and Sozze, 1993b), (Marcelli, Bizzoni, and Conte, 1992b). Dietary silymarin had no effect on small intestinal adenocarcinoma (Marcelli, Bizzoni, and Conte, 1992b), but exerted a preventive effect in mice with N-butyl-N-(4-hydroxybutyl) nitrosamine induced bladder cancer (Hruby, Caomos, and Thaler, 1984b) and in F344 rats with 4-nitroquinoline 1-oxide induced cancer of the tongue (unknown, 1999). Dietary silybin administered to nude mice with prostate carcinoma increased production of insulin-like growth factor-binding protein-3 in the plasma of mice and significantly inhibited tumour volume ($P < .05$) (Palasciano, Portincasa, and Palmieri, 1994b). Silibinin administered twice daily reduced the growth of colorectal tumour xenografts in mice for a period of 6 weeks (Bode, U. Schmidt, and Durr, 1977), (Miguez et al., 1994).

## How it works

Active constituents: silymarin; silibinin.

Antioxidant, protects hepatocyte membranes, enhances liver parenchyma regeneration, increases glutathione levels (medscape, 2015j).

Milk thistle seed might protect liver cells from toxic chemicals and drugs. It also seems to have antioxidant and anti-inflammatory effects. Milk thistle plant extract might enhance the effects of oestrogen.

## Efficacy

Possibly effective in diabetes and dyspepsia: Extensively studied; effective in treatment of cirrhosis, hepatitis, chemical- or alcohol-induced fatty liver: Effective in mushroom (Amanita phalloides) poisoning, if treatment begun early: IV form of silibinin approved in Europe for Amatoxin poisoning (medscape, 2015j).

## How effective is it?

*Natural Medicines Comprehensive Database* rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

The effectiveness ratings for **Milk thistle** are as follows:

### Possibly effective for...

- **Seasonal allergies (allergic rhinitis)** - Some research shows that people who take a milk thistle extract in combination with a conventional antihistamine have reduced symptoms compared to people who just use an antihistamine.
- **Diabetes** - Some research shows that taking silymarin, a chemical found in milk thistle, along with conventional treatment can decrease blood sugar, total cholesterol, LDL cholesterol, and triglycerides in people with diabetes.
- **Heartburn (dyspepsia)** - When used daily for 4 weeks, a specific combination product (Iberogast, Medical Futures, Inc) that contains milk thistle plus peppermint leaf, German chamomile, caraway, liquorice, clown's mustard plant, celandine, angelica, and lemon balm seems to reduce the severity of acid reflux, stomach pain, cramping, nausea, and vomiting.

- **Menopausal symptoms** - Research in women suggests that taking a specific product containing milk thistle, black cohosh, dong quai, red clover, American ginseng, and chasteberry (Phyto-Female) twice daily for 3 months reduces menopausal symptoms, including hot flashes and night sweats.
- **Skin damage caused by radiation treatment** - Research suggests that applying a specific product (Leviaderm) containing silymarin, a certain chemical found in milk thistle, to the skin reduces skin damage caused by radiation treatment in women with breast cancer.

Most studies of milk thistle's effectiveness have used a specific extract standardised to 70% to 80% silymarin. In the U.S., this formulation is found in the brand name product "Thisilyn" (Natures Way).

## Possibly ineffective for...

- **Obsessive-compulsive disorder (OCD)** - Research shows that taking milk thistle for 8 weeks does not improve OCD symptoms.
- **Hepatitis B** - Most clinical evidence suggests that milk thistle or specific chemicals from milk thistle do not improve liver function or reduce the risk of mortality in patients with hepatitis B.
- **Hepatitis C** - Most clinical evidence suggests that milk thistle or specific chemicals from milk thistle do not improve liver function or reduce the risk of mortality in patients with hepatitis C.

## Insufficient evidence to rate effectiveness for...

- **Liver disease caused by excessive use of alcohol** - There is conflicting evidence about the effectiveness of milk thistle for treating alcohol-related liver disease. Early research suggests that taking milk thistle by mouth might improve liver function and reduce risk of death. However, other research suggests it may not have an effect.
- **Alzheimers disease** - Early research suggests that taking a combination supplement containing silymarin, a chemical found in milk thistle, seems to improve mental function in people with Alzheimers disease.
- **Amanita mushroom poisoning** - Giving silibinin, a chemical found in milk thistle, intravenously (by IV) may lessen liver damage caused by Amanita phalloides mushroom (death cap) poisoning. However, it is hard to obtain silibinin in the U.S.
- **Chemotherapy toxicity** - Early research suggests that taking a milk thistle product containing the chemical silibinin beginning at the start of chemotherapy treatment does not significantly reduce liver toxicity caused by chemotherapy.
- **Liver scarring (cirrhosis)** - Early research suggests that milk thistle or silymarin, a chemical found in milk thistle, might reduce the risk of death and improve liver function in people with cirrhosis. However, milk thistle does not seem to benefit all patients with liver disease when those without cirrhosis are also considered.

- **Kidney disease in people with diabetes** - Early research shows that taking silymarin, a chemical found in milk thistle, together with conventional treatment might help treat kidney disease in people with diabetes.
- **Kidney failure treatment (haemodialysis)** - Early research suggests that taking a chemical found in milk thistle might increase levels of haemoglobin, a protein in red blood cells that carries oxygen, in people undergoing haemodialysis.
- **Hepatitis** - Research on the effects of milk thistle for treating hepatitis is inconsistent. Early research suggests that taking a specific product (Silipide) containing silybin, a chemical found in milk thistle, might improve liver function in people with long-term (chronic) hepatitis. Other research shows that a specific product (Legalon) containing the milk thistle chemical called silymarin can improve liver function in people with short-term (acute) hepatitis. However, conflicting results exists regarding the benefit of Legalon. Other research suggests that a different milk thistle product (Sylimarol), taken in combination with vitamins B and C, does not improve liver function in people with short-term (acute) viral hepatitis. Most research suggests that milk thistle or chemicals from milk thistle do not improve liver function or reduce the risk of death from hepatitis B or hepatitis C.
- **High cholesterol** - Evidence about how milk thistle affects cholesterol is inconsistent. Early evidence suggests that taking silymarin, a chemical found in milk thistle, does not affect cholesterol levels in people with high cholesterol. However, other research shows that taking the same chemical can reduce total cholesterol, LDL cholesterol, and triglycerides in people with diabetes and high cholesterol.
- **Infertility** - Early research shows that taking silymarin, a chemical found in milk thistle, along with fertility hormones might provide some benefits for women undergoing in-vitro fertilisation due to male infertility.
- **Multiple sclerosis** - Early research suggests that taking a combination supplement containing silymarin, a chemical found in milk thistle, can improve mental function and promote disease stabilisation in people with multiple sclerosis.
- **Parkinsons disease** - Early research suggests that taking a combination supplement containing silymarin, a chemical found in milk thistle, improves mental function and promotes disease stabilisation in people with Parkinson's disease.
- **Prostate cancer** - Prostate-specific antigen (Prostate-specific antigen (PSA)) is a protein in the blood that can be measured to diagnose and monitor prostate cancer. Early research suggests that taking a supplement containing silymarin, a chemical found in milk thistle, can delay the rise in PSA levels in men with a history of prostate cancer.
- **Liver damage caused by chemicals** - Early research suggests that milk thistle may limit liver damage caused by exposure to industrial poisons such as toluene and xylene. However, there is some inconsistent evidence. Taking silymarin, a chemical found in milk

thistle, does not seem to improve liver damage caused by tarcine, a medicine used to treat Alzheimer's. However, taking silibinin, another chemical found in milk thistle, seems to improve test results for liver damage caused by tuberculosis medications.

- **Spleen disorders**
- **Gallbladder problems**
- **Swelling of the lungs (pleurisy)**
- **Malaria**
- **Menstrual problems**
- **Other conditions**

More evidence is needed to rate the effectiveness of milk thistle for these uses.

## Contraindications

Hypersensitivity to Asteraceae/Compositae plants, chrysanthemums, daisies, marigolds; breast cancer, endometriosis, hormone sensitive conditions, ovarian cancer, uterine cancer, uterine fibroids (medscape, 2015j).

Milk thistle should not be used by pregnant or breastfeeding women.

People with a history of hormone-related cancers, including breast, uterine, and prostate cancer, should not take milk thistle.

Do not take milk thistle if you are allergic to ragweed, chrysanthemums, marigolds, chamomile, yarrow, or daisies (unknown, 2014j).

## Are there safety concerns?

Milk thistle is likely safe when taken by mouth for most adults. Milk thistle sometimes causes a laxative effect. Other less common side effects are nausea, diarrhoea, indigestion, intestinal gas, bloating, fullness or pain, and loss of appetite.

### Special precautions & warnings

- **Pregnancy and breast-feeding** - Not enough is known about the use of milk thistle during pregnancy and breast-feeding. Stay on the safe side and avoid use.
- **Allergy to ragweed and related plants** - Milk thistle may cause an allergic reaction in people who are sensitive to the Asteraceae/-Compositae plant family. Members of this family include ragweed, chrysanthemums, marigolds, daisies, and many others. If you have allergies, be sure to check with your healthcare provider before taking milk thistle.

- **Diabetes** - Certain chemicals in milk thistle might lower blood sugar in people with diabetes. Dosing adjustments to diabetes medications might be necessary.
- **Hormone-sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** - Extracts from milk thistle **plant** might act like oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use these extracts. In contrast, the more commonly used milk thistle **seed** extracts do not seem to act like oestrogen.

## Adverse Reactions

In most clinical trials, the incidence of adverse reactions was approximately equal in milk thistle and control groups (Rambaldi, B. P. Jacobs, and Gluud, 2007). The Agency for Healthcare Research and Quality and German Commission E report no serious adverse events when taken within the recommended dosage range (Post-White, Ladas, and Kelly, 2007), (Rainone, 2005). Consumption of the oral form of milk thistle (standardised to 70% to 80% silymarin) at 420 mg/day is considered safe for up to 41 months, based on clinical trial data (Tamayo and Diamond, 2007).

Other reported adverse reactions include headache, impotence, and skin reactions (eg, eczema, pruritus, rash, urticaria) (Tamayo and Diamond, 2007). A tea made from crude milk thistle resulted in a case report of anaphylaxis (WHO, 1999a). High dosages in cancer trials have been associated with asymptomatic hyperbilirubinemia and increases in ALT enzymes (Tamayo and Diamond, 2007).

Human studies of silymarin have shown minimal adverse effects in multiple large, blinded, placebo-controlled, randomised studies. Silymarin is well tolerated, with only rare reports of a mild laxative effect. Mild allergic reactions have been seen at high doses (>1,500 mg /day), although the details of these allergic reactions were not reported (Magula, Galisova, and Iliev, 1996b). A recent case report from Australia described a reaction to a milk thistle extract that included intermittent episodes of sweating, abdominal cramping, nausea, vomiting, diarrhoea, and weakness (Palasciano, Portincasa, and Palmieri, 1994b). All symptoms resolved when the silymarin was discontinued. The authors suggested that the capsules were contaminated; the type of contamination was unknown.

According to the German Commission E, there are no reported side effects with milk thistle within the recommended doses. Rare cases of milk thistle having a laxative effect have been reported. Human studies have reported stomach upset, heartburn, and transient headaches; however, none of these symptoms were attributed to supplementation with milk thistle, and supplementation was not discontinued (Saba, Galeone, and Salvadorini, 1976b). One human dosing study reported nausea, heartburn,

and dyspepsia in patients treated with 160 mg/day, dyspepsia in patients treated with 240 mg/day, and postprandial nausea and meteorism[334] in patients treated with 360 mg/day. None of these side effects were dose-related.

Silymarin has been well tolerated in high doses. Silymarin has been used in pregnant women with intrahepatic cholestasis at doses of 560 mg/day for 16 days, with no toxicity to the patient or the foetus (Fintelmann and Albert, 1980b). The published data on silymarin use in children focuses on intravenous doses of 20 to 50 mg/kg body weight for mushroom poisoning (Moscarella, Giusti, and Marra, 1993b). Silymarin has also proved nontoxic in rats and mice when administered in doses as high as 5,000 mg/kg body weight. Rats and dogs have received silymarin at doses of 50 to 2,500 mg/kg body weight for a 12-month period. Investigations, including postmortem analyses, showed no evidence of toxicity.

## Side-effects

Milk thistle is generally regarded as safe. Side effects are usually mild and may involve -

- **Stomach upset**,
- **Diarrhoea**,
- **Nausea and vomiting**,
- **Rash (from touching milk thistle plants)**

Tolerability of silymarin is good; the most common effects after oral ingestion include brief gastrointestinal disturbances -

- **abdominal bloating**,
- **abdominal fullness or pain**,
- **anorexia**, changes in bowel habits,
- **diarrhoea**,
- **dyspepsia**,
- **flatulence**.
- The moderate side-effects seem to be **rashes**, **headaches**, **heartburn**, **joint pain** and **impotence**.

[334] drumlike distention of the abdomen due to air or gas in the intestine or peritoneal cavity

- Milk thistle can produce allergic reactions, which tend to be more common among people who are allergic to plants in the same family (for example, ragweed, chrysanthemum, marigold, and daisy). Seek immediate medical attention if you notice any of the following symptoms of a serious allergic reaction: **rash**, **itching/swelling** (especially of the face/tongue/throat), **severe dizziness**, **trouble breathing**.

## Pregnancy/Lactation

Information is limited. Use in pregnant women has been reported in few clinical studies, without apparent ill-effect (Deep and R. Agarwal, 2007), (Greenlee et al., 2007). A study evaluated the efficacy and safety of silymarin to promote milk production in 50 women who had elected to stop breast-feeding because their infants did not consume the milk. Milk production was enhanced, and no change to the chemical composition of the milk was found (Di Pierro et al., 2008). Until further data are available, avoid the use of milk thistle in pregnant or breast-feeding women.

## Interactions

Silibinin inhibits phase 1 and 2 enzymes and inactivates cytochromes P450 3A4 and 2C9, potentially via an irreversible mechanism (Kroll, Shaw, and Oberlies, 2007), (J. W. Wu, L. C. Lin, and T. H. Tsai, 2009), (Bout-van den Beukel et al., 2006). Despite widespread usage of milk thistle, case reports of clinically significant interactions are lacking (Rainone, 2005). Studies conducted largely among healthy volunteers evaluated the effect of milk thistle on prescription drugs. These drugs included antiretrovirals (especially indinavir), digoxin, ranitidine, losartan, and metronidazole, with most studies finding some effect on the area under the curve, but no clinical effect (J. W. Wu, L. C. Lin, and T. H. Tsai, 2009), (Bout-van den Beukel et al., 2006), (E. Mills, Wilson, and Clarke, 2005a), (Y. Han et al., 2009), (Hu, X. Yang, and P. C. Ho, 2005). Milk thistle has been reported to decrease indinavir trough plasma concentrations; however, it is unlikely that milk thistle will interfere with therapy (Piscitelli et al., 2002), (DiCenzo, Shelton, and K. Jordan, 2003), (E. Mills, Wilson, and Clarke, 2005b).

Exercise caution when using milk thistle, especially at higher dosages or concomitantly with drugs of a narrow therapeutic index (Kroll, Shaw, and Oberlies, 2007).

If you are being treated with any of the following medications, you should not use milk thistle without talking to your doctor first.

- **Antipsychotics** – Includes butyrophenones (such as haloperidol) and phenothiazines (such as chlorpromazine, fluphenazine, and promethazine)
- **Phenytoin(Dilantin)** – A medication used for seizures

- **Halothane** – A medication used during general anesthesia
- **Birth control pills or hormone replacement therapy** – (unknown, 2014j).

Milk thistle may interfere with the following medications, because both milk thistle and these medications are broken down by the same liver enzymes -

- **Allergy drugs** – Such as fexofenadine (Allegra)
- **Drugs for high cholesterol** – Including statins such as lovastatin (Mevacor, Altocor)
- **Anti-anxiety drugs** – Including alprazolam (Xanax), diazepam (Valium), and lorazepam (Ativan)
- **Antiplatelet and anticoagulant drugs (blood thinners)** – Including clopidogrel (Plavix) and warfarin (Coumadin)
- **Some cancer drugs**
- **Drugs broken down by the liver** – Because milk thistle works on the liver, it may affect drugs broken down by the liver, of which there are many. Speak to your doctor (unknown, 2014j).

## Moderate

**Do not take this combination.**

- **Medications changed by the liver (Cytochrome P450 2C9 (CYP2C9) substrates)** - Some medications are changed and broken down by the liver. Milk thistle might decrease how quickly the liver breaks down some medications. Taking milk thistle along with some medications that are broken down by the liver can increase the effects and side effects of some medications. Before taking milk thistle, talk to your healthcare provider if you take any medications that are changed by the liver.
  Some medications that are changed by the liver include amitriptyline (Elavil), diazepam (Valium), zileuton (Zyflo), celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), warfarin (Coumadin), and others.
- **Medications changed by the liver (Cytochrome P450 2D6 (CYP2D6) substrates)** - Some medications are changed and broken down by the liver. Milk thistle might decrease how quickly the liver breaks down some medications. Taking milk thistle along with some medications that are broken down by the liver can increase the effects and side effects of some medications. Before taking milk thistle, talk to your healthcare provider if you take any medications that are changed by the liver.

Some medications that are changed by the liver include imipramine (Tofranil) and amitriptyline (Elavil); antipsychotics such as haloperidol (Haldoyl), risperidone (Risperdal), and chlorpromazine (Thorazine); beta-blockers such as propranolol (Inderal), metoprolol (Lopressor, Toprol XL), and carvedilol (Coreg); tamoxifen (Nolvadex); and others.

- **Medications changed by the liver (Cytochrome P450 3A4 (CYP3A4) substrates)** - Some medications are changed and broken down by the liver. Milk thistle might decrease how quickly the liver breaks down some medications. Taking milk thistle along with some medications that are broken down by the liver can increase the effects and side effects of some medications. Before taking milk thistle, talk to your healthcare provider if you take any medications that are changed by the liver.
  Some medications changed by the liver include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and many others.
- **Medications changed by the liver (Glucuronidated drugs)** - The body breaks down some medications to get rid of them. The liver helps break down these medications. Taking milk thistle might affect how well the liver breaks down drugs. This could increase or decrease how well some of these medications work.
  Some of these medications changed by the liver include acetaminophen, atorvastatin (Lipitor), diazepam (Valium), digoxin, entacapone (Comtan), oestrogen, irinotecan (Camptosar), lamotrigine (Lamictal), lorazepam (Ativan), lovastatin (Mevacor), meprobamate, morphine, oxazepam (Serax), and others.
- **Medications for diabetes (Antidiabetes drugs)** - Sylmarin, a chemical found in milk thistle, can decrease blood sugar levels. Diabetes medications are also used to lower blood sugar. Taking milk thistle along with diabetes medications might cause your blood sugar to be too low. Monitor your blood sugar closely. The dose of your diabetes medication might need to be changed.
  Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.
- **Sirolimus (Rapamune)** - Taking milk thistle might affect how well the liver breaks down sirolimus. This could increase or decrease how well some of these medications work. Before taking milk thistle, talk to your healthcare provider if you are taking sirolimus.
- **Tamoxifen (Nolvadex)** - Milk thistle might increase how much tamoxifen is absorbed by the body. Before taking milk thistle, talk to your healthcare provider if you are taking tamoxifen.

## Minor

**Be watchful with this combination**

- **Oestrogens** - Milk thistle might decrease hormones in the body. Milk thistle might help the body break down oestrogen pills to get rid of them. Taking milk thistle along with oestrogens might decrease the effectiveness of oestrogen pills. Milk thistle contains a chemical called silymarin. Silymarin might be the part of milk thistle that helps the body break down oestrogens.
  Some oestrogen pills include conjugated equine oestrogens (Premarin), ethinylestradiol, estradiol, and others.
- **Medications used for lowering cholesterol (Statins)** - Theoretically, milk thistle might change the levels of some medications used for lowering cholesterol (statins). This could increase or decrease how well these medications work.
  Some medications used for lowering cholesterol include atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), and rosuvastatin (Crestor).

## Are there interactions with herbs and supplements?

- **Herbs and supplements that might lower blood sugar** - Milk thistle can lower blood glucose levels. Using it with other herbs or supplements that have the same effect might cause blood sugar levels to drop too low. Some herbs and supplements that can lower blood sugar include alpha-lipoic acid, bitter melon, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.

## Are there interactions with foods?

There are no known interactions with foods.

## Available Forms

- Capsules of standardised dried herb (each capsule contains about 120 to 140 mg of silymarin),
- Liquid extract,
- Tincture,
- Silymarin phosphatidylcholine complex.

A few studies show that a silymarin-phosphatidylcholine complex may be absorbed more easily than regular standardised milk thistle. Phosphatidylcholine is a key element in cell membranes. It helps silymarin attach easily to cell membranes, which may keep toxins from getting inside liver cells. People who have alcohol-related liver disease should avoid alcohol extracts (unknown, 2014j).

## Dosage

Consumption of the oral form of milk thistle (standardised to 70% to 80% silymarin) at 420 mg/day in divided doses is considered safe for up to 41 months based on clinical trial data (Tamayo and Diamond, 2007).

Silibinin (as Siliphos) has been administered at 13 g/day in phase 1 clinical trials (Ramasamy and R. Agarwal, 2008), (Flaig, Gustafson, and L. J. Su, 2007).

### Paediatric

There are no studies showing whether or not it is safe to give milk thistle to a child. Liver problems can be serious and should be diagnosed by a doctor. Talk to your child's doctor before giving milk thistle to a child (unknown, 2014j).

As adjunctive therapy, Siliphos has been used in children at dosages of 5.1 mg/kg/day (Greenlee et al., 2007).

### Adult

If you think you have a liver problem, you should see a doctor. Liver disease can be life threatening (unknown, 2014j).

140 mg silymarin orally three times a day.

- **Glshepatitis, Chronic Active** - Silibinin constituent - 240 mg orally twice a day.
- **Hepatic Cirrhosis** - Silymarin 70–80% extract - 420 mgs a day orally (Tamayo and Diamond, 2007).
- **Dyspepsia** - 1 mL orally, three times a day (Iberogast, Medical Futures, Inc).
- **Diabetes** - Silymarin 200 mg orally three times a day, in combination with conventional treatment.

The following doses have been studied in scientific research -

### By mouth

- For seasonal allergies (allergic rhinitis): Milk thistle extract of silymarin 140 mg three times daily.
- For upset stomach (dyspepsia): A specific combination product containing milk thistle (Iberogast, Medical Futures, Inc) and several other herbs has been used in a dose of 1 mL three times daily (MedlinePlus, 2014e).

Extracts from the milk thistle ***plant*** might act like oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use these extracts. In contrast, the more commonly used milk thistle ***seed*** extracts do not seem to act like oestrogen (MedlinePlus, 2014f).

In clinical trials, milk thistle appears to be well tolerated in recommended doses. Occasionally, people report various gastrointestinal side effects. Milk thistle can produce allergic reactions, which tend to be more common among people who are allergic to plants in the same family (for example, ragweed, chrysanthemum, marigold, and daisy). Milk thistle may lower blood sugar levels. People with diabetes or hypoglycaemia, or people taking drugs or supplements that affect blood sugar levels, should use with caution (MedlinePlus, 2014f).

## Cautions

- Milk thistle may lower blood sugar levels. People with diabetes or hypoglycaemia, or people taking drugs or supplements that affect blood sugar levels, should use caution.
- Concurrent CYP3A4 substrates, CYP2C9 substrates.
- Silymarin has poor oral bioavailability and is sparsely water-soluble (medscape, 2015j).

## Toxicology

Acute oral toxicity of silymarin in rats, dogs, and monkeys has been estimated to be greater than 5 g/kg. Subacute toxicity studies suggest no toxicity in rats and monkeys for dosages of up to 2 g/kg for 13 weeks, and up to 1 g/kg in rats and dogs for up to 26 weeks. Investigations, including urine analysis and postmortem studies, showed no evidence of toxicity. No evidence of effect on reproduction in rats has been found, and silymarin was not mutagenic in several tests (WHO, 1999a), (Kidd and Head, 2005).

## Commentary

*Although milk thistle is reported as having a possible oestrogenic effect, I have seen nothing to back this up, so I would suggest that it not be used as a herbal hormone.*

Chapter 11

# P's

## Pueraria

### Common names

Kwao Krua, White Kwao Krua, Kwao Keur, Kwao Kruea, Butea Superba.

### Latin name

*Pueraria mirifica*

| | |
|---|---|
| *Pueraria Mirifica* | White Kwao Krua |
| *Butea Superba* | Red Kwao Krua |
| *Mucuna Collettii* | Black Kwao Krua |

**Table 11.1** – The three herbs known as 'Kwao Krua'

### Overview

Pueraria mirifica has been used in Thailand for medicinal purposes for many years, mainly as a female hormone supplement. Pueraria mirifica is a plant found in the wild in Myanmar and Northeastern Thailand. It is also known as kwao krua. The term pueraria mirifica was coined in 1952. Today, the extract from this plant is used to make supplements (herbwisdom, 2015m).

## Botany

The plant species Pueraria mirifica (pueraria) belongs to the Fabaceae, or bean, subfamily, and its tuberous roots contain several phytoestrogens (Manonai, Chittacharoen, Theppisai, et al., 2007). Pueraria mirifica is a woody vine commonly found in forests throughout Thailand (Malaivijitnond, Chansri, et al., 2006), with 28 cultivars presently documented. The tuberous root varies in size depending on soil condition, but may weigh as much as 100 kg. The plant's palmate-type leaves are simple or ovate and contain 3 leaflets in 1 petiole. The blue-to-purple flowers are composed of 5 petals and bloom from February to March.

## History

The plant species is rich in phytoestrogens, and postmenopausal women in Thailand have consumed it for more than 100 years citing its beneficial oestrogen effects (Manonai, Chittacharoen, Udomsubpayakul, et al., 2008). In traditional Thai medicine, it is common to use Pueraria mirifica as a skin moisturiser, to improve regrowth of hair, to improve body flexibility and sexual performance, and to firm and enlarge the breasts (Malaivijitnond, Chansri, et al., 2006). Commercial products containing pueraria are continually introduced into the world market (Sookvanichsilp, Soonthornchareonnon, and Boonleang, 2008) and have become popular in Thailand, Korea, and Japan (Malaivijitnond, Chansri, et al., 2006). Most commercial products are available as topical rejuvenating, antiaging, or skin-lightening creams or gels, as beauty soaps, or as capsules or tablets for increasing appetite, enlarging breasts, modulating hair growth or regrowth, and other rejuvenating purposes (Sookvanichsilp, Soonthornchareonnon, and Boonleang, 2008), (Malaivijitnond, Chansri, et al., 2006), (Chansakaow, Ishikawa, and Seki, 2000), (G. Liang, 2000), (Roufs et al., 2007), (Yagi, Shindo, and Masahiro, 2007), (Tehara, 2006), (X. Liu and W. A. Lin, 2005), (Konoike and Yamashita, 2006), (Ishiwatari, 2003). Since 1999, domestic and global demand for the raw materials from Pueraria mirifica roots or tubers has increased, resulting in intense harvesting of the plant from the forests of Thailand (Cherdshewasart, Subtang, and Dahlan, 2007).

## Chemistry

Isoflavones, coumestans, and lignans are the 3 main classes of phytoestrogens. The tuberous roots of Pueraria mirifica primarily contain the active component miroestrol and its derivative, deoxymiroestrol[335] (Chansakaow, Ishikawa, Seki, et al., 2000). The tuberous roots of Pueraria mirifica also contain daidzin, daidzein, genistin, genistein, puerarin (Ingham, Markham, et al., 1986), mirificoumestan, kwakhurin (Ingham, Tahara,

[335]Deoxymiroestrol is a highly active phytoestrogen derived from the tuberous roots of Pueraria candollei var. mirifica

and Dziedzic, 1986), (Tahara, Ingham, and Dziedzic, 1987), coumestrol (Ingham, Tahara, and Dziedzic, 1988), mirificin, and 2 steroids, estrone and estriol (Sookvanichsilp, Soonthornchareonnon, and Boonleang, 2008), (Ingham, Tahara, and Dziedzic, 1986), (Ingham, Tahara, and Dziedzic, 1989), (Chansakaow, Ishikawa, Sekine, et al., 2000). The manufacture and synthesis of miroestrol is documented (Corey and L. I. Wu, 1993), (Ishikawa and Higuchi, 2006). Deoxymiroestrol was isolated and identified as the most active phytoestrogen of the plant (Cherdshewasart, Cheewasopit, and Picha, 2004b), (Sookvanichsilp, Soonthornchareonnon, and Boonleang, 2008), (Ishikawa and Sekine, 2001) in 2000. These have been shown to be 3,000 more potent as oestrogens than soy isoflavones and, according to Doctor Garry Gordon -

> Pueraria Mirifica makes Black Cohosh and Red Clover look like placebos!

Thin-layer chromatography analysis has documented varying amounts of phytoestrogens collected from Pueraria mirifica in different locations in Thailand (Malaivijitnond, Chansri, et al., 2006), (Cherdshewasart and Sriwatcharakul, 2007). One of the challenges of large-scale manufacturing of Pueraria mirifica for drugs and cosmetics is resolving these variations in lots.

## Uses and Pharmacology

## Cancer

Spinasterol, an active cytotoxic component of Pueraria mirifica, was active against certain gynaecological cancer cell lines and activates oestrogen receptors ER-$\alpha$ and ER-$\beta$. The ethanol extract had antiproliferative effects on breast cancer cell lines MCF-7, ZR-75-1, MDA-MB-231, SK-BR-3, and Hs578T. Another component, known as PE-D, affected the growth in a dose-dependent and time-dependent[336] manner on some breast cancer cell lines (MCF-7, MDAMB-231), and on the growth of ovarian (2774) and cervical cancer cells (HeLa) (Baek, E, and Jun, 2003), (G. C. Jeon et al., 2005b). The oestrogenic effect of some components in Pueraria mirifica has been compared with estradiol, a major oestrogen in humans (G. C. Jeon et al., 2005b), (Cherdshewasart, Traisup, and Picha, 2008). The rank order of phytoestrogen potency is: deoxymiroestrol; miroestrol; 8-prenylnaringenin; coumestrol; genistein/equol; daidzein; resveratrol (Matsumura et al., 2005). Pueraria mirifica also had an oestrogenic effect on a human HepG2 hepatoma cell line that contained an oestrogen receptor and a luciferase

[336] the time that serum concentrations remain above the MIC during the dosing interval

reporter gene; this evidence indicates that metabolic activation of Pueraria mirifica promotes oestrogenic activity (Y. S. Lee et al., 2002). Another study also documents that oestrogenic activity may result from metabolic activation of liver enzymes (Cherdshewasart and Sriwatcharakul, 2008).

## Animal data

The proposed mechanism of action involves strong competitive binding of the plant's phytoestrogens to ER-$\alpha$ and/or synthesis suppressor of ER-$\alpha$ (Cherdshewasart, Panriansaen, and Picha, 2007).

Pretreatment of rats with Pueraria mirifica (1,000 mg/kg body weight per day tuberous root powder) resulted in decreased virulence of rat mammary tumour development from 7,12-dimethylbenz(a)anthracene (7,12-DMBA). Histopathological analysis of the mammary tumour tissues revealed lower ER-$\alpha$, ER-$\beta$, and ER-$\alpha$/ER-$\beta$ profile (Cherdshewasart, Panriansaen, and Picha, 2007).

# Menopause

## Animal data

In rabbits, Pueraria mirifica improved endothelial function through a nitric oxide pathway, decreased contractile responses to norepinephrine, and increased responses to estradiol. The plant caused no changes in lipid profile or liver enzymes (Wattanapitayakul, Chularojmontri, and Srichirat, 2005). In male and female gonadectomized rats, Pueraria mirifica had oestrogen-like activity and affected accessory sex organs. It increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in both sexes (Malaivijitnond, Kiatthaipipat, et al., 2004). The mechanism of action involved direct stimulation of the accessory sex organs and suppression of the hypothalamic-pituitary-gonadal axis. Overall activity was more potent in female rats than in male rats. Studies in mice found that Pueraria mirifica does not affect male fertility or the hypothalamus-pituitary-testis axis (Jaroenporn, Malaivijitnond, Wattanasirmkit, Trisomboon, et al., 2006). The testis, epididymis, and seminal vesicle all had normal histopathology in Pueraria mirifica -treated male mice.

Pueraria mirifica may greatly alter the length of menstrual cycles and suppress ovulation by reducing serum levels of gonadotropins. The length of the menstrual cycle increased in monkeys treated with Pueraria mirifica 10 and 100 mg/day of root extract and disappeared completely in monkeys treated with root extract 1,000 mg/day. Serum FSH, LH, estradiol, progesterone, and immunoreactive-irinhibin were lower in a dose-dependent manner during treatment. During the posttreatment period, only monkeys treated with Pueraria mirifica 10 and 100 mg/day of extract recovered from the changes in menstrual cycle length and hormone levels (Trisomboon, Malaivijitnond, Watanabe, and Taya, 2005). Other studies

document similar activity for the Pueraria mirifica 1,000 mg/day dose of (Trisomboon, Malaivijitnond, Watanabe, and Taya, 2004) root extract and the direct correlation in dose with gonadotrophin levels (Trisomboon, Malaivijitnond, Watanabe, Cherdshewasart, et al., 2006).

The plant had a dose-dependent oestrogenic effect on rat vaginal cornification (Cherdshewasart, Kitsamai, and Malaivijitnond, 2007). Pueraria mirifica phytoestrogens at a dose of root extract 1,000 mg/day decreased serum parathyroid hormone and calcium levels in aged menopausal monkeys and, thus, may be beneficial in treating bone loss caused by oestrogen deficiency (Trisomboon, Malaivijitnond, J. Suzuki, et al., 2004). Pueraria mirifica had an oestrogenic action in aged menopausal monkeys by changing the sexual skin area around the perineum to the base of the tail to a reddish pigmentation (Trisomboon et al., 2006). FSH may be a candidate marker for the study of Pueraria mirifica's oestrogenic effects in female monkeys if changes in urinary hormones are used as an indicator (Trisomboon et al., 2007a), (Trisomboon et al., 2007b).

## Clinical data

In a 24-week randomised, double-blind, placebo-controlled trial of 51 postmenopausal women, oral Pueraria mirifica exhibited oestrogenicity on vaginal tissue, alleviated vaginal dryness symptoms and dyspareunia[337], improved signs of vaginal atrophy, and restored atrophic vaginal epithelium (Manonai, Chittacharoen, Theppisai, et al., 2007). In another clinical trial of 51 postmenopausal women 46 to 60 years of age, Pueraria mirifica tuberous root had an oestrogen-like effect on bone turnover rate at a dose of 20, 30, and 50 mg/day for a 24-week period. One Phase 1 to 3 trials in Thailand compared the oestrogenic effect of Pueraria mirifica to conjugated equine oestrogen in relieving climacteric[338] symptoms in perimenopausal women (Lamlertkittikul and Chandeying, 2004), (Chandeying and Sangthawan, 2007).

In small clinical trials, the administration of Pueraria mirifica crude extract improved hot flushes, frustration, sleep disorder, skin dryness, high blood cholesterol, amenorrhoea, and other menopause-related symptoms in women. There was no change in blood cells or liver and renal function (Hosoyama, Kuwahata, and Suga, 2007), (Muangman and Cherdshewasart, 2001).

Menopause causes a variety of unpleasant symptoms, including hot flashes and night sweats. There was a study done in Thailand where a group of women were given a pueraria mirifica supplement for one month. At the end of the study, the subjects noticed a significant decrease in night

[337] pain in the pelvic area during or after sexual intercourse

[338] the syndrome of endocrine, somatic, and psychic changes occurring at menopause in women

sweats and hot flashes. In fact, many of the women started to notice an improvement within one week. Pueraria mirifica contains a compound called miroestrol. Researchers believe that this is the active constituent for alleviating menopausal symptoms (herbwisdom, 2015m).

- **Low Libido** - Pueraria mirifica has been shown to increase sex drive. It can also increase vaginal moisture (herbwisdom, 2015m).
- **Osteoporosis** - Osteoporosis is another condition that is extremely common in post-menopausal women. This condition causes the bones to become weak and brittle, which makes them more prone to breaking. Pueraria mirifica has been shown to improve skeletal health, which can reduce the risk of osteoporosis. Researchers believe that the phytoestrogens in pueraria mirifica are helping fight osteoporosis. Taking Pueraria with calcium, as is recommended to aid absorption, would further help combat osteoporosis (herbwisdom, 2015m).

  In sex-hormone-deficient male rats, treatment with Pueraria mirifica root powder completely inhibited bone loss in long bones and axial bones. At higher doses, it increased bone density without affecting accessory sex organs (Urasopon, Hamada, Asaoka, et al., 2007). In a similar study, Pueraria mirifica completely inhibited bone loss in long bones and axial bones in oestrogen-deficient female rats (Urasopon, Hamada, Cherdshewasart, et al., 2008). However, the highest dose of Pueraria mirifica root powder (1,000 mg/kg body weight per day) caused an undesired adverse reaction of increased uterine weight.
- **Aging** - Pueraria mirifica is a great choice for people who want to naturally fight aging. This supplement contains flavonoids and miroestrol compounds, which have all been shown to be effective for fighting aging. A reduction in gray hair and cellulite, increased energy, improved memory and improved circulation are some of the benefits that people have reported after taking pueraria mirifica (herbwisdom, 2015m).
- **Breast Enhancement** - Women who are looking for an alternative to breast augmentation often turn to pueraria mirifica. One study has suggested that 70% of women who use pueraria mirifica notice an increase in their breast size. Not only does it increase breast size, but it can also reduce the appearance of stretch marks (herbwisdom, 2015m).
- **Improve Skin** - Pueraria mirifica helps hydrate the skin and boost collagen production. This gives you a healthier, more youthful-looking complexion. It also helps protect against wrinkles. There was a study published in the Journal of Fertility and Sterility in 2005. One group of women was asked to take an oestrogen supplement while the other group was given a placebo. The results of the study showed that the women who took the oestrogen supplement had fewer wrinkles than the group who took the placebo. As discussed, researchers believe that human oestrogen and phytoestrogens have similar effects on the body (herbwisdom, 2015m).
- **Weight Loss** - Pueraria mirifica can be effective for reducing appetite, which can help you reach your goal weight (herbwisdom, 2015m).

- **Antioxidant** - Some of the isoflavonoids in Pueraria mirifica had antioxidant activity similar to that of $\alpha$-tocopherol or vitamin E (Cherdshewasart and Sutjit, 2008). Pueraria mirifica decreased neuronal cell death in a time-dependent and dose-dependent manner against neurotoxic agents in an Alzheimer disease model in-vitro (Sucontphunt et al., 2007), (Sawatsri, Yamkunthong, and Sidell, 2004). Mechanism of action may be associated with an effect on synaptic density by inducing synaptophysin expression via oestrogen receptor (Chindewa et al., 2008).
- **Insecticide** - The active ingredients from the root of Pueraria mirifica had lethal properties during various growth cycles against the yellow fever mosquito (Aedes aegypti) and other mosquito species with disease-spreading abilities (Lapcharoen et al., 2005).

## Drug/Laboratory tests

Increased triglyceride levels may occur (Manonai, Chittacharoen, Udomsubpayakul, et al., 2008).

## Cautions

Pregnant women and people who have cancer should not take this supplement. As pueraria contains phytoestrogens, it may affect periods such as delaying menstruation by making the menstrual cycle longer. This is thought to be beneficial in reducing the overall risk of hormone-related cancers, but it is still worth bearing in mind as a potential side effect that you may not be expecting (herbwisdom, 2015m).

## Adverse Reactions

Because of the oestrogen-like effect of Pueraria mirifica, use with caution in patients with asthma, diabetes mellitus, epilepsy, migraine, or SLE. Also use with caution in patients with abnormal triglycerides (Manonai, Chittacharoen, Udomsubpayakul, et al., 2008) or hypercalcaemia (Manonai, Chittacharoen, Udomsubpayakul, et al., 2008), (Urasopon, Hamada, Asaoka, et al., 2007), (Urasopon, Hamada, Cherdshewasart, et al., 2008).

## Pregnancy/Lactation

Avoid use during pregnancy and lactation because of the lack of clinical data and the plant's phytoestrogen activity.

## Interactions

Phytoestrogens have oestrogen-like effects. Theoretically, drug interactions may occur with the following:

- **Corticosteroids (eg, prednisone)** - May increase pharmacologic and toxicologic effects.
- **Hydantoins (eg, phenytoin)** - May affect concentration of these medications.
- **Thyroid hormones (eg, levothyroxine)** - May decrease serum free thyroxine concentrations.

## Dosage

Pueraria is widely available in the form of a capsule, liquid or powder. It can also be applied topically. For the best results, you should take this supplement along with a food or drink that is high in calcium, such as milk, cheese, sesame seeds or almonds, as it seems calcium helps increase the absorption of phytoestrogens, which are the main active ingredients in Pueraria and many other herbs (medscape, 2015k).

Commercial products are available as topical creams, gels, and soaps, or in oral capsule and tablet dosage forms (Sookvanichsilp, Soonthornchareonnon, and Boonleang, 2008), (Malaivijitnond, Chansri, et al., 2006), (Chansakaow, Ishikawa, and Seki, 2000), (G. Liang, 2000), (Roufs et al., 2007), (Yagi, Shindo, and Masahiro, 2007), (Tehara, 2006), (X. Liu and W. A. Lin, 2005), (Konoike and Yamashita, 2006), (Ishiwatari, 2003). Some clinical studies used 200 to 400 mg extract from root or tuber orally per day. Commercial manufacturers suggest a dosage of 250 mg of active ingredients from the root orally every morning and evening. For topical products, manufacturers suggest a twice-daily topical application to the breast area for 3 to 5 minutes until fully absorbed.

Capsule supplements should be taken two-three times a day preferably after the meals (30 minutes after).The recommended dosage is 600–800 mg a day (puerariamirificashop.com, 2014).

## Toxicology

High doses of Pueraria mirifica caused general and genotoxicity[339] in animals (Saenphet et al., 2005). Rats treated with aqueous and ethanolic root extracts of Pueraria mirifica had significantly lower body weight gain and lower packed red cell volume; the plant also had mutagenic activity (Sanchanta et al., 2005). A root extract dosage of 100 mg/kg had adverse effects on mating efficiency and reproduction in female mice (Jaroenporn, Malaivijitnond, Wattanasirmkit, Watanabe, et al., 2007). No oestrogen

[339] describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer

hormone activities were found in egg and chicken meat tissue or rats (Tubcharoen, Tungtakulsub, et al., 2003), (Tubcharoen, Chiwatansin, et al., 2003). The LD-50 of Pueraria mirifica root powder in mice was 2,000 mg/kg body weight per day (Cherdshewasart, 2003).

## Commentary

*This seems to be the most effective and efficacious of the herbal hormones, and if used sensibly it should produce some results. Exactly what these results may be may depend on your genetic makeup.*

Chapter 12

# R's

## Red Clover

### Common Names

Cow clover, meadow clover, purple clover, trefoil, wild clover, beebread, cow grass, Dutch = roode klaver, French = trefle commun, French = trefle rouge, German = Rotklee, Italian = trifoglio comune, Italian = trifoglio pratense, Russian = klever krasnyj, Spanish = Trebol rojo, Spanish = trebol violeta, Swedish = rodklover, Welsh = meillion coch.

### Latin Name

*Trifolium pratense*

### Overview

Red clover is a wild plant belonging to the legume family. Cattle and other animals graze on red clover. It has also been used medicinally to treat several conditions including cancer, whooping cough, respiratory problems, and skin inflammations, such as psoriasis and eczema. Health care practitioners believe that red clover "purified" the blood by acting as a diuretic and expectorant, improving circulation, and helping cleanse the liver.

Modern scientific tests have shown that red clover contains isoflavones, plant-based chemicals that produce oestrogen-like effects in the body. Isoflavones have shown potential in the treatment of several conditions associated with menopause, such as hot flashes, cardiovascular health, and

osteoporosis. However, as researchers have become aware of the side effects of taking oestrogen, there is also some concern about the safety of isoflavones. Plus, evidence that red clover helps reduce any menopausal symptoms, like hot flashes, is mixed (unknown, 2015e).

## Botany

This perennial herb is commonly found growing in light sandy soil in meadows throughout Europe and Asia. It is naturalised in North America where its nitrogen-fixing properties are utilised for pasture renovation. The plant is low and bushy with several hairy stems arising from a taproot. Dense terminal heads of up to 125 fragrant red-to-purple flowers are borne at the end of the branched stems. The leaves occur in groups of 3 ovate leaflets; a characteristic lighter water mark in the shape of an inverted V is visible at the centre of the group (Johnson, 2007).

## History

Dried red clover flowers are used in traditional medicine to treat a wide spectrum of ailments. These include jaundice, cancer, mastitis, joint disorders, and respiratory conditions such as whooping cough and bronchial asthma. The plant is thought to purify the blood by promoting urine and mucus production, improving circulation, and stimulating secretion of bile (unknown, 2004a). Red clover ointments have been used topically to accelerate wound healing and to treat psoriasis, eczema, and rashes. Respiratory complaints are treated with an infusion; fomentations and poultices have been used as topical applications for cancerous growths.

## Chemistry

The main chemical classes contained in red clover are carbohydrates, isoflavones, flavonins, and saponins. Other constituents include coumaric acid, fats, minerals, and vitamins. A volatile oil that includes methyl salicylate is distilled from the flowers (C. A. Newall, L. A. Anderson, and Phillipson, 1996b). Isoflavones are often termed phytoestrogens because of their functional similarity to oestrogens. The major isoflavones in red clover are biochanin A, formononetin, daidzein, and genistein; total phytoestrogen content is approximately 0.17%.

Red clover is considered to be one of the richest sources of isoflavones, which are water-soluble chemicals that act like oestrogens (known collectively as phytoestrogens). Red Clover is therefore used for hot flashes/flushes, PMS, breast enhancement and breast health as well as lowering cholesterol, improving urine production and improving circulation of the blood, to help prevent osteoporosis, reduce the possibility of blood clots and arterial plaques and limiting the development of BPH.

Red clover is also a source of many valuable nutrients including calcium, chromium, magnesium, niacin, phosphorus, potassium, thiamine, and vitamin C.

Because it contains chemicals called isoflavones, which belong to a larger class of plant chemicals known as phyto (plant-derived) oestrogens, red clover is often taken to relieve symptoms of PMS. Isoflavones are similar in shape to the female hormone, oestrogen. Therefore, they may attach to oestrogen receptors throughout the body particularly in the bladder, blood vessels, bones, and heart.

It has been found to be helpful in quitting smoking (herbwisdom, 2015n).

## Uses and Pharmacology

Red clover flowers have been used traditionally as a sedative, to purify the blood, and to treat respiratory conditions; topical preparations have been used for psoriasis, eczema, and rashes, and to accelerate wound healing. More recently, clinical trials have been conducted examining red clover's use in the treatment of menopausal symptoms, but with minimal to no possible effects. A few additional studies have shown positive effects on cardiovascular health and bone density, although they have included only a small number of subjects.

Much of the interest in red clover originated from observations of positive health benefits derived from the use of soy products. Both soy and red clover are sources of isoflavones and have similar oestrogenic activity; in-vitro studies have shown this to be approximately 1/400th that of 17-$\beta$-estradiol (Oerter-Klein et al., 2003).

### Oral

Menopausal symptoms and hot flashes, mastalgia, PMS, cancer prevention, indigestion, hypercholesterolemia, whooping cough, asthma, bronchitis, and sexually transmitted diseases (medscape, 2015k).

### Topical

Cancer, skin sores, burns, sore eyes, and chronic skin diseases including eczema (medscape, 2015k). Hot flashes/flushes, PMS, lowers cholesterol, helps prevent osteoporosis, reduces possibility of forming blood clots and arterial plaques, can limit development of BPH. Breast enhancement and breast health. Improve urine production, circulation of the blood and secretion of bile. They also act as detergent, sedative and tonic. Red clover has the ability to loosen phlegm and calm bronchial spasms. The fluid extract of red clover is used as an anti-spasmodic and alterative (herbwisdom, 2015n).

## Medicinal Uses and Indications

Red clover is a source of many nutrients including calcium, chromium, magnesium, niacin, phosphorus, potassium, thiamine, and vitamin C. Red clover is a rich source of isoflavones (chemicals that act like oestrogens and are found in many plants) (unknown, 2015e).

## Menopause

Researchers think that isoflavones, like those found in red clover, might help reduce symptoms of menopause, such as hot flashes and night sweats, because of their oestrogen-like effects. So far studies have been mixed. Several studies of a proprietary extract of red clover isoflavones suggest that it may significantly reduce hot flashes in menopausal women. However, the largest study showed no effect (unknown, 2015e).

The use of red clover as a natural hormone replacement therapy has been postulated because of its oestrogenic activity. Phytoestrogens appear to act as partial agonists in some tissues and antagonists in others, exhibiting hormonal and nonhormonal properties (Society., 2004). They have a greater affinity for $\beta$- rather than $\alpha$-oestrogen receptors. Weak oestrogenic activity has been demonstrated in rats (E., J. Liu, and Lantvit, 2002). Several nonhormonal mechanisms have also been demonstrated, including tyrosine kinase inhibition, antioxidant activity, and effects on ion transport (Tice et al., 2003).

Results from clinical studies assessing the use of red clover isoflavones in menopause have been mixed. However, the North American Menopause Society recommends that red clover may be considered as an option for the treatment of menopausal symptoms as adverse effects appear to be minimal and some women appear to benefit from treatment (Society., 2004).

For women with normal oestrogen levels, red clover isoflavones may displace some natural oestrogens, possibly preventing or relieving oestrogen-related symptoms, such as breast pain, that are associated with PMS. This effect may also reduce the possibility of developing oestrogen-dependent cancer of the endometrium (the lining of the uterus). In addition, results from a review of nearly 1000 women suggest that red clover may interfere with an enzyme known to promote the progression of endometrial cancer (herbwisdom, 2015n).

Several studies of a proprietary extract of red clover isoflavones suggest that it may significantly reduce hot flashes in menopausal women. Also, menopause increases a woman's risk for developing osteoporosis (significant bone loss) and some studies suggest that a proprietary extract of red clover isoflavones may slow bone loss and even boost bone mineral density in pre and perimenopausal women. The oestrogen-like effect of red clover isoflavones may be involved, and red clover also may have a direct effect by preventing the breakdown of existing bone (herbwisdom, 2015n).

However, this possible bone-strengthening effect has not been seen in men and post-menopausal women (herbwisdom, 2015n).

### Animal data

Research reveals no animal data regarding the effects of red clover on menopause.

### Clinical data

Four studies investigating the effects of red clover extracts were included in a systematic review of herbal medicine products used to treat symptoms of menopause (A. L. Huntley and Ernst, 2003). All trials used the proprietary product Promensil (Novogen Laboratories, North Sydney, Australia) containing biochanin A, formononetin, genistein, and daidzein. Use of the red clover supplement resulted in nonsignificant improvement over placebo in 2 trials; however, dietary isoflavone intake was not controlled, possibly affecting the validity of these results. In the remaining 2 trials, dietary intake of isoflavones was controlled and the patient population was comprised of women with a higher baseline frequency of vasomotor symptoms than in the negative studies; significant reduction in the incidence of hot flashes was associated with isoflavone supplementation in these trials. It was concluded that, although evidence for the use of red clover was not convincing, women with more severe menopausal symptoms might experience benefit. A large trial (N = 252), not included in the review, compared 2 commercial supplements ( Promensil and Rimostil ) with placebo over a 12-week period (Tice et al., 2003). Similar reductions in mean daily hot flashes were observed in all 3 groups at 12 weeks although reduction of hot flashes was more rapid with Promensil than with placebo.

## Cardiovascular effects

Researchers theorise that red clover might help protect against heart disease, but studies in humans have not found strong evidence. Red clover isoflavones have been associated with an increase in HDL cholesterol in pre and postmenopausal women, but other studies show conflicting results. One study found that menopausal women taking red clover supplements had stronger, more flexible arteries (called arterial compliance), which can help prevent heart disease. Red clover may also have blood-thinning properties, which keeps blood clots from forming. It appears to improve blood flow (unknown, 2015e).

It is believed that red clover may help to prevent heart disease in several ways. Although results from human studies are not definite, some show that taking red clover may lower the levels of LDL cholesterol and raise the levels of HDL cholesterol in the body. In addition, red clover may also promote an increase in the secretion of bile acid. Because cholesterol

is a major component of bile acid, increased bile acid production usually means that more cholesterol is used and less cholesterol circulates in the body. Additionally, red clover contains small amounts of chemicals known as coumarins, which may help keep the blood from becoming thick and gummy. Therefore, the possibility of forming blood clots and arterial plaques may be reduced. Red clover may also help the arteries remain strong and flexible (a quality often called 'arterial compliance'), which may also help to prevent some of the plaques deposits that may lead to a heart attack or a stroke (herbwisdom, 2015n).

Beneficial effects of soy protein on blood lipid profiles have been demonstrated. However, results from studies of red clover have been mixed, with either no effects on plasma lipids (Blakesmith et al., 2003), (Nestel, Pomeroy, and Kay, 1999) or, with only modest improvements observed (C. Atkinson, Oosthuizen, et al., 2004), (Schult et al., 2004). Results from studies investigating vascular effects of red clover have been more encouraging.

## Animal data

Research reveals no animal data regarding the use of red clover for cardiovascular effects.

## Clinical data

No improvements in cardiovascular risk factors were associated with the 1-year use of a red clover-derived isoflavone supplement by women aged 49 to 65 years. However, a trend toward potentially beneficial changes in triglycerides was observed in perimenopausal women (C. Atkinson, Oosthuizen, et al., 2004). A small but significant decrease in triglyceride levels was observed in another study of women receiving Promensil or Rimostil. Women with elevated baseline triglyceride levels showed greatest improvement (Schult et al., 2004). However, the effect was probably too small to be clinically important. These studies suggest that isoflavones may not be responsible for the well-documented effects of soy protein on blood lipids.

Arterial compliance, an index of the elasticity of large arteries, improved in a small, short-term study of postmenopausal women receiving Promensil (Nestel, Pomeroy, and Kay, 1999). These results were confirmed by a larger study of normotensive men and postmenopausal women (Teede et al., 2003). Ambulatory blood pressure remained unchanged but total peripheral resistance improved in these patients. Subjects received 80 mg/day of a red clover-derived isoflavone supplement containing mostly biochanin A or formononetin; improvements were greatest in the formononetin group.

## Effects on bone density

As oestrogen levels drop during menopause, a woman's risk for developing osteoporosis (significant bone loss) goes up. A few studies suggest that a proprietary extract of red clover isoflavones may slow bone loss and even boost bone mineral density in pre- and perimenopausal women. But the evidence is preliminary, and more research is needed (unknown, 2015e).

Diets rich in soy protein have been associated with reduced incidence of hip fracture and attenuation of bone loss. Because of this, red clover has been investigated also.

### Animal data

Research reveals no animal data regarding the effects of red clover on bone density.

### Clinical data

Isoflavone supplementation was associated with reduced losses of bone mineral content and bone mineral density at the lumbar spine in a large study (N = 205) (C. Atkinson, Compston, et al., 2004). Markers of bone formation were also increased in women, 49 to 65 years of age, who received Promensil for 12 months. Postmenopausal women appeared to gain most advantage. Between-group differences in bone mineral density at the hip were not significant. Another trial showed no differences in markers of bone turnover among menopausal women receiving Rimostil, Promensil, or placebo (Schult et al., 2004). However, the validity of the results may have been affected by the short study duration (12 weeks).

## Cancer

Based on its traditional use for cancer, researchers have begun to study the role of isoflavones from red clover in cancer prevention and treatment. Preliminary evidence suggests these isoflavones may stop cancer cells from growing or kill cancer cells in test tubes. Researchers theorise that red clover may help prevent some forms of cancer, such as prostate and endometrial cancer. However, because of the herb's oestrogen-like effects, it might also contribute to the growth of some cancers, just as oestrogen does. Until further research is done, doctors cannot recommend red clover to prevent cancer. Women with a history of breast cancer should not take red clover (unknown, 2015e).

Biochanin A has been reported to inhibit carcinogenic activity in cell cultures (C. A. Newall, L. A. Anderson, and Phillipson, 1996b). Men with low- to moderate-grade prostate carcinoma who received isoflavonoid supplements prior to radical prostatectomy showed no changes in serum

PSA, serum testosterone, or biochemical factors (Jarred, Keikha, and Dowling, 2002). However, analysis of prostatectomy specimens showed an increase in apoptosis, particularly in regions of low- to moderate-grade cancer, when compared with historical controls.

Red clover may also block enzymes thought to contribute to prostate cancer in men. It has shown a definite limiting effect, however, in the development of BPH, which is a non-cancerous enlargement of the prostate gland. An enlarged prostate may cause men to experience a weak or interrupted urine stream, dribbling after urinating, or the urge to urinate even after voiding. For most men,BPH is a normal part of aging (herbwisdom, 2015n).

## Efficacy

- **Hypercholesterolemia** - Does not significantly reduce total or LDL cholesterol, OR increase HDL in women 49–65. More studies are needed (medscape, 2015k).
- **Menopausal symptoms** - Does not seem to reduce menopausal symptoms (medscape, 2015k).
- **BPH** -
  - May decrease nocturnal urinary frequency, international prostate symptom scores, and improve the quality of life,
  - Does not affect urine flow rate, PSA values, or prostate size (medscape, 2015k).
- **Breast Cancer (prevention)** - May not significantly affect breast cancer risk (medscape, 2015k).
- **Endometrial cancer** - It is not known if has any effect on risk. More studies are needed (medscape, 2015k).
- **Mastalgia** - Preliminary evidence suggests reduction in breast pain and tenderness in 45% of patients (medscape, 2015k).
- **Osteoporosis** - More studies are needed. 40 mg isoflavones four times a day did not seem to increase bone mineral density (BMD) (medscape, 2015k).

## Available Forms

Red clover is available in a variety of preparations, including teas, tinctures, tablets, capsules, liquid extract, and extracts standardised to specific isoflavone contents. It can also be prepared as an ointment for topical (skin) application (unknown, 2015e).

## Dosage

Due to lack of long-term studies, self treatment should not exceed 3 to 6 months without the supervision of a health care professional (unknown, 2015e).

Formerly used as a sedative at doses of 4 g blossoms, red clover is now used chiefly as a source of isoflavones. Extracts standardised for isoflavone content (eg, Promensil and Rimostil; Novogen Laboratories, North Sydney, Australia) have been used frequently in clinical trials. These tablets contain biochanin A, formononetin, genistein, and daidzein; Promensil contains a higher proportion of biochanin A and genistein and lower proportions of formononetin and daidzein than Rimostil (E., J. Liu, and Lantvit, 2002). The usual dosage is 40 to 80 mg/day of total isoflavones (1 to 2 tablets).

## Paediatric

Red clover has been used traditionally as a short-term cough remedy for children. Products containing isolated red clover isoflavones are very different than the whole herb, however, and are not recommended for children. DO NOT give a child red clover without talking to your paediatrician first (unknown, 2015e).

## Adult

Dose may vary from person to person, but general guidelines are as follows -

- **Dried herb (used for tea)** - 1 to 2 tsp dried flowers or flowering tops steeped in 8 oz. hot water for $\frac{1}{2}$ hour; drink 2 to 3 cups daily,
- **Powdered herb (available in capsules)** - 40 to 160 mg per day, or 28 to 85 mg of red clover isoflavones,
- **Tincture (1:5, 30% alcohol)** - 60 to 100 drops (3 to 5 mL), 3 times per day; may add to hot water as a tea,
- **Fluid Extract (1:1)** - 1 mL, 3 times per day; may add to hot water as a tea,
- **Standardised red clover isoflavone extracts** - follow directions on product labels carefully,
- **Topical treatment (such as for psoriasis or eczema)** - an infusion, liquid extract, or ointment containing 10 to 15% flower heads; apply as needed unless irritation develops. DO NOT apply to an open wound without a doctor's supervision (unknown, 2015e).

Although some red clover isoflavones are being studied for a variety of conditions, it is important to remember that extracts of red clover isoflavones are very different from the whole herb. In fact, they represent only a small, highly concentrated part of the entire herb (unknown, 2015e).

- Standardised commercially prepared isoflavins - 40–80 mg a day,
- **Flower Tops** - 4 g oral three times a day,
- **Tea** - 1 cup orally three times a day; 4 g flower tops in 150 mL water,
- **Liquid Extract** - 1.5–3 mL orally three times a day; 1:1 in 25% alcohol,
- **Tincture** - 1–2 mL orally three times a day; 1:10 in 45% alcohol,
- **Topical** - Dosage varies,

- **Hot Flush** - Isoflavone extract: 40–160 mg a day orally,
- **Cyclic Mastalgia** - Isoflavones: 40–80 mg a day,
- **Osteoporosis** - Specific extract (Promensil): 40 mg a day (medscape, 2015k).

## Pregnancy/Lactation

Pregnant or breastfeeding women should not take red clover (unknown, 2015e). The oestrogenic effects of red clover are well documented and may have an effect on the foetus. Use is contraindicated.

## Contraindications

Cancer (breast, ovarian, uterine), endometriosis, hormone sensitive conditions, uterine fibroids (medscape, 2015k).

## How it works

Anti-spasmodic, expectorant constituents, Isoflavones (e.g., daidzein, genistein) are phytoestrogens: weak oestrogenic/anti-oestrogenic[340] properties (medscape, 2015k).

## Cautions

Coagulation disorders, concurrent CYP3A4 substrates (medscape, 2015k).

## Interactions

An additive effect may occur if the phytoestrogens of red clover are taken with hormonal therapies; avoid concurrent use with oral contraceptives, oestrogen, or progesterone therapies.

Red clover contains coumarin derivatives; however, there is little risk of anticoagulant abnormalities (A. M. Heck, DeWitt, and Lukes, 2000), (Booth, Nikolic, and Breeman, 2004).

Red clover may interfere with the body's ability to process some drugs that are broken down by liver enzymes. For that reason, you should check with your doctor before taking red clover.

- **Oestrogens, hormone replacement therapy, and birth control pills** - Red clover may increase the effects of oestrogen.
- **Tamoxifen** - Red clover may interfere with tamoxifen.

[340] lowers the oestrogen levels in the blood

- **Anticoagulants (blood thinners)** - Red clover may enhance the effect of these drugs, increasing the risk of bleeding. The same is true of herbs and supplements that have blood-thinning effects (such as ginkgo, ginger, garlic, and vitamin E) (unknown, 2015e).

## Side-effects

No serious side effects have been reported in people taking red clover for up to 1 year. General side effects may include **headache**, **nausea**, and **rash**.

## Adverse Reactions

However, animals that graze on large amounts of red clover have become infertile. People who have been diagnosed with breast cancer should not use red clover without discussing it with their physician. Red clover may increase the risk of bleeding, particularly in those people who are taking blood-thinning medications (unknown, 2015e).

Few adverse effects of red clover have been reported in clinical trials (Jarred, Keikha, and Dowling, 2002), (Howes et al., 2004). Loss of appetite, foot oedema, and abdominal tenderness have been reported after administration of a high (4 or 8 mg/kg) dose of isoflavones (genistein, daidzein, glycitenz) (Busby, Jeffcoat, and Bloedon, 2002). Free and total genistein and daidzein disappeared rapidly from the plasma in this study and appear unlikely to accumulate in the body with regular use 2 to 3 times daily.

Oestrogen like effects, rash (medscape, 2015k).

## Toxicology

The phytoestrogens in red clover may be expected to act through oestrogenic mechanisms with the associated risk of oestrogen-like adverse effects, including increased incidence of endometrial, ovarian, and breast cancers. Red clover induced a proliferation of oestrogen-sensitive breast cancer cells in an in-vitro study (Bodinet and Freudenstein, 2004). However, another study showed that mammographic breast density, a marker for oestrogenic and anti-oestrogenic effects, was unaffected by administration of Promensil for 1 year in women 49 to 65 years of age (C. Atkinson, Warren, and Sala, 2004). A small pilot study found no antiproliferative effects on the endometrium associated with use of red clover isoflavones (Beck et al., 2003).

Infertility and growth disorders have been observed in grazing animals receiving high proportions of red clover in their feed. This has been attributed to the oestrogenic activity of red clover. A syndrome characterized by infertility, abnormal lactation, dystonia, and prolapsed uterus, known as clover disease, has been described in sheep.

## Commentary

*Although red clover has oestrogenic affects they seem to be very variable, which could be due to the variability of red clover extracts, or due to an individual's own genetic makeup. Either way, it is impossible to say that it is efficacious. It should not be taken with other forms of exogenous oestrogen, such as HRT, as it competes for the same oestrogen receptors in the body.*

Chapter 13

# S's

## Sage

### Common Names

Culinary sage, Dalmatian sage, garden sage, kitchen sage, true sage, meadow sage, Broadleaf Sage, Common Sage, Narrow-leaved sage, Salvia, Sarubia, Spanish sage, Tibbi Adacayi, black sage, broad-leafed sage, Feuille de la Bergère, Herbe Sacré, Salvia lavandulaefolia, Sauge Ananas, Sauge des Prairies, Sauge Divinatoire, Sauge Divine, Sauge Domestique, Sauge Officinale, Scarlet Sage, Spanish Sage, True Sage, Vraie Sauge. Arabic = Salima, Arabic = Salmya, French = Herbe sacrée, French = Sauge, French = Sauge officinale, French = Thé de Gréce, German = Echter Salbei, German = Garten-Salbei, Italian = Salvia, Russian = alfej apteny, Spanish = Salvia, Swedish = Kryddsalvia

### Scientific Name

*Salvia officinalis*

### Overview

Sage has one of the longest histories of use of any culinary or medicinal herb. Ancient Egyptians used it as a fertility drug. In the first century C.E. Greek physician Dioscorides reported that the aqueous decoction of sage stopped bleeding of wounds and cleaned ulcers and sores. He also recommended sage juice in warm water for hoarseness and coughs. It was used by herbalists externally to treat sprains, swelling, ulcers, and bleeding. Internally, a tea made from sage leaves has had a long history of use to treat sore throats and coughs; often by gargling. It was also used by herbalists for

rheumatism, excessive menstrual bleeding, and to dry up a mother's milk when nursing was stopped. It was particularly noted for strengthening the nervous system, improving memory, and sharpening the senses. Sage was officially listed in the United States Pharmacopoeia from 1840 to 1900.

Sage Tea or infusion of Sage is a valuable agent in the delirium of fevers and in the nervous excitement frequently accompanying brain and nervous diseases. It has a considerable reputation as a remedy, given in small and often-repeated doses. It is highly serviceable as a stimulant tonic in debility of the stomach and nervous system and weakness of digestion generally. It was for this reason that the Chinese valued it, giving it the preference to their own tea. It is considered a useful medicine in typhoid fever and beneficial in biliousness and liver complaints, kidney troubles, haemorrhage from the lungs or stomach, for colds in the head as well as sore throat, quinsy, measles, for pains in the joints, lethargy and palsy. It has been used to check excessive perspiration in phthisis cases, and is useful as an emmenagogue. A cup of the strong infusion will be found good to relieve nervous headache.

The German Commission E approved internal use for mild gastrointestinal upset and excessive sweating as well as for external use in conditions of inflamed mucous membranes of the mouth and throat. An unpublished, preliminary German study with people suffering from excessive perspiration found that either a dry leaf extract or an infusion of the leaf reduced sweating by as much as 50%.

In Germany, sage tea is also applied topically as a rinse or gargled for inflammations. Sage extract, tincture, and essential oil are all used in prepared medicines for mouth and throat and as gastrointestinal remedies in fluid (e.g., juice) and solid dosage forms.

Sage has been used effectively for throat infections, dental abscesses, infected gums and mouth ulcers. The phenolic acids in Sage are particularly potent against Staphylococcus aureus. In-vitro, sage oil has been shown to be effective against both Escherichia coli and Salmonella species, and against filamentous fungi and yeasts such as Candida albicans. Sage also has an astringent action due to its relatively high tannin content and can be used in the treatment of infantile diarrhoea.

Its antiseptic action is of value where there is intestinal infection. Rosmarinic acid contributes to the herb's anti-inflammatory activity.

Sage has an anti-spasmodic action which reduces tension in smooth muscle, and it can be used in a steam inhalation for asthma attacks. It is an excellent remedy for helping to remove mucous congestion in the airways and for checking or preventing secondary infection. It may be taken as a carminative to reduce griping and other symptoms of indigestion, and is also of value in the treatment of dysmenorrhoea. Its bitter component stimulates upper digestive secretions, intestinal mobility, bile flow, and pancreatic function, while the volatile oil has a carminative and stimulating

effect on the digestion. It has a vermifuge action. There also seems to be a more general relaxant effect, so that the plant is suitable in the treatment of nervousness, excitability and dizziness. It helps to fortify a generally debilitated nervous system.

In 1997, the National Institute of Medical Herbalists in the United Kingdom sent out a questionnaire to its member practitioners on the clinical use and experience of sage. Of 49 respondents, 47 used sage in their practice and 45 used it particularly in prescriptions for menopause. Almost all references were to sage's application for hot flushes, night sweats, and its oestrogenic effect. The age range of the menopause patients was 40 to 64, with an average of 49.76. Three-quarters were aged 47 to 52. Forty-three practitioners also noted its use in infections, mainly of the upper respiratory tract, 29 reported its use in sore throat, and 15 reported its use in mouth and gum disease, taken in the form of gargles and mouthwashes. Another main area emphasised by the respondents was its use as a general tonic, for fatigue, nervous exhaustion, immune system depletion, and poor memory and concentration, at any age. Dosage form preference was also reported. Sage was prescribed as tea (aqueous infusion) by 37 practitioners, alcoholic tincture by 30, fresh tincture by 14, alcoholic fluid extract by 2, fresh juice by 2, and fresh leaf by 1.

It is well documented that Sage leaf helps to reduce menopausal sweats. In one study, excessive sweating was induced by pilocarpine. The sweating was reduced when participants were given an aqueous extract of fresh Sage leaf. In a further study 40 patients were given dried aqueous extract of fresh sage (440mg) and 40 were given infusion of sage (4.5g) herb daily. Both groups of patients experienced a reduction in sweating.

Sage has a strong anti-hydrotic[341] action, and was a traditional treatment for night sweats in tuberculosis sufferers. Its oestrogenic effects may be used to treat some cases of dysmenorrhoea and menstrual irregularity or amenorrhoea and can reduce breast-milk production.

Research has suggested that the presence of volatile oil in Sage is largely responsible for most of its therapeutic properties, especially its antiseptic, astringent and relaxing actions. Sage is also used internally in the treatment of night sweats, excessive salivation (as in Parkinson's disease), profuse perspiration (as in TB), anxiety and depression. Externally, it is used to treat insect bites, skin, throat, mouth and gum infections and vaginal discharge.

It is thought that Sage is similar to Rosemary in its ability to improve brain function and memory. In a study involving 20 healthy volunteers Sage oil caused indicated improvements in word recall and speed of attention. Meanwhile the activity of Sage and its constituents have been investigated in the search for new drugs for the treatment of Alzheimer's disease with promising results.

[341] reduces excessive sweating and perspiration

ESCOP (European Scientific Cooperative on Phytotherapy) indicate its use for inflammations such as stomatitis, gingivitis and pharyngitis, and hyperhidrosis (herbwisdom, 2015o).

## Botany

At least 95 species and many varieties exist within the sage genus Salvia. This small, evergreen perennial plant can grow up to 1 m, and its short woody stems branch extensively. The plant is native to the Mediterranean region and grows throughout much of the world. Its violet-blue flowers bloom from June through September. This plant should not be confused with red sage or desert brush sage, which are unrelated (N. USDA, 2009), (Chevallier, 1996), (Blumenthal, Goldberg, and Brinckmann, 2000), (Leung, 1980).

This plant is native to southern Europe and the Mediterranean region but has been naturalised to other warmer temperate climates, including North America. Garden sage (Salvia Officinalis) prospers in an alkaline soil in full sun. It is commonly found in dry banks and rocky soil. It is quite simple to grow garden sage from seeds which are usually easy to come by.

Garden sage is a fragrant shrub with silver-green leaves. It has a woody stem and blue to purplish flowers. This plant may reach a height of 60 centimeters and a spread of 45 centimeters. The garden sage plant flowers in mid-summer (Resource, 2015k).

## History

The name Salvia derives from the Latin "salvere", meaning to cure. Traditionally, sage and its oil have been used to treat a wide range of illnesses. Ethanolic tinctures and decoctions have been used to treat inflammation of the oral cavity and gastrointestinal tract; sage has been used as a tonic and anti-spasmodic.

The plant has been used topically as an antiseptic and astringent and to manage excessive sweating. Sage tea has been ingested for the treatment of dysmenorrhoea, diarrhoea, gastritis, tonsillitis, and sore throat. The dried leaves have been smoked to treat asthma.

Dried sage leaf is used as a culinary spice and as a source of sage oil, which is obtained by steam distillation. Sage oil is used as a fragrance in soaps and perfumes. Sage is used as a food flavouring, and its aroma is said to suppress the odour of fish. Sage oleoresin is also used in the culinary industry (Chevallier, 1996), (Leung, 1980), (J. Duke, 1985).

## Properties

Antibacterial, anti-fungal, anti-hydrotic, anti-inflammatory, antimicrobial, antiseptic, anti-spasmodic, antiviral, aromatic, astringent, carminative, emmenagogue, oestrogenic, relaxant, spasmolytic, vermifuge (herbwisdom, 2015o).

## Indicated for

Aiding digestion, Alzheimer's disease, asthma, bacterial and fungal infections, biliousness, bites, calming and stimulating the nervous system, candida, colds, coughs, dental abscesses, diarrhoea (infantile), dysmenorrhoea, encouraging healing, excessive menstrual bleeding, flatulent dyspepsia, gastrointestinal upset, gingivitis, glossitis, headache (nervous), hot flashes (menopausal sweats) hyperhidrosis, improving memory, indigestion, infected gums, intestinal infection, insect bites, irregular and scanty periods, joint paint, kidney problems, lack of appetite, lethargy, liver complaints, lungs or stomach haemorrhaging, measles, mouth ulcers, night sweats, oral inflammation, palsy, perspiration (excessive), pharyngitis, phthisis, quinsy, reducing lactation, rheumatism, rhinitis, skin, throat, mouth and gum infections, soothing the digestive tract, stimulating upper digestive secretions, intestinal mobility, bile flow, and pancreatic function, stings, stomatitis, strengthening the nervous system, throat infections, typhoid fever, uvulitis, vaginal discharge. Taken internally or as a gargle or mouthwash; galactorrhoea, hyperhydrosis, inflammations of the mouth, tongue or throat.

Sage should not be used by pregnant or nursing women or by people who have epileptic fits.

Sage should not be used to suppress perspiration in fevers.

## Chemistry

Sage officinalis contains 1% to 2.8% essential oil, along with flavones, phenolic acids, phenylpropanoid glycosides (eg, martynoside), triterpenoids, and diterpenes, including phenolic, quinoidal, and rearranged abietane and apianane derivatives. The plant's compounds include salvigenin, lupeol, beta-sitosterol, stigmasterol, physcion, carnosol, rosmadial, rosmanol, epirosmanol, isorosmanol, columbaridione, atuntzensin A, miltirone, carnosic acid, and 12-O-methyl carnosic acid (Leung, 1980), (Capek, Hribalova, et al., 2003), (Hohmann et al., 2003), (Miura, Kikuzaki, and Nakatani, 2001), (Ninomiya, Matsuda, and Shimoda, 2004).

Monoturpenes have been identified using gas chromatography and other techniques, with $\alpha$- and $\beta$-thujones accounting for about $\frac{1}{2}$ of the oil's composition (Loizzo, Saab, and Tundis, 2008b), (Bozin et al., 2007), (Raal, Orav, and Arak, 2007). Capillary electrophoresis has been used to identify

the polyphenols (Ben Hameda, Gajdoová, and Havel, 2006), (Fecka and Turek, 2007), while high performance liquid chromatography and nuclear magnetic resonance techniques have been applied to cold water extracts in identifying polysaccharides (Capek, 2008), (Capek and Hríbalová, 2004).

Salvia lavandulaefolia (Spanish sage) and Sage officinalis have similar compositions except that Sage officinalis has a much higher concentration of thujone, which is toxic in large doses (D. O. Kennedy and A. B. Scholey, 2006). Sage lavandulaefolia also contains variable amounts of camphor, cineol, limonene, camphene, and pinene. Sage oil is often adulterated by the addition of thujone derived from the leaves of Juniperus virginiana (red cedar) (Leung, 1980), (Raal, Orav, and Arak, 2007), (Tildesley, O., and E. K. Perry, 2003), (Savelev et al., 2003).

## Uses and Pharmacology

Dried sage leaf is used as a culinary spice and as a source of sage oil. Sage extracts are being investigated for their potential in memory enhancement and Alzheimer disease; however, clinical trials are lacking. Anti-inflammatory and antimicrobial properties have been identified, as well as potential effects in diabetes and gastric ulcers.

Traditionally, the leaves have been made into a poultice and used externally to treat sprains, swelling, ulcers and bleeding. It was also commonly used in tea form to treat sore throats and it is also considered one of the good herbs for the coughs.

Considered by many herbalists as a good medicinal herb for treating eczema, canker sores, halitosis, gingivitis or bad breath and also to treat dandruff.

Garden sage is useful in treating the symptoms of menopause, including "hot flashes".

Salvia officinalis has shown anti-fungal, antiviral and antibacterial properties that make it a useful weapon in combating many illnesses. Some studies have shown it to be effective against candida albicans, herpes simplex virus II, and influenza virus II.

This herb has shown great promise in aiding digestion and enhancing overall tone of the digestive tract.

It also has shown antioxidant properties equal to that of $\alpha$-tocopherol.

Sage helps reduce excessive perspiration and salivation.

Salvia officinalis may also support liver and pancreatic function.

Sage tea does appear to have a mild calming effect as well.

Garden sage may be helpful in Type II diabetes for lowering blood sugar levels through insulin support (although only a mild effect.)

It has been used commonly as a flavour preserver in foods, as well as a flavouring during cooking.

It has shown some promise in clinical trials as an herbal remedy for Alzheimer's Disease.

Leaves of the plant can be placed in bath water to enhance dark hair.

Garden sage leaves may be applied to an aching tooth to relieve pain (Resource, 2015k).

### CNS effects

Improved memory retention has been demonstrated in animal studies (M. Eidi, A. Eidi, and Bahar, 2006), as well as in clinical studies. In one study, mood and cognitive performance were improved in young healthy volunteers given 300 and 600 mg of dried S. officinalis leaf. An anxiolytic effect was also observed (D. O. Kennedy, Pace, et al., 2006). In another study, ethanolic leaf extract increased memory and attention in older healthy volunteers (mean, 72.95 years of age) at lower dosages (333 mg extract), but had no effect at higher dosages (A. B. Scholey, Tildesley, and Ballard, 2008). Adverse reactions were similar to those reported with cholinesterase inhibitors (Akhondzadeh and Abbasi, 2006).

Limited studies have evaluated the efficacy of sage extracts in Alzheimer disease (D. O. Kennedy and A. B. Scholey, 2006), (Akhondzadeh and Abbasi, 2006), (Akhondzadeh, Noroozian, et al., 2003). While the results are promising, some methodological issues remain, and larger, long-term trials are needed before a definitive role for sage in the management of Alzheimer disease can be seen (D. O. Kennedy and A. B. Scholey, 2006). Similar results have been obtained in studies using other Salvia species, including S. lavandulaefolia and Salvia miltiorrhiza, as well as rosmarinic acid alone (D. O. Kennedy and A. B. Scholey, 2006), (Tildesley, O., and E. K. Perry, 2003), (Tildesley, D. O. Kennedy, et al., 2005), (Imanshahidi and Hosseinzadeh, 2006), (Pereira et al., 2005), (Orhan and Aslan, 2009), (N. S. Perry et al., 2003).

## Other effects

- **Anti-inflammatory activity** - Proinflammatory cytokines were suppressed in in-vitro experiments with human leukocytes (Poeckel, Greiner, and Verhoff, 2008) and in induced colitis in mice (Juhás, Cikos, and Czikková, 2008). No histological changes were apparent (Juhás, Cikos, and Czikková, 2008). The chloroform extracts, in particular ursolic acid, of S. officinalis leaves showed strong anti-inflammatory properties after topical application. Ursolic acid exhibited dose-

dependent inhibition of croton oil-induced ear oedema in mice. The anti-inflammatory effect of ursolic acid was 2-fold more potent than that of indomethacin (Imanshahidi and Hosseinzadeh, 2006), (Baricevic, Sosa, and Della Loggia, 2001).

- **Antimicrobial activity** - In-vitro antimicrobial activity has been demonstrated by both the aqueous extracts of sage leaves and the essential oil. A wide antibacterial spectrum has been suggested, while activity against fungi is uncertain (Bozin et al., 2007), (Hayouni el, Chraief, and Abedrabba, 2008), (Pozzatti et al., 2008), (Weckesser et al., 2007). Interest centres on activity against vancomycin-resistant enterococci (Horiuchi et al., 2007), herpes simplex and corona viruses (Loizzo, Saab, and Tundis, 2008b), (Schnitzler et al., 2008) and HIV (Geuenich, Goffinet, and Venzke, 2008), (Bailly et al., 2005).
- **Antioxidant activity** - Aqueous extracts of sage, sage tea, and volatile and phenolic sage compounds have been used in experiments demonstrating the antioxidant potential of sage and other related species. Oxygen radical absorbance capacity assay and electron spin resonance techniques have been used in assay and in-vitro experiments. In-vivo markers, such as glutathione levels, have been used in rats. Inhibition of lipid peroxidation and increasing food oil stability have been demonstrated, but clinical applications are lacking (Bozin et al., 2007), (Orhan and Aslan, 2009), (Poeckel, Greiner, and Verhoff, 2008), (C. F. Lima, Carvalho, and Fernandes, 2004), (C. F. Lima, P. B. Andrade, et al., 2005), (C. F. Lima, Valentao, et al., 2007), (Aherne, Kerry, and O'Brien, 2007), (Oboh and Henle, 2009), (Celik and Isik, 2008), (Capek, Machová, and Turjan, 2009).

  Antioxidants work to stop free radicals from attacking the cell tissues, prevents the indications of early aging, and also the uncertainty of illnesses like cancer, not to mention cardiovascular disease. Sage tea is a powerful generator of antioxidants which assists to stave off these dangerous effects of free radicals (Rogers, 2015).
- **Cancer** - Sage essential oil and its constituent monoterpenes were effective in protecting against ultraviolet-induced mutations in bacterial studies (Vukovic-Gacic et al., 2006).
- **Diabetes** - Studies in animals have shown effects of methanol leaf extracts and sage tea on fasting plasma glucose levels, but not on glucose tolerance tests or insulin (M. Eidi, A. Eidi, and Zamanizadeh, 2005), (C. F. Lima, M. F. Azevedo, et al., 2006). Sage essential oil had no effect on serum glucose (M. Eidi, A. Eidi, and Zamanizadeh, 2005). Other Salvia species have also been evaluated for effects on serum glucose (Loizzo, Saab, and Tundis, 2008a).
- **Gastro-Intestinal activity** - There is some evidence that sage oil may exert a centrally-mediated, antisecretory action; the carminative effect is likely caused by the irritating effects of the volatile oil (Blumenthal, Goldberg, and Brinckmann, 2000). A hydroethanolic extract was protective against ethanol-induced gastric lesions in rats (B. Mayer, Baggio, and Freitas, 2009).

- **Functions as an antiseptic** - Sage is really a frequent ingredient in natural toothpaste as a result of its antiseptic qualities. The powdered leaf can be used and moistened to pack between your gingiva and teeth in instances of oral infections. The distinctive aroma of sage is a result of essential oils like camphor, cineole, and thujone, that are strong antimicrobial compounds. Sage is frequently burned in a package like a smudge stick to purify a dwelling. When it's burned it releases the essential oils in the atmosphere. These antimicrobial properties may be utilised when treating head colds as well by boiling the herb and inhaling the steam that comes from it (Rogers, 2015).
- **Impacts diabetes** - Sage is amongst the herbs that are thought to help individuals with diabetes. This is due to the fact that it can help to lower the level of blood sugar in one's body (Rogers, 2015).
- **Astringent qualities** - This is beneficial when gargling the herb as a tea to take care of sore throats. Sage is readily consumed as a tea to alleviate night sweats or stuffy noses. The property of sage can be powerful as a rinse for hair because it helps with oil and gives hair a nice shine (Rogers, 2015).
- **Helps Our skin** - Cooled sage tea is frequently advised for people who have acne prone skin. Make an easy face wash by taking away the leaves and brewing a cooling tea. The brew is cleaning and astringent. Due to the powerful astringent properties, sage frequently appears in external herbal preparations for deodorants and body washes. The tea also works well as a foot soak for foot and toenail fungus (Rogers, 2015).
- **Great for teeth** - Sage leaves once acted as cleansers and teeth whiteners, notably with Native American tribes. Merely sipping on some sage tea on a regular basis might help you to have healthier teeth and gums. If you don't like to drink it you can just use it as a mouthwash with great results (Rogers, 2015).
- **As an anti-inflammatory** - Sage is frequently added to skin lotions to treat psoriasis, bug bites and shingles. This is also quite effective at reducing any sort of swelling that you might be experiencing in your mouth from an infection if you can't immediately see your dentist (Rogers, 2015).
- **Aids digestion** - Sage can also help quite a bit with digestion. The herb helps to break up food so that it can be digested easier, and it stimulates better overall digestion (Rogers, 2015).
- **Helps With menopause** - Sage is sometimes used in cutting down the harshness of menopausal symptoms. Sage is contained in several herbal formulas specifically made with menopause in mind, both as a tincture or in capsules (Rogers, 2015).

- **May help with brain function** - It's believed that sage resembles rosemary in the way it can enhance memory and brain function. In a research study involving 20 healthy volunteers, sage oil caused suggested improvements in speed and phrase recall of interest. Meanwhile, the action of sage and its particular components are being investigated within the hunt for new medicines for the medical treatment of Alzheimer's with promising results (Rogers, 2015).
- **As incense** - Sage has been used for tens of thousands of years in purification rituals. Called smudging, burning dried sage leaves within the house is thought to remove negative energy (Rogers, 2015).

## What the Science Says

- Sage has not been well studied as a treatment for sore throat, so there is little scientific evidence to support its use for that ailment.
- Two small studies suggest that sage may improve mood and mental performance in healthy young people and memory and attention in older adults. Results of another small clinical study suggest that a sage extract was better than placebo at enhancing thinking and learning in older adults with mild to moderate Alzheimer's disease.
- Laboratory studies suggest that essential oils from sage may have antimicrobial properties (S Foster, 2012).

## Adverse reactions

Reported adverse reactions from the ingestion of sage include cheilitis, stomatitis, dry mouth, and local irritation (J. Duke, 1985). There were no clinically important adverse reactions reported by healthy patients in 2 clinical trials (Tildesley, O., and E. K. Perry, 2003), (Akhondzadeh, Noroozian, et al., 2003); however, effects were similar to those reported with cholinesterase inhibitors (Akhondzadeh and Abbasi, 2006). Increases in blood pressure were reported in a trial evaluating S. lavandulaefolia essential oil in 2 patients with preexisting hypertension (N. S. Perry et al., 2003).

## Side Effects and Cautions

In some individuals **stomach discomfort**, **nausea**, **vomiting** or **abdominal discomfort** may happen. It's also possible to feel extraordinarily irritated or dizzy.

If you go over the advised dosage of sage leaf it might cause serious unwanted side effects like **nerve or liver injury**. In addition, sage leaf includes a toxin called thujoine that might cause **seizures** when taken in big doses. Should you experience these serious side effects after having sage leaf seek immediate treatment from your doctor.

- Sage is generally regarded as safe by the FDA and is approved for food use as a spice or seasoning. However, some species of sage contain thujone, which can affect the nervous system. Extended use or taking large amounts of sage leaf or oil may result in **restlessness**, **vomiting**, **vertigo**, **rapid heart rate**, **tremors**, **seizures**, and **kidney damage**. It also may lead to **wheezing**. Ingesting 12 drops or more of the essential oil is considered a toxic dose.
- Drug interactions with sage have not been thoroughly studied.
- Sage can stimulate allergic or hypersensitivity reactions. Skin contact may result in inflammation. Ingesting sage powder or dust may cause breathing difficulties (S Foster, 2012).

## Pregnancy/Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking.

## Interactions

None well documented. Interactions with cholinergic drugs, such as pilocarpine and scopolamine, is expected based on studies evaluating the effect of sage extracts in Alzheimer disease (M. Eidi, A. Eidi, and Bahar, 2006), (Akhondzadeh and Abbasi, 2006).

Using sage leaf might not be right for you if you're taking certain drugs. Since your blood sugar may be severely lowered by this mixture of treatments, prevent combining sage leaf with drugs indicated for diabetes. Getting sage leaf might decrease the potency of seizure drugs like phenytoin and phenobarbital. Additionally, stay away from sage leaf in the event that you are taking a sedative (might lead to extreme drowsiness) (Rogers, 2015).

## Special Precautions & Warnings

- **Pregnancy and breast-feeding** - Taking sage during pregnancy is likely unsafe because of the possibility of consuming thujone, a chemical found in some sage. Thujone can bring on a woman's menstrual period, and this could cause a miscarriage. Avoid sage if you are breast-feeding, too. There is some evidence that thujone might reduce the mother's milk supply.
- **Diabetes** - Sage might lower blood sugar levels in people with diabetes. Watch for signs of low blood sugar (hypoglycaemia) and monitor your blood sugar carefully if you have diabetes and use sage. The dose of your diabetes medications may need to be adjusted by your doctor.

- **Hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids** - Spanish sage (Salvia lavandulaefolia) might have the same effects as the female hormone oestrogen. If you have any condition that might be made worse by exposure to oestrogen, don't use Spanish sage.
- **High blood pressure, low blood pressure** - Spanish sage (Salvia lavandulaefolia) might increase blood pressure in some people with high blood pressure, while common sage (Salvia officinalis) might lower blood pressure in people with blood pressure that is already low. Be sure to monitor your blood pressure.
- **Seizure disorders** - One species of sage (Salvia officinalis) contains significant amounts of thujone, a chemical that can trigger seizures. If you have a seizure disorder, don't take sage in amounts higher than those typically found in food.
- **Surgery** - Common sage might affect blood sugar levels. There is a concern that it might interfere with blood sugar control during and after surgery. Stop using common sage as a medicine at least 2 weeks before a scheduled surgery.

## Dosage

Dried sage leaf has been investigated in memory studies at doses of 300 and 600 mg (D. O. Kennedy and A. B. Scholey, 2006). Ethanolic extract 333 mg has been studied in Alzheimer disease (A. B. Scholey, Tildesley, and Ballard, 2008), (Akhondzadeh, Noroozian, et al., 2003). Typical dosage has been described as 4 to 6 g/day of the leaf.

Garden sage may be taken in tea form, added to foods while cooking, added raw to salads and sandwiches, and also in tablet/capsule form. The recommended dosage is 400 mg taken one to three times daily. It may also be used in aromatherapy (Resource, 2015k).

- **Tincture** - Take $\frac{1}{8}$ to $\frac{1}{2}$ teaspoon of dried sage leaves in a sip of water up to two times a day.
- **Herbal Tea** - Drink several cups of sage tea every day for several weeks.
- **Gargle or take small sips of sage tea** - Gargle or drink throughout the day as needed.
- **Alzheimer's disease** - Take up to 1 gram of sage by mouth per day.
- **Genital herpes** - Apply 23 mg per day of sage extract and rhubarb extract cream to affected areas every 2 to 4 hours for 10 to 14 days (Balentine, 2015).

### How to Prepare Sage Tea

Based on herbalist Barbara Griggs, sage tea could be brewed with both fresh or dried leaves. Dried leaves are more concentrated, and also you might need to work with fewer leaves. Change the strength to satisfy your personal preference, and should you want to you can add honey. Griggs proposes pouring 1 cup of boiling water over a few fresh or dried sage leaves to prepare just one cup (Rogers, 2015).

## Toxicology

Doses of more than 200 nL/mL essential oil are hepatotoxic (C. F. Lima, Carvalho, and Fernandes, 2004), and at concentrations of 120 mcg/mL, decreased cell viability was found (Aherne, Kerry, and O'Brien, 2007). The intraperitoneal lethal dose in rats of a methanolic extract of sage leaves was calculated at 4,000 mg/kg (M. Eidi, A. Eidi, and Bahar, 2006). Constituents thujone and camphor are recognised as neurotoxic (C. F. Lima, Carvalho, and Fernandes, 2004), while rosmarinic acid, carnosic acid, and carnosol were not genotoxic at dosages used in experiments (Pereira et al., 2005), (Poeckel, Greiner, and Verhoff, 2008).

The plant is toxic in excess or when taken for extended periods, though the toxic dose is very large.

## Commentary

*Although Sage has oestrogenic possibilities, it can have some nasty side-effects, and it also has several interactions and contraindications that are significant. Its usage should therefore only be in culinary purposes, and at low doses in all other areas.*

# Saw Palmetto

## Common names

SAbal, American dwarf palm tree, cabbage palm, fan palm, scrub palm Baies du Chou Palmiste, Baies du Palmier Scie, Chou Palmiste, Ju-Zhong, Palma Enana Americana, Palmier de Floride, Palmier Nain, Palmier Nain Américain, Palmier Scie, Sabal, Sabal Fructus, Sabal serrulata, Saw Palmetto Berry, Serenoa serrulata.

## Latin name

*Serenoa repens*.

## Overview

Saw palmetto is a small palm tree native to the eastern United States. Its fruit was used medicinally by the Seminole Tribe of Florida. Saw palmetto is used as a traditional or folk remedy for urinary symptoms associated with an enlarged prostate gland, also called BPH, as well as for chronic pelvic pain, bladder disorders, decreased sex drive, hair loss, hormone imbalances, and prostate cancer.

The ripe fruit of saw palmetto is used in several forms, including ground and dried fruit or whole berries. It is available as liquid extracts, tablets, capsules, and as an infusion or a tea (NIH, 2012b).

Saw palmetto is an extract derived from the deep purple berries of the saw palmetto fan palm (Serenoa repens), a plant indigenous to the coastal regions of the southern United States and southern California (herbwisdom, 2015p).

Saw palmetto is a palm-like plant with berries. The berries were a staple food and medicine for the Native Americans of the southeastern United States. In the early 1900s, men used the berries to treat urinary tract problems, and even to increase sperm production and boost libido. Today, the primary use of saw palmetto is to treat BPH, a non-cancerous enlargement of the prostate gland. Researchers aren't sure exactly how saw palmetto works. But it contains plant-based chemicals that may be effective for BPH. Researchers think that saw palmetto may affect the level of testosterone in the body, and perhaps reduce the amount of an enzyme that promotes the growth of prostate cells. Saw palmetto also seems to have an anti-inflammatory effect on the prostate. At least one study has shown even greater anti-inflammatory activity when saw palmetto is combined with lycopene and selenium (unknown, 2014l).

## Botany

The saw palmetto is a low, scrubby palm that grows in the coastal plain of Florida and other southeastern states. Its fan-shaped leaves have sharp saw-toothed edges that give the plant its name. Dense clumps of saw palmetto can form an impenetrable thicket. The abundant 2 cm long berries are harvested in the fall and are dried for medicinal use. They also serve as a source of nutrition for deer, bears, and wild pigs (Bennett and Hicklin, 1998).

## History

Native tribes of Florida relied on saw palmetto berries for food; however, Europeans often found the taste of the berries objectionable (Bennett and Hicklin, 1998). While native medicinal use of saw palmetto is not recorded, it was introduced into Western medical practice in the 1870s and was a favourite of eclectic medical practitioners for prostate and other urologic

conditions. Saw palmetto berries were officially included in the US Pharmacopeia in 1906 and 1916, and in the National Formulary from 1926 to 1950. While use in the United States declined after that time, saw palmetto has long been a staple phytomedicine in Europe. Interest in the plant has been rekindled, and saw palmetto is ranked among the top 10 herbal products in the United States, primarily for its activity in BPH (Winston, 1999).

## Properties

Anti-inflammatory, antiseptic, expectorant, mild diuretic, sedative (herbwisdom, 2015p).

BPH, diuretic, a sedative, an anti-inflammatory, alopecia, prostate cancer (in combination with other herbs), and antiseptic (medscape, 2015l).

## Indicated for

BPH. Increasing breast size, improving sexual vigour and as an aphrodisiac. Stimulating hair growth, colds, coughs, irritated mucous membranes, sore throat, asthma, chronic bronchitis, migraines and cancer. Prostate cancer. Nutritive tonic, relieving the symptoms of menstruation, improving muscle tone and muscle building (herbwisdom, 2015p).

Saw palmetto is a remarkable herb for both men and women and is used by natural health practitioners to treat a variety of ailments such as testicular inflammation, urinary tract inflammation, coughs and respiratory congestion. It is also used to strengthen the thyroid gland, balance the metabolism, stimulate appetite and aid digestion. This wonderful herb is becoming famous for its uses in hair restoration, prostate health, sexual vigour, breast enhancement and as a nutritive tonic.

Saw palmetto berry also tones the urethra and it may be used to uphold the healthy function of the thyroid gland and urinary system (herbwisdom, 2015p).

Saw palmetto is best known for its use in decreasing symptoms of an enlarged prostate (BPH). According to many research studies, it is effective for this use.

Saw palmetto is used for treating certain types of prostate infections. It is also sometimes used, in combination with other herbs, to treat prostate cancer.

Some people use saw palmetto for colds and coughs, sore throat, asthma, chronic bronchitis, chronic pelvic pain syndrome, and migraine headache. It is also used to increase urine flow (as a diuretic), to promote relaxation (as a sedative), and to enhance sexual drive (as an aphrodisiac) (NIH, 2012b).

## Chemistry

Saw palmetto berries contain large quantities of beta-sitosterol and other plant sterols (Elghamry and Hänsel, 1969), as well as free and esterified fatty acids (Shimada, V. E. Tyler, and J. L. McLaughlin, 1997). Most standardised commercial preparations are liposterolic extracts containing nonpolar constituents (eg, fatty acids and sterols) produced either by conventional hexane extraction or by supercritical carbon dioxide extraction. The fatty acid components have been quantitated by gas chromatography (De Swaef, 1996a) and supercritical fluid chromatography (De Swaef, 1996b), while the alcohols and sterols have been analysed by thin-layer chromatography and electrospray mass spectrometry of ferrocenyl derivatives (Van Berkel et al., 1998). An acidic polysaccharide with anti-inflammatory activity has been isolated from saw palmetto fruit (Wagner and Flachsbarth, 1981), (Wagner, Flachsbarth, and G. Vogel, 1981).

## Uses and Pharmacology

In the United States, its medicinal uses were first documented in 1879 by Dr. J.B. Read, a physician in Savannah, Georgia, who published a paper on the medicinal benefits of the herb in the April 1879 issue of American Journal of Pharmacy. He found the herb useful in treating a wide range of conditions.

> "By its peculiar soothing power on the mucous membrane it induces sleep, relieves the most troublesome coughs, promotes expectoration, improves digestion and increases fat, flesh and strength. Its sedative and diuretic properties are remarkable,"

Read wrote.

> "Considering the great and diversified power of the saw palmetto as a therapeutic agent, it seems strange that it should have so long escaped the notice of the medical profession."

Since the 1960s, extensive clinical studies of saw palmetto have been done in Europe. A review of 24 European trials appeared in the November 1998 issue of the Journal of the American Medical Association. The trials involved nearly 3,000 men, some taking saw palmetto, others taking Proscar and a third group taking a placebo.

The men taking saw palmetto had a 28% improvement in urinary tract symptoms, a 24% improvement in peak urine flow and 43% improvement in overall urine flow. The results were nearly comparable to the group taking Proscar and superior to the men taking a placebo.

There is much scientific documentation outlining the effectiveness of the herb in treating irritable bladder and urinary problems in men with BPH, an enlargement of the prostate gland. BPH results in a swelling of the prostate gland that obstructs the urethra. This causes painful urination, reduced urine flow, difficulty starting or stopping the flow, dribbling after urination and more frequent nighttime urination. In addition to causing pain and embarrassment, BPH can lead to serious kidney problems if undiagnosed and left untreated. It is a common problem in men over the age of 40. Estimates are that 50-60% of all men will develop BPH in their lifetimes.

Saw palmetto does not reduce prostate enlargement. Instead, it is thought to work in a variety of ways. First, it inhibits the conversion of testosterone into dihydrotestosterone (DHT). BPH is thought to be caused by an increase in testosterone to DHT. Secondly, saw palmetto is believed to interfere with the production of oestrogen and progesterone, hormones associated with dihydrotestosterone (DHT) production.

In a controlled clinical trial with patients with enlarged prostate glands, 50 patients who received saw palmetto (320 mg per day - 4 tablets taken in two separate doses with meals) were compared to 44 patients receiving placebo. Patients treated with saw palmetto urinated less frequently, produced a better flow rate and amount of urine and had less pain and discomfort in urinating than control subjects. There were actually fewer adverse side effects in patients receiving saw palmetto than in controls (herbwisdom, 2015p).

Saw palmetto's active ingredients include fatty acids, plant sterols, and flavonoids. The berries also contain high molecular weight polysaccharides (sugars), which may reduce inflammation or strengthen the immune system (unknown, 2014l).

## Benign prostatic hyperplasia

Evidence is mixed about whether saw palmetto works to treat BPH. Several studies suggest that the herb is effective for treating symptoms, including too frequent urination, having trouble starting or maintaining urination, and needing to urinate during the night. The urethra, the tube that empties urine from the body, runs through the prostate gland in men. When the prostate gland is enlarged, men may have trouble urinating.

Some studies show that saw palmetto is as effective in treating symptoms as finasteride (Proscar) without side effects, such as loss of libido. Other studies suggest that saw palmetto may actually shrink the size of the prostate gland. Due to the short duration (usually less than 3 months) of these studies, it is not possible to say for sure whether saw palmetto is truly effective for preventing complications of BPH. Two well-conducted studies, for example, found that saw palmetto was no better than placebo in relieving the signs and symptoms of BPH.

It is important to receive a proper diagnosis of BPH from your doctor to rule out prostate cancer (unknown, 2014l).

Saw palmetto's mechanism of action in suppressing the symptoms of BPH is poorly understood. Animal and human in-vitro studies have led to several different hypotheses.

## Animal data

The leading hypothesis involves the inhibition of testosterone 5-alpha reductase, an enzyme that converts testosterone to 5-alpha-dihydrotestosterone in the prostate. Hexane extracts of saw palmetto inhibited the enzyme from human foreskin fibroblasts, while they had no direct effect on androgen receptor binding (E. M. Düker and Kopanski, 1989). Investigators found various saw palmetto extracts to be much weaker 5-alpha reductase inhibitors in-vitro than the synthetic drug finasteride (Rhodes, Primka, and C. Berman, 1993). Similarly, in humans, serum levels of DHT were reduced markedly by finasteride, but not by saw palmetto (Strauch, Perles, and Vergult, 1994).

Further studies using both known 5-alpha reductase isozymes found that finasteride inhibited only type 1 reductase, while saw palmetto inhibited formation of all testosterone metabolites in cultured prostate epithelial cells and fibroblasts (Délos et al., 1995). A different saw palmetto extract, IDS 89, dose-dependently inhibited 5-alpha reductase in both the stroma and epithelium of human BPH tissue. This inhibition was related to the free fatty acids present in the extract (Weisser et al., 1996). A tracer study found that radiolabeled oleic acid in saw palmetto extract was taken up preferentially by rat prostate compared with other tissues (Chevalier et al., 1997). Studies in a coculture model of human prostate epithelial cells and fibroblasts found that saw palmetto inhibited types 1 and 2 isoforms of 5-alpha reductase without altering the secretion of PSA (Bayne et al., 1999). Other work has shown that saw palmetto extract inhibits trophic as well as androgenic effects of prolactin in a rat model of prostatic hyperplasia (Van Coppenolle, Le Bourhis, and Carpentier, 2000). Structure-activity studies of pure fatty acid inhibition of steroid 5-alpha reductase found gamma-linolenic acid was the most potent and specific inhibitor of the enzyme (T. Liang and Liao, 1992). It is possible that the C18 monounsaturated fatty oleic acid in saw palmetto was partly responsible for the observed effects on 5-alpha reductase, though more extensive analysis of saw palmetto fatty acids is required.

There is less support for other hormonal mechanisms. One study found 5-alpha reductase inhibition and inhibition of DHT binding to androgen receptors (Sultan, Terraza, and Devillier, 1984), and another study demonstrated inhibition of DHT and testosterone receptor binding (el-Sheikh, Dakkak, and Saddique, 1988). Administration of saw palmetto extract over 30 days led to no changes in plasma levels of testosterone, FSH, or LH (Casarosa, Cosci di Coscio, and Fratta, 1988). Hormonal

pathways were invoked to explain reduced prostate weights in castrated rats treated with estradiol, testosterone, and saw palmetto extract as opposed to estradiol and testosterone alone (Paubert-Braquet, Richardson, and Servent-Saez, 1996). In the human prostate cancer line LNCaP, saw palmetto induced a mixed proliferative/differentiative effect that was not seen in the nonhormone-responsive PC3 human prostate cancer cell line (Ravenna, Di Silverio, and M. A. Russo, 1996). Treatment of patients for 3 months with saw palmetto preceding prostatectomy caused a reduction in DHT levels in BPH tissue, along with a corresponding rise in testosterone levels. A marked reduction in epidermal growth factor concentration was also observed in the periurethral region of the prostate (Di Silverio, Monti, and Sciarra, 1998).

Other observations of saw palmetto extracts include the following: a spasmolytic effect on rat uterus, suggested to be caused by effects on cyclic AMP and calcium mobilisation (Gutiérrez, Hidalgo, and Cantabrana, 1996); an inhibition of smooth muscle contraction in rat deferens and guinea pig ileum and bladder, postulated as alpha-adrenoreceptor antagonistic (Odenthal, 1996), as found in other studies to be noncompetitive in nature (Goepel et al., 1999); and interference with 5-lipoxygenase metabolites in neutrophils (Paubert-Braquet, Mencia Huerta, et al., 1997). A few studies have suggested an increase in apoptosis with administration in mice and humans (Wadsworth et al., 2007), (Vela-navarrete et al., 2005).

## Clinical data

Although the mechanism of action of saw palmetto is not completely understood, clinical trials in BPH have shown convincing evidence of moderate efficacy. A 6-month, double-blind, head-to-head[342] study versus finasteride in 1,098 men found equivalent efficacy and a superior adverse reaction profile for saw palmetto (Bach, 1996). Likewise, a 3-year study of IDS 89 in 435 patients with BPH found clear advantage to placebo in reduction of BPH symptoms (Braeckman et al., 1997a). A 1-year study of 132 patients comparing 2 dose levels of saw palmetto demonstrated efficacy in symptom reduction, but little difference between dose levels (Marandola, 1997). One study observed Serona repens compared with placebo in 189 patients with a mild International Prostate Symptom Score (IPSS). Patients were observed for clinical progression into moderate or severe IPSS. After 24 months the Serona repens group had fewer patients with clinical progression of bladder outlet obstruction (Djavan, Fong, and Chaudry, 2005). In contrast, a 1-year double-blind study of 225 men compared American Urological Association BPH Symptom Index in saw palmetto versus placebo-treated patients and found no difference between the 2 groups (Bent, Kane, and Shinohara, 2006). The general consensus has been that saw palmetto extracts reduce BPH symptoms without reducing prostate size, therefore delaying surgical intervention (Wilt et al., 1998). A

[342] in direct confrontation, opposition, or competition

meta-analysis that included a total of 18 clinical trials in BPH concluded that saw palmetto was better tolerated than finasteride and equivalent in efficacy (Berges et al., 1995). A clinical trial in BPH of the saw palmetto constituent beta-sitosterol showed efficacy similar to that seen with saw palmetto itself (Braeckman et al., 1997b).

Studies have compared the use of saw palmetto in combination with other products versus current prescription therapy. A randomised double-blind trial compared PRO 160 /120 (Prostagutt), a fixed combination preparation of 160 mg sabal fruit extract WS 1473 and 120 mg Urtica root extract WS 1031, per capsule versus tamsulosin in lower urinary tract symptoms. In the 140 subjects with moderate to severe IPSS, there was a decrease in IPSS total scores in both groups after 60 weeks (Engelmann et al., 2006). Similar results were found in an earlier trial comparing PRO 160/120 with placebo (Lopatkin, Sivkov, and Walther, 2005). An open-label extension of this trial observed patients for a total of 96 weeks. All patients received PRO 160/120 for the last 48 weeks. A decrease was found in IPSS total score and residual urine volume, along with an increase in peak and average urinary flow (Lopatkin, Schläfke, et al., 2007). Another study had 3 arms comparing Serenoa repens 320 mg daily, tamsulosin 0.4 mg daily, and S. repens 320 mg plus tamsulosin 0.4 mg daily. After 6 months of therapy in the 60 study subjects, the groups were not statistically different in urinary flow rate and decrease in IPSS (Hizli and Uygur, 2007).

## Other uses

Animal studies show that saw palmetto inhibits the growth of tumour cells, indicating that it may be helpful in the treatment of prostate cancer. Other studies show that saw palmetto improves urinary tract symptoms related to BPH. While these studies are promising, more research is needed to determine whether saw palmetto is effective for these conditions (unknown, 2014l).

## How it works

Active constituents - sitosterols; anthranilic, caffeic, chlorogeneic acids. Inhibits 5-alpha-reductase conversion of testosterone to DHT, anti-inflammatory inhibition of cycloxygenase, lipoxygenase pathways (medscape, 2015l).

Saw palmetto doesn't shrink the overall size of the prostate, but it seems to shrink the inner lining that puts pressure on the tubes that carry urine.

## What the Science Says

- Several small studies suggest that saw palmetto may be effective for treating BPH symptoms. However, a 2011 NCCIH-cofunded study in 369 older men demonstrated that saw palmetto extract administered at up to three times the standard daily dose (320 mg) did not reduce the urinary symptoms associated with BPH more than placebo. In addition, a 2009 review of the research concluded that saw palmetto has not been shown to be more effective than placebo for this use.
- In 2006, an NIH-funded study of 225 men with moderate-to-severe BPH found no improvement with 320 mg of saw palmetto daily for 1 year versus placebo.
- There is not enough scientific evidence to support the use of saw palmetto for reducing the size of an enlarged prostate or for any other conditions.
- Saw palmetto does not appear to affect readings of PSA levels. PSA is a protein produced by cells in the prostate. The PSA test is used to screen for prostate cancer and to monitor patients who have had prostate cancer (NIH, 2012b).

## Efficacy

BPH - Saw palmetto fruit extract did not reduce lower urinary tract symptoms more than placebo 2 trial randomised controlled trials.

Insufficient reliable test results to determine efficacy for other suggested uses (medscape, 2015l).

Natural Medicines Comprehensive Database rates effectiveness based on scientific evidence according to the following scale: Effective, Likely Effective, Possibly Effective, Possibly Ineffective, Likely Ineffective, Ineffective, and Insufficient Evidence to Rate.

The effectiveness ratings for saw palmetto are as follows -

### Possibly effective for...

- **Prostate surgery (transurethral resection of the prostate; TURP)** - Research shows that taking 320 mg of saw palmetto daily for 2 months before prostate surgery can reduce the time spent in surgery, blood loss, the development of problems during surgery, and the total time spent in the hospital. However, one small study found that taking 160 mg daily 5 weeks before surgery does not lower the risk of problems during surgery.

## Possibly ineffective for...

- **BPH** - There is conflicting and contradictory research about the benefits of saw palmetto for prostate symptoms. Some research has shown that saw palmetto might modestly improve symptoms such as going to the bathroom at night in some men with BPH. However, higher quality and more reliable research seems to indicate that saw palmetto has little or no benefit for reducing these symptoms. Any benefit is modest at best.

## Insufficient evidence to rate effectiveness for...

- **Prostate swelling and chronic pelvic pain syndrome** - Some early research found that saw palmetto can improve prostate swelling symptoms. Other early research found that taking saw palmetto, selenium, and lycopene, but not saw palmetto alone, can improve symptoms of prostate swelling and chronic pelvic pain syndrome. Taking certain herbal combinations containing saw palmetto seems to improve the effects of sparfloxacin or prulifloxacin in treating prostate swelling symptoms due to infection. However, saw palmetto doesn't seem to improve prostate swelling symptoms not due to infection.
- **Prostate cancer** - Research studies to date have found that taking saw palmetto doesn't seem to prevent prostate cancer.
- **Baldness** - Some men report that using saw palmetto with beta-sitosterol makes them grow more and better hair.
- **Bladder control (neurogenic bladder)** - Early research suggests that taking 90–120 drops of a combination of echinacea and saw palmetto for 77 days improves the amount of urine the bladder can hold and the amount left in the bladder after urination in women with neurogenic bladder.
- Colds and coughs.
- Sore throat.
- Asthma.
- Chronic bronchitis.
- Migraine headache.
- Increasing breast size.
- Reducing bleeding after prostate surgery.
- Other conditions.

More evidence is needed to rate the effectiveness of saw palmetto for these uses.

## Contraindications

Pregnant women should avoid contact - it has the potential for transdermal absorption, or exposure from semen (medscape, 2015l).

## Adverse Reactions

Saw palmetto products are generally well tolerated, with occasional reports of adverse gastrointestinal effects.

Because of well-documented antiandrogen and antiestrogenic activity, avoid taking with any hormone therapy, including oral contraceptive and hormone replacement therapy.

A study assessing the affects of several herbal medications including saw palmetto on platelet function in adult volunteers found no effect of saw palmetto on platelets after 2 weeks at the recommended dose (Beckert et al., 2007). However, there has been 1 case report linking saw palmetto to intraoperative haemorrhage (P. Cheema, El-Mefty, and Jazieh, 2001). A 53-year-old white man with normal preoperative prothrombin time and activated partial thromboplastin time underwent surgical resection of meningioma. Surgery was terminated early after administration of 4 litres of crystalloid fluids, 4 units of packed red blood cells, 3 units of pooled platelets, and 3 units of fresh frozen plasma. After surgery, the patient had an elevated bleeding time, which normalized over the next 5 days. No other medication use or events were reported that could be linked to the elevated bleeding time; saw palmetto dose, duration of therapy, or manufacturer were not reported in the case report.

Two case reports link saw palmetto to intraoperative floppy-iris syndrome, which is also associated with multiple alpha [1] -adrenergic antagonist. This condition can cause complications during cataract surgery (Yeu and Grostern, 2007).

There is some concern that saw palmetto might cause liver or pancreas problems in some people. There have been two reports of liver damage and one report of pancreas damage in people who took saw palmetto. However, there is not enough information to know if saw palmetto was the actual cause of these side effects.

Saw palmetto is possibly safe when administered into the rectum appropriately for up to 30 days. However, it is not known if it is safe to use for longer periods of time.

## Side-effects

Saw palmetto is generally thought to be safe when used as directed. Side effects are very rare, although -

- **headache**,
- **nausea**,
- **diarrhoea**, and
- **dizziness** have been reported (unknown, 2014l).

Saw palmetto is likely safe for most people. Side effects are usually mild. Some people have reported -

- **dizziness**,
- **headache**,
- **nausea**,
- **vomiting**,
- **constipation**, and
- **diarrhoea**.

Some people have reported that saw palmetto causes impotence. However, these side effects do not seem to occur any more often with saw palmetto than with a sugar pill.

Saw palmetto appears to be well tolerated by most users. It may cause mild side effects, including stomach discomfort (NIH, 2012b).

## Pregnancy/Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking; however, anti-androgenic activity suggests that saw palmetto should not be used in pregnancy.

Saw palmetto is likely unsafe when used during pregnancy or breast-feeding. It acts like a hormone, and this could be dangerous to the pregnancy. Don't use during pregnancy or breast-feeding.

## Interactions

Two men stabilised on warfarin experienced an increase in the international normalized ratio (INR) after taking an herbal combination containing cucurbita, saw palmetto, and vitamin E (Yue and Jansson, 2001). In both patients, the INR returned to previous values when the herbal product was discontinued. Although neither cucurbita nor saw palmetto can be ruled out as the cause of the increase in INR, it is more likely that vitamin E interfered with vitamin K-dependent clotting factors, adding to the anti-coagulant effects of warfarin.

- **Finasteride (Proscar)** - Because saw palmetto may work similarly to finasteride (Proscar), you should not use this herb in combination with finasteride, or other medications used to treat BPH, unless directed to by your doctor.
- **Antiplatelet and anticoagulant drugs (blood-thinners)** - Saw palmetto may affect the blood's ability to clot, and could interfere with blood-thinning drugs, including -
  - Warfarin (Coumadin),
  - Clopidogrel (Plavix),
  - Aspirin.

- **Oral contraceptives and hormone replacement therapy** - Saw palmetto may reduce the number of oestrogen and androgen receptors, and thus have hormone-like effects. It may make oral contraceptives less effective, raising the risk of unplanned pregnancy (unknown, 2014l).

## Are there interactions with medications?

### Moderate

Be cautious with this combination.

- **Birth control pills (Contraceptive drugs)** - Some birth control pills contain oestrogen. Saw palmetto might decrease the effects of oestrogen in the body. Taking saw palmetto along with birth control pills might decrease the effectiveness of birth control pills. If you take birth control pills along with saw palmetto, use an additional form of birth control such as a condom.
  Some birth control pills include ethinylestradiol and levonorgestrel (Triphasil), ethinylestradiol and norethindrone (Ortho-Novum 1/35, Ortho-Novum 7/7/7), and others.
- **Oestrogens** - Saw palmetto seems to decrease oestrogen levels in the body. Taking saw palmetto along with oestrogen pills might decrease the effectiveness of oestrogen pills.
  Some oestrogen pills include conjugated equine estrogens (Premarin), ethinylestradiol, estradiol, and others.
- **Medications that slow blood clotting (anti-coagulant / anti-platelet drugs)** - Saw palmetto might slow blood clotting. Taking saw palmetto along with medications that also slow clotting might increase the chances of bruising and bleeding.
  Some medications that slow blood clotting include aspirin, clopidogrel (Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.

## Are there interactions with herbs and supplements?

- **Herbs and supplements that might slow blood clotting** - Using saw palmetto with other herbs that can slow blood clotting might increase the risk of bleeding in some people. These other herbs include angelica, cloves, danshen, garlic, ginger, ginkgo, Panax ginseng, red clover, turmeric, vitamin E, willow, and others.

## Are there interactions with foods?

There are no known interactions with foods (medlineplus, 2015b).

## Available Forms

Saw palmetto can be purchased as dried berries, powdered capsules, tablets, liquid tinctures, and liposterolic extracts. The product label should indicate that contents are standardised and contain 85 to 95% fatty acids and sterols. Read labels carefully, and buy only from reputable companies (unknown, 2014l).

## Dosage

The crude saw palmetto berries are usually administered at a dosage of 1 to 2 g/day; however, lipophilic extracts standardised to 85% to 95% fatty acids in soft native extract or 25% fatty acids in a dry extract are more common. Brand-name products include Permixon, Prostaserene, Prostagutt, Remigeron, Quanterra Prostate, and LG 166/S. Typical dosages of standardised extracts range from 100 to 400 mg given twice daily for BPH to the most commonly used dosage in clinical trials of 160 mg twice daily or 320 mg daily (Casarosa, Cosci di Coscio, and Fratta, 1988), (Gutiérrez, Hidalgo, and Cantabrana, 1996), (Braeckman et al., 1997b), (Gerber et al., 1998), (Marks, Partin, and Epstein, 2000).

The following doses have been studied in scientific research -

- **For benign prostatic hyperplasia (BPH)** - 160 mg twice daily or 320 mg once daily.
- **For the treatment of bald spots** - 200 mg twice daily combined with beta-sitosterol 50 mg twice daily (medlineplus, 2015b).

### Paediatric

Saw palmetto is not recommended for children.

### Adult

- **Liposterolic extract in capsules** - One studied dosage for early stages of BPH is 160 mg, twice a day. The supplement should be a fat soluble saw palmetto extract that contains 85 to 95% fatty acids and sterols.
- **Liquid extract** - This preparation has not been tested in any studies, so its effectiveness is not known.
- **Tea** - Saw palmetto can be taken as a tea. But its active ingredients (fatty acids) are not soluble in water. So tea may not be effective. It has not been tested in any studies. Capsules are recommended instead of tea.

It may take up to 8 weeks to see beneficial effects (unknown, 2014l).

- **Whole berries** - 1–2 g orally daily,
- **Lipophilic extract** - 320 mgs a day orally four times a day OR 160 mg orally twice a day,

- **Standardised extracts** - 100–400 mgs orally twice a day (medscape, 2015l).

## Precautions

In at least one case, significant bleeding during surgery was attributed to saw palmetto. There have been two reports of liver damage and one report of pancreas damage in people who took saw palmetto. But there is not enough information to know if saw palmetto was the cause of these effects.

Do not self treat for BPH with saw palmetto. See your doctor for a proper diagnosis to rule out prostate cancer.

Saw palmetto may have effects similar to some hormones, and should not be used in pregnant or nursing women, or women who have had or are at risk for hormone-related cancers.

Saw palmetto may interfere with the absorption of iron (unknown, 2014l).

## Warning

Before taking saw palmetto, tell your doctor if you -

- are pregnant or breastfeeding,
- have a hormone-sensitive cancer, like breast or prostate cancer,
- are using hormone-related drugs such as testosterone and oestrogen replacements,
- are using Warfarin (Coumadin(R)) (herbwisdom, 2015p).

It has been found that Saw Palmetto (even in concentrated extract form) is completely ineffective as an anti-androgen. Saw Palmetto may have an anti-oestrogenic effect. If you're trying to ADD oestrogen to your body, and the rumour that is can be an anti-oestrogen is true, Saw Palmetto can work against that goal. It tends to be marketed as a hair-loss blocker and an alternative to pharmaceuticals such as Propecia, Rogaine, etc (unknown, 2013b).

### Surgery

Saw palmetto might slow blood clotting. There is some concern that it might cause extra bleeding during and after surgery. Stop using saw palmetto at least 2 weeks before a scheduled surgery.

## Toxicology

Research reveals little or no information regarding toxicology with the use of saw palmetto.

## Commentary

*There is no evidence to show the usage of Saw Palmetto as a herbal hormone, so I would suggest saving your money. It has a reputed anti-oestrogenic effect but I have seen no evidence of this, and it is completely ineffective as an anti-androgen.*

# Soy

## Common names

Soybean, soya,Chinese = da dou, French = soia and soja, German = Sojabohne, Hindi = bhat, Hindi = bhatwar, Japanese = daizu, Korean = kong, Russian = soja, Spanish = frijol de soya and also soya, Swedish = sojaböna, Vietnamese = dâu nành and also dâu tuog, Phillipines = balatong, Indonesian = katjang bulu and also katjang jepun and kedelai.

## Latin name

*Glycine max*

## Overview

Soy, a plant in the pea family, has been common in Asian diets for thousands of years. It is found in modern American diets as a food or food additive. Soybeans, the high-protein seeds of the soy plant, contain isoflavones-compounds similar to the female hormone oestrogen. Traditional or folk uses of soy products include menopausal symptoms, osteoporosis, memory problems, high blood pressure, high cholesterol levels, breast cancer, and prostate cancer.

Soy is available in dietary supplements, in forms such as tablets and capsules. Soy supplements may contain isoflavones or soy protein or both. Soybeans can be cooked and eaten or used to make tofu, soy milk, and other foods. Also, soy is sometimes used as an additive in various processed foods, including baked goods, cheese, and pasta (herbsataglance, 2012).

For more than five thousand years China has been using soybeans as an additional nitrogen supplement for soil during crop rotation. Found in many East Asian and Hawaiian dishes, green baby soybeans are commonly known as edamame (Japanese for twig bean) or as maodou (Chinese for hairy bean).

Brought to America in the 1930s, soybeans have proved to be useful in a variety of ways. Soy products are derived from soybeans that are labeled as field or vegetable types. Also classified as oil, field types are generally grown to produce soy oil. High in Omega fatty acids, soy is also used in

feed for livestock and fowl. Vegetable soybeans known as garden types are higher in protein than field types and are used to produce soy milk, tofu, and other soy based food products. It is important to cook the beans before use - they cannot be eaten raw.

Soy is used to make a wide range of vegan and vegetarian products like soy vegetable oil, soy milk, soy lecithin, and tofu. Miso, soy sauce, and tempeh, are some fermented food products made from soy. Textured vegetable protein is made from fat free soy flour that can be used as a meat substitute to make high protein, fat free meals.

Processed soy is used in various dairy-free products such as ice cream, cheese, yogurt, milk, cream cheese, and margarine. Although they are high in protein, soy-based dairy products do not contain large amounts of calcium. To manufacture products like sprouted soybeans, tofu, soy concentrate, or soy protein isolates, dissoluble soy carbohydrates are broken down as the whey ferments.

For babies who may be allergic to the proteins in pasteurized cow's milk, or for vegetarian and vegan families, soy companies offer soy based infant formulas that the FDA have concluded as safe to use for sole or supplemental nutrition. Soy based infant formulas should not be used if there is an indication of food allergies.

The United States FDA declares that supplemental vitamin products must have a source of full protein. Full, or complete protein contains adequate amounts of essential amino acids that is required by the human body. Soy products offer complete protein for those who would like to replace or reduce their consumption of meat. Animal based food products are high in protein, but are also very high in saturated fat. Soy products offer high protein with no fat.

Since 1990, protein quality has been measured by The Protein Digestibility Corrected Amino Acid Score (PDCAAS). Their primary focus is the evaluation of protein quality according to human amino acid requirements, and how well they can be digested. According to score criteria, soy protein products are nutritionally equivalent to eggs and meat, and includes casein, which promotes health and human growth.

Concentrated soy protein absorbs nearly all of the fibre from the initial soybean. Soy's high protein content makes it an extensively used ingredient for manufactured cereals and baked goods, and for protein powders and beverage drinks.

Not only high in protein, soy-based products offer other healthy benefits such as Omega-3 fatty acids that contribute to numerous body actions, and isoflavones that are considered useful in the prevention of prostate, uterine and breast cancer. There is still some medical doubt regarding isoflavones ability to prevent any type of cancer (herbwisdom, 2015q).

Over the past 2 decades, soy foods have been the subject of a vast amount of research, primarily because they are uniquely rich sources of isoflavones. Isoflavones are classified as both phytoestrogens and selective oestrogen receptor modulators. The phytoestrogenic effects of isoflavones have led some to view soy foods and isoflavone supplements as alternatives to conventional hormone therapy. However, clinical research shows that isoflavones and oestrogen exert differing effects on a variety of health outcomes. Nevertheless, there is substantial evidence that soy foods have the potential to address several conditions and diseases associated with the menopausal transition. For example, data suggest that soy foods can potentially reduce ischaemic heart disease through multiple mechanisms. Soy protein directly lowers blood low-density lipoprotein-cholesterol concentrations, and the soybean is low in saturated fat and a source of both essential fatty acids, the omega-6 fatty acid linoleic acid and the omega-3 fatty acid alpha-linolenic acid. In addition, soflavones improve endothelial function and possibly slow the progression of subclinical atherosclerosis. Isoflavone supplements also consistently alleviate menopausal hot flushes provided they contain sufficient amounts of the predominant soybean isoflavone genistein. In contrast, the evidence that isoflavones reduce bone loss in postmenopausal women is unimpressive. Whether adult soy food intake reduces breast cancer risk is unclear. Considerable evidence suggests that for soy to reduce risk, consumption during childhood and/or adolescence is required. Although concerns have been raised that soy food consumption may be harmful to breast cancer patients, an analysis in 9514 breast cancer survivors who were followed for 7.4 years found that higher postdiagnosis soy intake was associated with a significant 25% reduction in tumour recurrence. In summary, the clinical and epidemiologic data indicate that adding soy foods to the diet can contribute to the health of postmenopausal women (M. Messina, 2014).

## Botany

Legumes such as soy are able to fix free nitrogen from the air into a useable form for growth via the bacterium Rhizobium japonicum, which is associated with the roots. Soybean is an annual plant that grows 0.3 to 1.5 m in height. The bean pods, stems, and leaves are covered with short, fine hairs and the pods contain up to 4 oval, yellow to brown seeds. Cotyledons (seed leaf) account for most of a seed's weight and contain nearly all of the oil and protein (Ensminger et al., 1994), (NRCS, 2011).

## History

In 2838 BC, Chinese emperor Shung Nang described soybeans as China's most important crop. The plant was introduced to Japan, Europe, and eventually to the United States by the early 1800s. The United States now produces 49% of the world's soybeans. Soy foods have become increasingly popular among health-conscious individuals since the early 1990s. In 2000,

approximately 27% of US consumers reported using soy products at least once a week, nearly double the 1998 figure. As a food source, soy has been used in Asian cultures for thousands of years, with Asian populations consuming 60 to 90 g/day of soy, compared with Western diets that contain approximately one-tenth of that amount. Soybean products are numerous and include milk, flour, curd, sufu, tofu, tempeh (Indonesian ingredient), miso (fermented soybean paste), sprouts, soy sauce, soybean oil, textured soy proteins (in meat extenders), soy protein drinks, and livestock feeds. Because of its low cost, good nutritional value, and versatility, soy protein is used as part of food programs in less developed countries (Ensminger et al., 1994), (Polunin, 1997), (S. Craig, Haigh, and Harrar, 1997), (M. J. Messina and Loprinzi, 2001).

## Chemistry

Soybeans are high in nutritional value and contain up to 35% oil, 24% carbohydrate, and 50% protein (Ensminger et al., 1994). Isolation of certain proteins and the determination methods used often characterise soybeans and their products (Garcia et al., 1997). Fatty acids in beans include linoleic (55%), palmitic (9%), and stearic (6%) acids. Soybeans are rich in minerals and trace elements, including calcium, iron, potassium, amino acids, and vitamins, and are a good fibre source (Ensminger et al., 1994), (Polunin, 1997). Soybeans contain isoflavone compounds known as phytoestrogens. The plant's isoflavones include genistein and daidzein, the most abundant, as well as glycitein and equol (M. J. Messina and Loprinzi, 2001), with soy protein preparations varying widely depending on the processing technique (Garcia et al., 1997). Isoflavones remain in soy preparations that are not extracted with alcohol. The dehulling, flaking, and defatting of soybeans produces a relatively pure preparation that is low in isoflavones. Isoflavone concentrations range from approximately 2 mg/g of protein in textured soy protein, soy flour, and soy granules to 0.6 to 1 mg/g protein in isolated soy protein (Sacks et al., 2006).

Lecithinum ex soja, lecithin from soybean, extracted from Glycine max, enriched extract with 73%–79% 3-sn-phosphatidylcholine.

The extract also includes -

- Phosphatidylethanolamine maximum 7%,
- Phosphatidylinositic acid <0.5%,
- Oil 2%–6%,
- Vitamin E 0.2%–0.5%.

The given range includes both production and analytical variances.

## Pharmacology

Isoflavones, the phytoestrogens in soybean, have weak functional effects similar to those of the female hormone estradiol, including hormonal and nonhormonal actions (M. J. Messina and Loprinzi, 2001). Hydrolysis of isoflavone glycosides by intestinal glucosidases yields genistein, daidzein, and glycitein, which undergo further metabolism to equol and p-ethyl phenol. This metabolism is highly variable and may depend, for example, on the effect of carbohydrate intake on intestinal fermentation. Isoflavones are secreted into bile via the enterohepatic circulation. Plasma half-life of genistein and daidzein is approximately 8 hours, with peak concentration achieved in 6 to 8 hours in adults. Elimination is in urine, primarily as glucuronide conjugates (Barnes et al., 1998).

Soy Isoflavones, usually Genistein and Daidzein, are bioflavonoids found in soy products and other plants that are able to interact with various hormones such as oestrogen (herbwisdom, 2015q).

## Uses

Soy is commonly used as a source of fibre, protein, and minerals. A number of meta-analyses are now available; however, evidence is lacking to support a definitive place in therapy for menopausal symptoms, osteoporosis, diabetes, or heart disease. Epidemiologic data suggest an association with a lower incidence of certain cancers with higher intake of dietary soy.

Menopausal vasomotor symptoms, osteoporosis, decrease risk of breast cancer, cardiovascular disease (medscape, 2015m).

Soy is rich in isoflavones, which are the most active phytoestrogens in the human diet. These may help to relieve menopausal symptoms. After the menopause, the level of oestrogen in a woman's body falls and it is thought that phytoestrogens may provide a substitute for the body's own oestrogen, relieving symptoms such as hot flushes and dry skin. The interest in phytoestrogens has developed because of the evidence that women in Japan and Asia who consume diets rich in these compounds, do not appear to suffer the same way with hot flushes and sweats as in the western world. In these countries, the diet is rich in soya containing foods, and menopausal symptoms are reported much less. Amongst the main phytoestrogens in the human diet are the isoflavones, which are found primarily in legume type plants such as soya.

Phytoestrogens can be consumed by purely increasing dietary intake, but this involves eating large amounts of legume food plants, such as peas and beans, with variable phytoestrogen content. Supplements of Soya Isoflavones are a convenient alternative.

Cholesterol reduction is another healthful advantage that comes with soy protein and soy based foods. Diets high in cholesterol and saturated fats are primary targets for heart disease. Fat free textured vegetable protein and processed soy products contain no added cholesterol or saturated fat (herbwisdom, 2015q).

Less severe forms of hypercholesterolemia in which diet and other non-medical interventions (e.g., exercise program, weight control) have not shown results.

Improvement of subjective complaints, such as loss of appetite and feeling of pressure in region of liver in toxic/nutritional liver disease and chronic hepatitis. Prerequisite to the therapy of chronic liver disease is the recognition and avoidance of noxious agents - in the case of alcoholic liver disease, alcohol abstinence. In chronic hepatitis adjuvant therapy with phospholipids of soybeans is only indicated when improvement of symptoms is discernible from other therapy (herbalgram, 1994).

## Pharmakinetics

Lecithin extract from soybeans consists on the average of 76% phosphatidylcholine and almost entirely of phosphoglycerides, of which the fatty acid linoleic acid predominates. The quota of phospholipids, which are the chief constituents of cell membrane, are in major part obtained by eating (0.5–3 g/day from food) and in lesser degree from synthesis by the liver.

A deficiency in phospholipids is the inevitable result of chronic parenteric nutrition.

Under pharmacodynamic characteristics are "hepatoprotective" effects in numerous experimental models, e.g., protection against ethanol, alkyl alcohols, tetrachlorides, paracetamol and galactosamine. Furthermore, in chronic models (ethanol, thioacetamide, organic solvents), there appears a defense against steatosis and fibrosis of the liver. The compound works by speeding regeneration and stabilisation of membranes, stopping lipid peroxidation and, it is assumed, by collagen synthesis.

The pharmacokinetics of orally administered lecithin have been examined in animal studies in which the phosphatidylcholine was radioactively marked, the marking on a fatty acid in position 1 or position 2, choline, or a phosphorous. The respective marker substitutions show the pharmacokinetics. Phospholipids are degraded to lyso-phosphatidylcholine in the intestine and absorbed primarily in this form. In the gut wall phospholipids are in part re-synthesised, then circulated through the lymphatic system. In part the re-synthesised phosphatidylcholine is processed in the liver to form fatty acids, choline, and glycerine-3-phosphate. In plasma, phosphatidylcholine and other phosphoglycerides are tightly bound to lipoproteins and/or albumin.

Phosphatidylcholine and other phosphoglycerides are degraded chiefly through a series of so-called phospholipases to fatty acids, choline and "glycerin" metabolites to be in turn re-synthesised in the liver and other organs. The administered metabolites in large part may be integrated within a few hours into body phospholipids. Their removal corresponds to the excretion of phospholipids and their corresponding metabolites (herbalgram, 1994).

## Breast Cancer

### Animal data

Isoflavones are selective oestrogen receptor modulators, but also possess nonhormonal properties. The weak oestrogenic action of soy isoflavones and other phytoestrogens suggest that they could lessen the deleterious effects of more potent endogenous oestrogens on breast and endometrial cancer.

In 1990 and 2005, The National Cancer Institute held workshops following reports of decreased chemically induced rat mammary cancer after the addition of soy protein to a typical diet and recommended that the impact of isoflavones on breast tissue should be evaluated at the cellular level in high-risk women (M. Messina, McCaskill-Stevens, and Lampe, 2006).

### Clinical data

Reviews of cohort and case-control studies evaluating the risk of breast cancer incidence and a meta-analysis of prospective studies on the risk of breast cancer recurrence are available (Enderlin et al., 2009), (J. Y. Dong and Qin, 2011). Overall, the data are not persuasive that adult consumption of soy affects the risk of developing breast cancer or that soy consumption affects the survival of breast cancer patients. Summary relative risk (RR) for the association of soy isoflavone consumption and incidence of breast cancer were 0.89 (95% confidence interval [CI], 0.79 to 0.99) in 1 meta-analysis of 14 prospective studies; however, when the data were evaluated by ethnicity, a protective effect was only found for Asian populations (J. Y. Dong and Qin, 2011). Data for risk of breast cancer recurrence from 4 studies yielded similar results (summary RR = 0.84 [95% CI, 0.7 to 0.99]. Another modifier may be menopausal status because no association was evident in premenopausal women. No dose-response relationship was revealed (J. Y. Dong and Qin, 2011).

However, it should be noted that data also exist of increased breast cancer risk and it is possible that isoflavones in soy may actually stimulate breast tumour growth through their oestrogenic activity (Enderlin et al., 2009), (Lemos, 2001), (Bolca, Urpi-Sarda, and Blondeel, 2010). There was a modest

increase in breast tissue density among premenopausal women but not in postmenopausal women in a meta-analysis of 8 clinical trials of isoflavone supplementation. The clinical importance of this finding is unclear (Hooper, Madhavan, et al., 2010).

## Prostate Cancer

Soy isoflavones have oestrogenic, anti-androgenic, and other activities that could prevent prostate cancer or slow its progression (M. J. Messina, 2003). Prostate cancer incidence appears to decrease with increased isoflavone intake (Sirtori, 2001).

### Animal data

Rats fed soy-protein diets showed a reduced incidence of prostate tumours compared with rats fed casein. Tumour latency was increased only in the rats fed a diet containing isoflavone-rich, isolated soy protein (Sirtori, 2001). In prostate cancer cells, genistein reduced the synthesis of PSA, a marker of prostate cancer development and progression (Sarkar and Y. Li, 2003). Genistein inhibits the growth of androgen-dependent and androgen-independent prostate cancer cells in-vitro in a dose-dependent manner (Yan and Spitznagel, 2009).

### Clinical data

Meta-analyses of observational studies of soy consumption and risk of prostate cancer have been published (Yan and Spitznagel, 2009), (Y. W. Hwang et al., 2009). An inverse association has been observed for soy consumption and risk of prostate cancer (RR/odds ratio [OR] = 0.7 [95% CI, 0.63 to 0.89] (Yan and Spitznagel, 2009). Available data suggest benefits may be limited to nonfermented soy products and Asian populations (Yan and Spitznagel, 2009), (Y. W. Hwang et al., 2009). Randomised clinical trials have been conducted. In a pilot study, soy isoflavones reduced adverse urinary, intestinal, and sexual effects of radiation in men with prostate cancer (I. U. Ahmad, Forman, and Sarkar, 2010). A 12-week study of 20 g daily soy protein supplementation (isoflavone 160 mg) found no effect on any of the outcomes measured (cognition, sleep quality, vasomotor symptoms, or quality of life) (P. Sharma, Wisniewski, and Braga-Basaria, 2009). Another trial showed no effect on PSA levels after 6 months of genistein 450 mg and daidzein 300 mg despite an increase in serum isoflavone levels (White et al., 2010).

## Other Cancers

### Animal data

Inhibition of early cancer markers in human epithelial cells has been demonstrated by genistein (Katdare, Osborne, and Telang, 1998). Another report found genistein to slow growth of implanted tumours in mice and in-vitro (Record et al., 1997). These anticancer effects of genistein may be related to its ability to reduce expression of stress response-related genes. Induction of stress proteins in tumour cells protects them against cell death, so inhibition of this stress response by the isoflavone is beneficial (Y. Zhou and A. S. Lee, 1998).

### Clinical data

Meta-analyses of endometrial, ovarian, gastric, and colorectal cancer have been published. A protective effect was reported for high soy intake over low intake in a meta-analysis of 7 case-control and cohort studies in endometrial and ovarian cancer (OR = 0.61 [95% CI 0.53 to 0.72] (Sirtori, 2001), (Myung et al., 2009). However, there was no association between risk of ovarian cancer and soy phytoestrogen consumption in the Women's Lifestyle and Health Cohort study (Hedelin et al., 2011). Among Japanese and Korean populations, a meta-analysis showed a significant increase in risk of gastric cancer, with high intake of fermented soy products (OR = 1.22 [95% CI, 1.02 to 1.44]) and a significant decrease in risk of gastric cancer with high intake of nonfermented products (OR = 0.64 [95% CI, 0.54 to 0.77]) (J. Kim et al., 2011). A meta-analysis of studies evaluating the protective effect of soy against colorectal cancer established no association, except when a subgroup analysis was conducted by gender, revealing a decreased risk in women (Yan, Spitznagel, and Bosland, 2010).

## Cardiovascular disease

### Animal data

Soy isoflavones exhibit strong biological properties in animals, causing arterial vasodilation, the lowering of serum cholesterol, and the inhibition of atherosclerosis in postmenopausal monkeys (Anthony, Clarkson, and J. K. Williams, 1998), (Clarkson, Anthony, and T. M. Morgan, 2001). However, beneficial effects observed in animal models have not translated well to studies in humans. The widespread availability of clinical trial data now make data from animal studies largely irrelevant (Sacks et al., 2006).

## Clinical data

Soy protein has gained considerable attention for its potential role in improving risk factors for cardiovascular disease (Sacks et al., 2006). However, based on a review of the evidence, the American Heart Association (Sacks et al., 2006) and an expert panel from the American College of Cardiology (J. H. Vogel, Bolling, and Costello, 2005) found that the evidence for clinical benefit of soy in reducing the risk of cardiovascular disease is uncertain and cannot be routinely recommended. Delineation of the efficacy of isoflavone content in soy preparations or the relevance of baseline lipid profiles have not been established with any certainty, nor has a dose-response relationship been determined (Sacks et al., 2006), (J. H. Vogel, Bolling, and Costello, 2005).

Several meta-analyses of clinical trials conducted up to 2009 have been published. Findings are generally consistent with regard to small decreases in LDL cholesterol. However, influences on total cholesterol, triglycerides, and HDL cholesterol, as well as on lipoprotein(a) and blood pressure are inconsistent (Sacks et al., 2006), (Taku, Umegaki, et al., 2007), (Harland and Haffner, 2008), (Reynolds et al., 2006), (Hooper, Kroon, and Rimm, 2008), (Taku, N. Lin, and Cai, 2010). Clinical trials conducted subsequent to the meta-analyses likewise have found equivocal results (Maki, Butteiger, and Rains, 2010), (A. S. Santo, A. M. Santo, and Browne, 2010), (Beavers et al., 2010), (S. C. Campbell et al., 2010).

# Diabetes

## Animal data

Encouraging data from rats fed a high soy-isoflavone diet that revealed improved insulin secretion and better glycaemic control have led to studies in humans (Ricci et al., 2010), (Z. M. Liu, Y. M. Chen, and S. C. Ho, 2011). The widespread availability of clinical trial data has made data from animal studies largely irrelevant.

## Clinical data

Meta-analyses have been conducted on the effects of soy isoflavone supplementation, genistein, and high soy-isoflavone diets on markers of diabetes. A meta-analysis of 10 trials in non-Asian perimenopausal and postmenopausal women found no effect of soy isoflavones on fasting blood glucose (Ricci et al., 2010). Another analysis, which included Asian populations, also found no changes in measures of glycaemic control in general, but suggested in a subgroup analysis that whole soy foods might be favourable for reducing fasting glucose parameters (Z. M. Liu, Y. M. Chen, and S. C. Ho, 2011). Among Chinese postmenopausal women with early diabetes a mild, positive effect on body weight and body mass index was

reported in a randomised trial with soy protein with isoflavones over 6 months (Z. M. Liu, Y. M. Chen, S. C. Ho, et al., 2010). Decreased abdominal fat and overall fat was observed in a randomised clinical trial among white and black postmenopausal obese women with soy supplementation. No effect on glucose metabolism was found (D. R. Christie et al., 2010).

## Food allergy/intolerance in infants

### Animal data

Research reveals no animal data for food allergy/intolerance in infants.

### Clinical data

Allergy to cow's milk affects approximately 2.5% of children. The allergy is characterised by a specific immunoglobulin E (IgE) response. In clinical practice, alternate protein sources from vegetables (eg, soy) are substituted for cow's milk (Muraro, 2001). Food intolerance does not imply a specific mechanism but is a reproducible adverse reaction to a specific food. Cow-milk protein intolerance is most common in infants. It has been suggested that exposure to cow's milk early in life may predispose an infant to increased risk of allergy and intolerance. There is insufficient evidence to suggest that substitution with soy milk can prevent the development of atopy (hereditary hypersensitivity) or food intolerance. Many infants with food intolerance become tolerant over time, with the risk of persistent intolerance increasing with evidence of atopy (Osborn and Sinn, 2006).

## Menopausal symptoms

Because of their weak oestrogenic activity, soy isoflavones have been hypothesised to improve several oestrogen-dependent conditions, including perimenopausal vasomotor symptoms (eg, hot flashes) and postmenopausal bone loss. Interest in the use of soy and its derivatives for the treatment of menopausal symptoms has been encouraged by observations of a lower prevalence of menopausal complaints, especially hot flashes, among women in Asian countries where soy is an important component of the traditional diet (A. E. Lethaby et al., 2007).

### Animal data

The widespread availability of clinical trial data has made data from animal studies largely irrelevant.

## Clinical data

Reviews and meta-analyses of clinical trials evaluating the efficacy of soy products and phytoestrogens in managing the symptoms of menopause are available and include a Cochrane meta-analysis (A. E. Lethaby et al., 2007), (Kronenberg and Fugh-Berman, 2002a), (Krebs et al., 2004). Problems of heterogeneity of included study populations, treatment regimens, and outcomes measures exist, as well as of trial methodology. A placebo effect is acknowledged, making adequate blinding and randomisation[343] vital to the results in these studies (A. E. Lethaby et al., 2007).

Findings from the included studies provide conflicting data. Subgroup analyses in 1 meta-analysis suggest weak evidence to support the use of soy concentrates (genistein or daidzein) or soy extracts, but not dietary supplementation with soy, in the management of menopausal vasomotor symptoms (Bolaños, Del Castillo, and Francia, 2010), while the Cochrane meta-analysis found no evidence for effect (A. E. Lethaby et al., 2007). Another analysis evaluated the effect of soy protein and isoflavones on circulating hormones in pre- and postmenopausal women. No effect on hormones (estradiol, estrone, sex hormone-binding protein, FSH and LH was reported in postmenopausal populations, and only a modest effect was found on FSH and LH in premenopausal women (Hooper, Ryder, and Kurzer, 2009). A small randomised clinical trial published subsequent to the meta-analyses evaluated the effect of dietary soy, HRT, and placebo on menopausal symptoms and revealed a reduction in the severity of hot flashes, bone/joint pain, and vaginal dryness for soy and hormone therapy (Carmignani et al., 2010). The outcomes of the 2-year SPARE (Soy Phytoestrogens As Replacement Oestrogen) study evaluating the effect of soy isoflavones as replacement oestrogen in menopausal women are awaited (Levis et al., 2010).

# Osteoporosis

## Animal data

The effect of soy protein with and without isoflavones has been studied in a number of animal models with conflicting results (Gallo, Zannoni, and Apollonio, 2005), (Breitman, Fonseca, and W. E. Ward, 2005), (Nakai, Cook, and Pyter, 2005), (Register, Jayo, and Anthony, 2003). The widespread availability of clinical trial data now make data from animal studies largely irrelevant.

[343] Method analogous to tossing a coin to assign patients to treatment groups (the experimental treatment is assigned if the coin lands heads and a conventional, control or placebo treatment is given if the coin lands tails). Usually done by using a computer that generates a list of random numbers, which can then be used to generate a treatment allocation list

## Clinical data

Several meta-analyses have been conducted on clinical trials evaluating the efficacy of soy preparations in protecting against decreases in BMD, and include trials up to 2008 (D. F. Ma et al., 2008a), (D. F. Ma et al., 2008b), (J. Liu, S. C. Ho, et al., 2009), (Taku, Melby, et al., 2010), (Darling et al., 2009). Heterogeneity is present among the included trials and the influence of ethnicity, basal BMD, and duration of intervention have not been determined. Data from the meta-analyses are conflicting, with some reporting small improvements in bone density (D. F. Ma et al., 2008a), (D. F. Ma et al., 2008b), (Darling et al., 2009) and others reporting no effect (J. Liu, S. C. Ho, et al., 2009), (Taku, Melby, et al., 2010). Data from long-term clinical trials have been published subsequent to the meta-analyses, finding no treatment effect after 3 years of supplementation (SIRBL [Soy Isoflavones for Reducing Bone Loss] study) (Alekel, Van Loan, and Koehler, 2010), an increase in whole BMD after 2 years but no influence at common spine and hip fracture sites (W. W. Wong, R. D. Lewis, and Steinberg, 2009), and no effect after 3 years on biomarkers in general in healthy postmenopausal women (Shedd-Wise, Alekel, and Hofmann, 2011). Studies evaluating reductions in fracture rates in women with osteoporosis are lacking.

## Other effects

- **Gastrointestinal effects** - In 1 report, the use of fibre-supplemented soy formula reduced the duration of diarrhoea in 44 infants (Vanderhoof et al., 1997). Soy also has been investigated in studies for the treatment of infantile colic (Lucassen et al., 1998) and recurrent abdominal pain in childhood (Huertas-Ceballos, Macarthur, and Logan, 2002). However, there is no evidence to suggest soy has any beneficial effect in these conditions.
- **Osteoarthritis** - Avocado/soybean unsaponifiables consist of one-third avocado oil and two-thirds soybean oil. Preclinical studies showed this combination to have some antiosteoarthritis activity, possibly via effects on interleukin-1 and collagen synthesis. A meta-analysis of 4 clinical trials (664 patients; knee and hip osteoarthritis) suggests greater improvement in pain scores and functional indices, especially for osteoarthritis of the knee (R. Christensen et al., 2008). However results of avocado/soybean unsaponifiables relating to structure-modifying properties are yet to be confirmed by radiographic evidence through independent trials (R. Christensen et al., 2008), (Maheu, Mazières, and Valat, 1998), (Ernst, 2003).

## What the Science Says

- Research suggests that daily intake of soy protein may slightly lower levels of LDL cholesterol.

- Some studies suggest that soy isoflavone supplements may reduce hot flashes in women after menopause. However, the results have been inconsistent.
- There is not enough scientific evidence to determine whether soy supplements are effective for any other health uses (herbsataglance, 2012).

## How it works

Partial oestrogen receptor agonists; anti-oestrogenic effects in pre-menopausal women, but weak oestrogenic effects in postmenopausal women, may stimulate osteoblastic activity, increases sex hormone binding globulin (SHBG) levels; antioxidant activity (medscape, 2015m).

## Efficacy

Studies show reasonable efficacy for breast cancer, diabetes, osteoporosis prevention/treatment, hot flashes, cardiovascular disease risk, mixed results for cancer prevention (medscape, 2015m).

## Side Effects and Cautions

- Soy is considered safe for most people when used as a food or when taken for short periods as a dietary supplement.
- Minor stomach and bowel problems such as **nausea**, **bloating**, and **constipation** are possible.
- Allergic reactions such as **breathing problems** and **rash** can occur in rare cases.
- The safety of long-term use of soy isoflavones has not been established. Evidence is mixed on whether using isoflavone supplements over time can increase the risk of endometrial hyperplasia[344]. Studies show no effect of dietary soy on risk for endometrial hyperplasia.
- Soy's possible role in breast cancer risk is uncertain. Until more is known about soy's effect on oestrogen levels, women who have or who are at increased risk of developing breast cancer or other hormone-sensitive conditions (such as ovarian or uterine cancer) should be particularly careful about using soy and should discuss it with their health care providers (herbsataglance, 2012).

Soybeans and their products are generally well tolerated. A 2-year trial of 80 and 120 mg daily soy isoflavones reported no effect on all measured laboratory indices except a minimal increase in blood urea nitrogen at the 2-year mark (Steinberg, M. J. Murray, and R. D. Lewis, 2011).

[344] a thickening of the lining of the uterus that can lead to cancer

The effects of phytoestrogens in soy-based infant formulas and in commercial soy preparations have been of concern (Bluck and Bingham, 1997), (Huggett et al., 1997). However, a meta-analysis of 15 clinical studies showed no effect on testosterone or see sex-hormone-binding globulin (SHBG) levels (Hamilton-Reeves et al., 2010), and semen quality in healthy men was unaffected by 2 months of high-dose isoflavones in another clinical trial (Beaton et al., 2010).

A randomised clinical trial evaluated the effect of soy phytoestrogens in subclinical hypothyroidism over 8 weeks. Six participants in the study, receiving higher-dose phytoestrogen (16 mg daily), developed overt hypothyroidism, while secondary outcomes for the study populations were positive for decreased blood pressure and insulin resistance (Sathyapalan, Manuchehri, and Thatcher, 2011). Soy formula-fed infants may be at risk of thyroid dysfunction, although case reports are lacking, and the National Toxicology Program (US Department of Health and Human Services) has concluded that there is minimal concern for developmental effects in infants fed soy infant formula (Fitzpatrick, 2000), (Program, 2010).

Allergy, including asthma and anaphylaxis, has been reported. Soybeans and peanuts, as well as other beans, are phylogenetically and antigenetically similar. However, there are insufficient data to recommend soy avoidance in peanut-allergic patients (Codina et al., 1997), (Sicherer, Sampson, and Burks, 2000), (Inomata et al., 2005).

Occasional gastrointestinal effects, i.e., **stomach pain**, **loose stool**, and **diarrhoea** (herbalgram, 1994).

Less severe forms of hypercholesterolemia in which diet and other non-medical interventions (e.g., exercise program, weight control) have not shown results.

Improvement of subjective complaints, such as loss of appetite and feeling of pressure in region of liver in toxic/nutritional liver disease and chronic hepatitis. Prerequisite to the therapy of chronic liver disease is the recognition and avoidance of noxious agents - in the case of alcoholic liver disease, alcohol abstinence. In chronic hepatitis adjuvant therapy with phospholipids of soybeans is only indicated when improvement of symptoms is discernible from other therapy (herbalgram, 1994).

## Pregnancy/Lactation

Generally recognized as safe (GRAS) when used as food. Avoid dosages above those found in food because safety and efficacy are unproven.

## Interactions

A subtherapeutic international normalized ratio (INR) was reported in a 70-year-old man stabilised on warfarin after he started drinking soy milk (Cambria-Kiely, 2002). The INR returned to the therapeutic range when he stopped drinking soy milk.

## Cautions

With the many benefits offered, there are also some health risks associated with soy products. For those with food allergies, soy based foods can trigger allergic reactions such as **swelling** or **hives**. In extreme cases, allergic reactions to soy can be just as severe as the symptoms triggered by shellfish or peanut allergies.

Soy products such as tofu can be hard to digest, especially when trying it for the first time. Before incorporating soy products into your diet, or taking concentrated soy protein powders or supplements, discuss any health issues with your doctor (herbwisdom, 2015q).

## Dosage

One gram of soy protein in traditional soy foods contains approximately isoflavones 3.5 mg (aglycone weight) (Hamilton-Reeves et al., 2010).

A large number of clinical trials have been conducted for conditions (eg, menopause, osteoporosis, breast cancer, cardiovascular diseases) using daily doses of isoflavones from 40 to 120 mg (J. Y. Dong and Qin, 2011), (Taku, Umegaki, et al., 2007), (Hooper, Kroon, and Rimm, 2008), (Taku, N. Lin, and Cai, 2010), (A. E. Lethaby et al., 2007), (D. F. Ma et al., 2008a), (D. F. Ma et al., 2008b), (J. Liu, S. C. Ho, et al., 2009), (Taku, Melby, et al., 2010), (Darling et al., 2009). An avocado/soybean unsaponifiable fraction has been studied in osteoarthritis at 300 to 600 mg daily (R. Christensen et al., 2008), (Maheu, Mazières, and Valat, 1998), (Ernst, 2003).

### Daily dosage

- 1.5–2.7 g phospholipids from soybean with 73%–79% 3-sn-phosphatidylcholine in a single dose (herbalgram, 1994).

### Isoflavones

40 mg orally four times a day

- **Menopausal symptoms** - 34–120 mgs a day,
- **Hypertension** - 18 mg orally twice a day,
- **Lung cancer prevention** - 8.3–83.2 mcgs a day (medscape, 2015m).

### Ipriflavone

- 200 mgs orally three times a day [Creatinine clearance 40–80 mL/min],
- 200 mgs orally twice a day [Creatinine clearance <40 mL/min],
- 200 mgs orally four times a day (medscape, 2015m).

## Toxicology

Evidence exists from animal studies on the adverse effects of genistein on the developing female reproductive tract, including decreased age at vaginal opening; abnormal estrous cyclicity; decreased fertility, implants, and litter size; and histopathology of the female reproductive tract (Program, 2010).

Doses of phosphatidylcholine of up to 10 g/kg body weight in mice and rats and 4.5 g/kg body weight in rabbits given intravenously, intraperitoneally, and orally in a single dose are not toxic. The no-effect dosage[345] over 48 weeks administration to rats lies upward of 3750 mg/kg body weight per day. Repeated IV application over 12 weeks places the lowest systemic toxic dosage between 0.1 and 1 g/kg body weight and lowest local toxic dosage at over 1 g/kg body weight in rats, and application over 4 weeks to dogs places the lowest toxic dosage at more than 0.1 g/kg body weight in dogs.

Doses of up to 3750 mg/kg body weight in pregnant animals, animal embryos, and animal neonates showed no pathology of toxicity to reproduction. The lowest teratogenic or embryo-toxic dosage in rats in oral and IV was more than 1 g/kg bw. In rabbits teratogenic dosages were greater than 1 g/kg bw for oral administration and greater than 0.5 g/kg bw in IV. Various in-vitro tests cannot demonstrate any mutagenic potential. Carcinogenicity has not been tested (herbalgram, 1994).

## Commentary

*Although soy has a weak oestrogenic activity there is conflicting evidence whether it would be effective for menopausal symptoms. And because of varying carbohydrate intake in the diet the metabolism of soy isoflavones is highly variable. So, at the moment, I don't feel that soy has enough evidence to back it as to being a herbal hormone.*

[345] the amount of the drug that has no effect on the test animal over a specified period of time

Chapter 14

# W's

## Wild Yam

### Common Names

Wild yam root, colic root, yuma, devil's bones, rheumatism root, China root, Mexican wild yam, Aluka, Barbasco, Shan-yao, Papua New Guinea = boku, Vietnamese = cur tuwf tron, Indonesian = huwi upas, Philippines = pakit, Indian = rui-han, Philippines = ubing basol, Indonesian = uwi in tuwa.

### Scientific Names

Dioscorea villosa.

### Overview

In the 18th and 19th centuries, herbalists used wild yam to treat menstrual cramps and problems related to childbirth, as well as for upset stomach and coughs. In the 1950s, scientists discovered that the roots of wild yam – not to be confused with the sweet potato yam – contain diosgenin. Diosgenin is a phytoestrogen, or plant-based oestrogen, that can be chemically converted into a hormone called progesterone. Diosgenin was used to make the first birth control pills in the 1960s.

Although herbalists continue to use wild yam to treat menstrual cramps, nausea and morning sickness, inflammation, osteoporosis, menopausal symptoms, and other health conditions, there's no evidence to show it works for these uses. Several studies have found that it has no effect at all. That is because the body cannot change diosgenin into progesterone; it has to be done in a lab. Wild yam, by itself, does not contain progesterone.

Early Americans used wild yam to treat colic, a reason for another name for the plant, colic root. Traditionally, it has been used to treat inflammation, muscle spasms, and a range of disorders, including asthma. However, there is no scientific evidence that it works. Several studies show wild yam has powerful anti-fungal properties and may help fight yeast and other fungal infections (unknown, 2014m).

## Botany

D. villosa is a twining vine native to the central southeastern US and found less frequently in the Appalachian region. It is a dioecious plant with inconspicuous white to greenish-yellow female flowers and smooth, heart-shaped leaves. Plant synonyms include Dioscorea hirticaulis Bartlett and D. villosa L. var. hirticaulis (Bartlett) H.E. Ahles.

There are more than 500 species of Dioscorea worldwide, with Chinese yam (D. oppositifolia), water yam (Dioscorea alata L.), and wild yam commonly studied (USDA, 2008b).

Also known as colic root, wild yam is a twining, tuberous vine. One species is native to North America; another is native to China. Both contain diosgenin and have similar medicinal properties. There are an estimated 600 species of yam in the genus Dioscorea. Many of them are wild species that flourish in damp woodlands and thickets, and not all of them contain diosgenin. Wild yam is a perennial vine with pale brown, knotty, woody cylindrical rootstocks, or tubers. Unlike sweet potato yams, the roots are not fleshy. Instead they are dry, narrow, and crooked, and bear horizontal branches of long creeping runners. The thin, reddish-brown stems grow to a length of over 30 feet. The roots initially taste starchy, but soon after taste bitter and acrid.

The wild yam plant has clusters of small, greenish-white and greenish-yellow flowers. The heart-shaped leaves are long and broad and long-stemmed. The upper surface of the leaves is smooth while the underside is downy (unknown, 2014m).

## History

Wild yam was popularized by the Eclectic medical movement in the 19th century for its supposed anti-spasmodic properties and was therefore prescribed for biliary colic and spasm of the bowel. It was also promoted for the relief of nausea in pregnancy and for amenorrhoea and dysmenorrhoea. Wild yam has been used for UTIs, rheumatoid arthritis, cholera, nervous excitement, and flatulence (F. Brinker, 1996), (Kong, Y. Z. Zhang, and X. Wu, 2009).

## Properties

Anti-inflammatory, anti-spasmodic, blood purifier, and diaphoretic, hepatic, anti-rheumatic, cholagogue, uterine tonic (herbwisdom, 2015r).

## Indicated for

Relaxing muscles, soothing nerves and relieving pain. Uterine tonic. Menstrual cramps. Allaying colic and flatulence caused by muscle spasms; for poor circulation and neuralgia; for the inflammatory stage of rheumatoid arthritis; and for abdominal and intestinal cramping. Wild Yam can be very beneficial for nervousness, restlessness and other nervous conditions. As a stimulant for increased bile flow, it helps to relieve hepatic congestion, bilious colic, gallstones, kidney and gallbladder problems and rheumatic conditions (herbwisdom, 2015r).

Wild Yam is a very good anti-spasmodic so is good for menstrual cramps, relaxing muscles, soothing nerves, relieving pain, poor circulation and neuralgia, for the inflammatory stage of rheumatoid arthritis and for abdominal and intestinal cramping.

It has long been used for its benefits in women's reproductive health, including premenstrual syndrome and menopausal problems. It can be taken in capsules or in tea (though there are mixed opinions on the flavour). The powder can be added to creams or vaginal ointments.

Wild Yam's traditional use is for easing menstrual cramps. Its anti-spasmodic property is beneficial for any kind of muscular spasm and colic, such as intestinal and bilious colic, flatulence, ovarian and uterine pain; for poor circulation and neuralgia; for the inflammatory stage of rheumatoid arthritis; and for abdominal and intestinal cramping. Wild Yam can be very beneficial for nervousness, restlessness and other nervous conditions.

As a stimulant for increased bile flow, it can help to relieve hepatic congestion, bilious colic and gallstones.

Also known to have a therapeutic action on overall liver health, it is believed that wild yam root's ability to lower blood cholesterol levels and lower blood pressure indirectly helps the liver by increasing its efficiency and reducing stress.

Its steroidal saponins are also anti-inflammatory, making it a useful herb when treating rheumatoid arthritis and inflammatory conditions of the bowel. Its diuretic effect, combined with the anti-spasmodic action, soothes painful conditions of the urinary tract (herbwisdom, 2015r).

## Chemistry

Extracts of D. villosa contain steroidal saponins, diosgenin, alkaloids, tannins, phytosterols, and starch (unknown, 2004b).

Oestrogenic compounds have been reported for D. alata (W. Y. Cheng, Kuo, and C. J. Huang, 2007).

Analytical techniques for the identification of constituents have been described (unknown, 2004b).

Wild yam contains alkaloids, steroidal saponins, tannins, phytosterols and starch (herbwisdom, 2015r).

The dried root, or rhizome, is used in commercial preparations. It contains diosgenin, a phytoestrogen that can be chemically converted to the hormone progesterone. However, diosgenin on its own does not seem to act like oestrogen in the body (unknown, 2014m).

## Uses and Pharmacology

Much of the current herbal use of wild yam is predicated on the misconception that the diosgenin contained in the product can be converted by the human body into steroid hormones, particularly progesterone, through the intermediate dehydroepiandrosterone. This notion appears to be based on historical interest in diosgenin as a synthetic precursor of cortisone (Ulbricht, Basch, and Ulbricht, 2003). However, evidence suggesting that diosgenin or dioscin can be converted into human hormones is lacking (Komesaroff et al., 2001).

Clinical trials are generally lacking for topical formulations of Dioscorea for menopausal symptoms.

Women with hormone-dependent conditions such as endometriosis, uterine fibroids, and cancers of the breast, ovaries, or uterus should not take or use wild yam due to its possible oestrogenic effects. Men with prostate cancer should also avoid taking wild yam (herbwisdom, 2015r).

## Gastro-Intestinal

Chinese yam polysaccharides have been evaluated in laboratory studies for potential as prebiotics, with varying results (Kong, Y. Z. Zhang, and X. Wu, 2009), (Iwata, Hotta, and Goto, 2009). However, clinical studies are lacking.

D. oppositifolia (synonym Dioscorea batatas) tubers have been used as a saliva substitute (M. S. Park et al., 2010), (Syed, Au, and Cahill, 2008).

## Menopause

Topical formulations of Dioscorea are poorly evaluated, and it is unlikely that they are a source of progesterone (D. G. Carroll, 2006), (Haimov-Kochman and Hochner-Celnikier, 2005b), (Kelley and D. G. Carroll, 2010). Oestrogenic compounds have been reported for D. alata (W. Y. Cheng, Kuo,

and C. J. Huang, 2007), while weak effects on progesterone receptor activity in human breast cells have also been demonstrated in-vitro (M. K. Park et al., 2009). Inhibition of human breast cancer MCF-7 cell proliferation was also shown in-vitro for D. villosa extracts (M. K. Park et al., 2009).

### Animal data

Research reveals no animal data regarding the use of wild yam for menopausal symptoms.

### Clinical data

Limited clinical trials exist evaluating the effect of wild yam and its extract on menopausal symptoms. One uncontrolled clinical study evaluated the effect of consuming 390 g of yam over 30 days and found increases in serum estrone and sex-hormone-binding globulin, but not in estradiol (W. H. Wu et al., 2005). Another randomised, double-blind, placebo-controlled trial evaluated daily topical application of D. villosa extract in menopausal women, finding no change in serum oestrogen or progesterone, no effect on symptoms, and no effect on lipids, weight, or blood pressure (unknown, 2004b), (Komesaroff et al., 2001). Commercial preparations of topical progesterone creams have been evaluated for use in managing menopausal symptoms.

Although wild yam is often advertised as a natural source of oestrogen, there is no scientific evidence that wild yam works to treat menopausal symptoms or osteoporosis. In fact, several studies have found that wild yam does not reduce the symptoms of menopause, such as hot flashes, or raise levels of oestrogen or progesterone in the body. Some preparations of wild yam may contain progesterone, but only because a synthetic version of progesterone (medroxyprogesterone acetate or MPA) has been added to them (unknown, 2014m).

## High Cholesterol

Researchers have speculated that taking wild yam may help lower cholesterol levels, although studies have shown mixed results. Diosgenin seems to block the body from absorbing cholesterol, at least in animal studies. But in studies of people, cholesterol levels have not gone down – although fats in the blood (triglycerides) have decreased. More research is needed to determine whether wild yam would help people with high cholesterol (unknown, 2014m).

## Other uses

Isolated diosgenin decreased total cholesterol and increased HDL in rats (Son et al., 2007).

Allantoin from yam decreased plasma glucose in diabetic rats (Niu, W. Chen, and H. T. Wu, 2010).

Dioscorin protein from the tuber of D. alata and Dioscorea japonica showed immune-stimulatory effects in mice (Y. W. Liu et al., 2009), (P. L. Lin et al., 2009) and exhibited hypotensive effects in rats (Y. H. Liu, Y. S. Lin, and D. Z. Liu, 2009).

D. alata was hepatoprotective in rats exposed to acetaminophen (S. C. Lee, C. C. Tsai, and J. C. Chen, 2002).

## Contraindications

Women with hormone-dependent conditions such as endometriosis, uterine fibroids, and cancers of the breast, ovaries, or uterus should not take or use wild yam due to its possible oestrogenic effects. Men with prostate cancer should also avoid taking wild yam.

Pregnant women should not take wild yam because it may stimulate the uterus to contract, possibly causing a miscarriage (herbwisdom, 2015r).

Anyone with a personal or family history of hormone-related cancer (such as breast cancer, ovarian cancer, and uterine cancer) should check with their doctor before using any form of natural hormone replacement, including wild yam. Although it does not seem to act like a hormone in the body, there is a slight risk that wild yam could produce similar effects to oestrogen.

Pregnant women and nursing mothers should avoid wild yam.

People who have protein S deficiency should not take wild yam without talking to their doctor. Some doctors think wild yam may possibly increase the risk of forming clots, because of its oestrogen-like effects (unknown, 2014m).

## Adverse Reactions

A clinical study evaluating the consumption of yam 390 g per day reported no adverse events (W. H. Wu et al., 2005). Topical preparations of wild yam extract are relatively free from adverse effects (unknown, 2004b), (Komesaroff et al., 2001).

Acute animal toxicity studies reveal no reno- or hepatotoxicity (Wojcikowski et al., 2008). A study in rats, however, found an increase in fibrosis in the kidneys and inflammation in the livers of rats fed D. villosa for 28 days (Wojcikowski et al., 2008).

## Pregnancy/Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking.

Pregnant women should not take wild yam because it may stimulate the uterus to contract, possibly causing a miscarriage.

Because very little information is available on how wild yam might affect an infant or a small child, its use is not recommended while breast-feeding or during early childhood (herbwisdom, 2015r).

## Interactions

- **Hormone Replacement Therapy or Birth Control Pills** – An animal study indicated that the active component of wild yam, diosgenin, may interact with estradiol. Estradiol is a hormone that occurs naturally in the body and also is used in some birth control medications and certain hormone replacement therapies.

If you are currently being treated with either of these medications, you should not use wild yam without first talking to your health care provider (unknown, 2014m).

## Available Forms

Wild yam is available as liquid extract and as a powder. The powdered form may be purchased in capsules or compressed tablets. The fluid extract can be made into tea. Creams containing wild yam are also available (unknown, 2014m).

## Dosage

There are inadequate clinical trials on which to base dosing guidelines. Commercially available topical preparations of yam extracts recommend the application of 1 teaspoonful of cream twice daily (Komesaroff et al., 2001). Based on a single study in rats, oral D. villosa should be avoided in people with compromised renal function (Wojcikowski et al., 2008).

### Paediatric

Wild yam hasn't been studied in children, so it is not recommended for paediatric use (unknown, 2014m).

### Adult

Wild yam frequently comes in capsule form as a dried herb. Often it is dosed in a tincture, which is an alcohol extract. It is also available as a 12% cream for topical use.

Ask your doctor to help you find the right dose.

Wild yam is often combined with other herbs said to have oestrogen-like effects, such as black cohosh. Wild yam creams, as well as tablets and powders, may contain synthetic hormones. Check the ingredients carefully (unknown, 2014m).

## Toxicology

D. villosa has been evaluated in topical preparations with an upper limit of 3.5% diosgenin phytosterol and was not found to be systemically toxic or genotoxic. No data are available on the carcinogenicity of D. villosa (unknown, 2004b).

## Commentary

*With so many questions going unanswered about wild yam, and with the lack of reputable clinical studies, I would suggest against taking it as there are too many variables and unanswered questions.*

Chapter 15

# Appendix

## Side-effects vs. Adverse effects

These two terms are often used interchangeably by health professionals, which is not correct, they are two distinct terms with specific definitions and meanings. As these terms have occurred at various places in this document, I felt that I should show the distinction between them.

### Side-effects

A side-effect of any substance is an effect beyond the chief or primary action that is intended by the person, most often the doctor prescribing the drug. This extra action too is foreseen by the doctor. For example, the patient might not be aware of the side effect of diarrhoea while using antibiotics but the doctor is very well aware about it. Doctors generally advise patients not to pay attention to side-effects unless severe and often warn their patients regarding their possibility. Side-effects are published by pharmaceutical companies as soon as a new drug is launched in the market owing to the extensive clinical trials that are conducted before launching it in the market for general use.

A side-effect is often used as a therapeutic benefit in the pharmaceutical industry. For instance, a drug like dexamethasone is harmful if used during pregnancy; hence, it is always tapered off as early as possible. But the side-effect of dexamethasone is that it increases foetal pulmonary maturation. Thus, it is used in cases of premature labour where there is foetal pulmonary maturation and growth are incomplete. In this case, the side-effect of the drug is controlled and employed for a beneficial and therapuetic effect judiciously (Rachita., 2014).

These are symptoms shown by a patient after taking a medication that are a natural consequence of the chemical formula of the drug on the body of the patient. Side-effects are mostly anticipated as a drug comes to the market after several trial studies have been conducted and even if a patient

is unaware of these side-effects, doctors should know of all such side-effects. Mostly side-effects are harmless and require no medication. Doctors advise patients not to pay any attention to side-effects as they tend to go away in a few days or even hours. However, in some cases, some of the side-effects may be serious and require intervention by the doctor. He may reduce the dosage of the drug or stop it altogether to remove these troublesome side-effects (Olivia., 2011).

## Adverse effects

An adverse effect, is an effect wherein the reaction occurs over and beyond the chief and desired action of a drug. The adverse reaction is unexpected by both the doctor as well as the patient. Side-effects are most often mild in nature and often self resolving but adverse effects can be fatal and need to be reversed or antidote immediately. Adverse effects reduce either by reducing the dose of the medicines or by stopping the drug altogether. Occasionally, if the adverse effect is too serious, there might be a need for hospitalisation. Adverse effects can occur due to incorrect drug dosage whereas side-effects are produced due to medications alone.

An adverse effect is an undesired effect and is usually very harmful. Adverse drug effects are experienced by patient's due to lack of doctors knowledge about the complete action of the drug and hence, can be called as iatrogenic in nature. The adverse effects can often lead to deterioration of the health condition for which the drug was originally initiated and worsen the prognosis of the disease.

Adverse effects can be classified as reversible or irreversible depending on the severity of the error. If it is related to medication then it is reversible but if it is due to a surgery that some tissue is amputated or damaged, then it is irreversible. Adverse effects are further classified as minor adverse effects and major/serious adverse effects depending upon the degree of the reaction (Rachita., 2014).

As the name implies, some patients, apart from side-effects of a drug also report some undesirable effects that are not anticipated even by the doctors. These effects may be harmful for the patient and prompt the doctor to discontinue the administration of the drug. Adverse effects may hamper the treatment procedure, may complicate the disease or may even worsen the situation or produce a new ailment in the patient (Olivia., 2011).

# Free radicals and antioxidants

Free radicals are atoms or groups of atoms with an odd (unpaired) number of electrons and can be formed when oxygen interacts with certain molecules. Once formed these highly reactive radicals can start a chain reaction, like dominoes. Their chief danger comes from the damage they can do when they react with important cellular components such as DNA, or the cell membrane. Cells may function poorly or die if this occurs. To prevent free radical damage the body has a defense system of antioxidants.

Antioxidants are molecules which can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Although there are several enzyme systems within the body that scavenge free radicals, the principle micronutrient (vitamin) antioxidants are vitamin E, beta-carotene, and vitamin C. Additionally, selenium, a trace metal that is required for proper function of one of the body's antioxidant enzyme systems, is sometimes included in this category. The body cannot manufacture these micronutrients so they must be supplied in the diet.

- **Vitamin E** - d-alpha tocopherol. A fat soluble vitamin present in nuts, seeds, vegetable and fish oils, whole grains (esp. wheat germ), fortified cereals, and apricots. Current recommended daily allowance (RDA) is 15 IU per day for men and 12 IU per day for women.
- **Vitamin C** - Ascorbic acid is a water soluble vitamin present in citrus fruits and juices, green peppers, cabbage, spinach, broccoli, kale, cantaloupe, kiwi, and strawberries. The RDA is 60 mg per day. Intake above 2000 mg may be associated with adverse side effects in some individuals.
- **Beta-carotene** - this is a precursor to vitamin A (retinol) and is present in liver, egg yolk, milk, butter, spinach, carrots, squash, broccoli, yams, tomato, cantaloupe, peaches, and grains. Because beta-carotene is converted to vitamin A by the body there is no set requirement. Instead the RDA is expressed as retinol equivalents (RE), to clarify the relationship. (NOTE: Vitamin A has no antioxidant properties and can be quite toxic when taken in excess.) (M. A. Jenkins, 1996).

A balance between free radicals and antioxidants is necessary for proper physiological function. If free radicals overwhelm the body's ability to regulate them, a condition known as oxidative stress ensues. Free radicals thus adversely alter lipids, proteins, and DNA and trigger a number of human diseases (Lobo et al., 2010).

For a really good article explaining about free radicals and antioxidants you should read 'Free radicals, antioxidants and functional foods: Impact on human health' (Lobo et al., 2010).

# Glossary

**A**

**abortifacient** causing abortion 124, 209, 247, 264, 272, 326

**acaricidal** a pesticide that kills ticks and mites 278

**acute** Sudden, severe, and not long lasting 105, 132, 164, 181, 191, 195, 196, 200, 282, 296, 313, 343, 346, 347, 361, 370, 379, 450

**adaptogen** used to improve the health of your adrenal system 76, 134, 136, 137

**adaptogenic** generating a substance that balances the body, particularly when the body is under stress, by either stimulating or relaxing 78, 79, 99–101, 136

**adjunctive** an accessory or auxiliary agent or measure 48, 355, 366, 378

**adrenergic** working on adrenaline (epinephrine) or noradrenaline (norepinephrine) 34, 84, 141, 423

**adulterants** a substance or chemical which is added to a drug to increase the quantity, reduce manufacturing costs and change the potency of the drug 80, 88, 137

**adverse effects** An unwanted side-effect 14, 48, 52, 55, 56, 58, 72, 76, 81, 105, 116, 139, 180, 181, 196, 201, 202, 215, 221, 247, 285, 290, 354, 355, 372, 387, 392, 399, 444, 450

**adverse events** An unwanted medical problem that occurs during treatment. Adverse events may be unrelated to the treatment or they may be caused by the therapy or procedure. For example, an adverse event may be caused by the toxic effects of a particular drug or dietary supplement or by an interaction with another therapy. Also called adverse effect and side effect 39, 88, 145, 150, 188, 341, 343, 346, 372, 450

**alterative** causing alteration 22, 63, 64, 137, 213, 245, 391

**alternative remedies** A group of diverse medical and health care systems, practices, and products that are used in place of conventional medicine 183

**amenorrhoea** absence of menstruation 18, 162, 216, 220, 224, 261, 272, 273, 275, 277, 325, 384, 403, 446

**analgesic** an agent that relieves pain without causing loss of consciousness 113, 162, 256, 260, 261, 273, 277, 282, 338, 343, 348

**anaphylaxis** a serious allergic reaction that is rapid in onset and may cause death 88, 150, 372, 442

**androgenic** pertaining to the development of male characteristics, including body hair, the genital organs and muscle mass 131, 418

**andropause** also colloquially known as the 'male menopause', and is thought to be the result of a gradual drop in testosterone 277, 278

**angiogenic** of vascular origin 259

**ANLL** An aggressive (fast-growing) disease in which too many myeloblasts (immature white blood cells that are not lymphoblasts) are found in the bone marrow and blood 347

**anodyne** a drug used to lessen pain through reducing the sensitivity of the brain or nervous system 300, 338

**anthelmintic** can expel parasitic worms and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host 208

**anti-androgenic** having the ability to block the male hormone testosterone from binding to androgen receptors 131, 217, 424, 435

**anti-bilious** serving to prevent or cure biliousness 228

**anti-carcinogenic** pertaining to a substance or device that neutralises the effects of a cancer-causing substance 81, 138, 280, 357

**anti-coagulant** reduces the ability of the blood to clot 69, 72, 89, 115, 202, 203, 261, 262, 264, 265, 274, 294, 311, 424, 425

**anti-complement** a substance that counteracts the action of a complement 137

**anti-diabetic** something that stabilises and controls blood glucose levels amongst people with diabetes 62, 66, 67, 89, 289, 290

**anti-fungal** effective against fungal infections 112, 113, 168, 250, 281, 303, 405, 406, 446

**anti-hydrotic** reduces excessive sweating and perspiration 403, 405

**anti-inflammatory** a substance or treatment that reduces inflammation or swelling 42, 62, 67, 83, 113, 114, 140, 161–164, 168, 169, 175, 193, 198, 200, 204, 250, 260, 261, 277, 280, 288, 290, 316, 320, 322, 353, 357, 359, 367, 368, 402, 405–408, 414–416, 420, 447

**anti-oestrogenic** lowers the oestrogen levels in the blood 398, 399, 427, 441

**anti-parasitical** indicated for the treatment of parasitic diseases 213

**anti-platelet** decrease platelet aggregation and inhibit thrombus formation 203, 262, 264, 265, 281, 311, 425

**anti-putrid** having the ability to arrest putrefaction 228

**anti-rheumatic** counteracting rheumatism and rheumatoid disease 113, 447

**anti-scorbutic** preventing or relieving scurvy 64

**anti-spasmodic** preventing spasms 10, 22, 110, 111, 113, 121, 122, 156, 207, 249, 257, 258, 260, 261, 275, 277, 338, 391, 398, 402, 404, 405, 446, 447

**anti-ulcer** used to treat ulcers in the stomach and the upper part of the small intestine 62, 67

**antiapoptotic** something that prevents apoptosis 83, 140, 367

**antibacterial** having the ability to destroy bacteria or suppress their growth or their ability to reproduce 110, 112, 113, 122, 156, 168, 230, 250, 262, 298, 303, 359, 405, 406, 408

**antidipsotropic** to reduce or prevent alcoholic drinking 307

**antihistaminic** opposes the activity of histamine receptors in the body 207

**antimicrobial** tending to destroy microbes, prevent their development, or inhibit their pathogenic action 122, 175, 250, 265, 277, 281, 405, 406, 408–410

**antineoplastic** inhibiting or preventing development of neoplasms; checking maturation and proliferation of malignant cells 79, 366

**antioxidant** a substance that in small amounts will inhibit the oxidation of other compounds. Also see Free radicals and antioxidants 21, 54, 83, 101, 134, 137, 140, 143, 193, 196, 226–228, 232, 234, 260, 277, 286, 287, 291, 292, 303, 308, 315, 319, 322, 353, 355, 357, 359, 360, 363–365, 367, 368, 386, 392, 406, 408, 441, 455

**antiprogestational** an abortifacient 131

**antipyretic** something that reduces fever or quells it 15, 64, 162, 168, 228, 277

**antiseptic** prevents infection by inhibiting the growth of infectious agents 10, 15, 16, 119, 121, 122, 155, 156, 159, 207, 228, 244, 245, 257, 300, 402–405, 409, 415

**antithrombotic** reduces the formation of blood clots 239, 271, 281

**antitumour** used in the treatment of cancer 65, 137, 281, 290, 291

**antiviral** destroying or inhibiting the growth and reproduction of viruses 137, 364, 405, 406

**anxiolytic** having the ability to inhibit anxiety 83, 141, 348, 407

**aperient** having a gentle laxative effect 64, 245

**aphrodisiac** a substance that, when consumed, increases sexual desire 24, 123, 130, 135, 137, 156, 212, 243–246, 254, 286, 300, 415

**apoptosis** A natural process of self-destruction in certain cells that is determined by the genes and can be initiated by a stimulus or by removal of a repressor agent 81, 138, 216, 232, 260, 319, 340, 360, 396, 419

**apthous ulcers** ulcers in the mouth which typically last for 10-14 days and they heal without leaving a scar 321, 323, 333

**aromatic** Having an agreeable, somewhat pungent, spicy odour 109, 112, 119, 120, 122, 126, 213, 217, 243, 244, 253, 276, 277, 297, 405

**atherosclerosis** hardening of the arteries 9, 18, 66, 77, 78, 135, 199, 255, 258, 292, 430, 436

**auto-immune stimulant** stimulates the auto-immune system 137

## B

**bacterial theory** a fundamental tenet of medicine that states that microorganisms, which are too small to be seen without the aid of a microscope, can invade the body and cause certain diseases 110

**bacteriostatic** the prevention of the further growth of bacteria 230, 249, 281

**bioavailability** the fraction of a dose of drug that is absorbed from its site of administration and reaches, in an unchanged form, the systemic circulation. This will differ when using a different route of administration 193, 237, 317, 332, 354, 379

**blinded** a process used in clinical trials to assign individuals to the control group (to receive the standard treatment) or the test group (to receive the new treatment under study) without the individuals or the researchers knowing to which group they have been assigned. Blinding helps ensure that information collected in the study is true and not biased (flawed). In a single-blinded study, the individuals do not know whether the standard treatment or a new treatment is being given. In a double-blinded study, neither the individuals nor the researchers know which treatment is being given 33, 184, 361, 372

**bloating** abdominal distention due to swallowed air or intestinal gas 10, 113, 119, 121, 122, 206, 208, 209, 217, 266, 322, 323, 371

**blue cohosh** A plant that has been used to treat menstrual disorders and to start labour. It may be unsafe and should not be confused with black cohosh. Latin name: *Caullophylum thalictroides* 180, 181, 188

## C

**cancerous ulcerations** a tumour growing under the skin breaks through the skins surface, and forms an ulcer or open sore 299

**canker sores** small white or yellowish sores or ulcers that develop inside the mouth. They are painful, self-healing, and can recur 314, 316, 406

**carcinogen** cancer causing 153, 265, 267, 303

**carcinogenesis** the actual formation of a cancer, whereby normal cells are transformed into cancer cells 274, 303

**carcinogenic** Has the ability to cause cancer 98, 107, 159, 263, 303, 395, 444, 452

**carminative** relieving flatulence 10, 112–114, 121, 122, 130, 137, 207, 245, 276, 277, 284, 287, 316, 402, 405, 408

**case report** A detailed record of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some information about the patient (such as age, gender, and ethnic origin) 38, 73, 88, 89, 145, 146, 180, 181, 189, 190, 216, 223, 237–239, 262, 264, 272, 282, 283, 310, 333, 341, 372, 374, 423, 442

**case study** involves an up-close, in-depth, and detailed examination of a subject (the case), as well as its related contextual conditions 190

**case-control** A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition 174, 347, 434, 436

**causative** acting as a cause 74, 230, 341

**cell lines** Cells of a single type that have been adapted to grow and divide in the laboratory and are used in research 52, 171, 174, 186, 216, 260, 303, 308, 319, 353, 355, 360, 364–367, 382

**cell-mediated immunity** an immune response that does not involve antibodies, but rather involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen 100

**cells** The individual unit that makes up the tissues of the body. All living things are made up of one or more cells, which are the smallest units of living structure capable of independent existence 52, 62, 65, 81, 82, 85–87, 99, 100, 104, 138, 139, 142, 143, 176, 181, 186, 187, 193, 229, 230, 233, 234, 236, 251, 259, 262, 271, 285, 286, 291, 302, 303, 308, 310, 340, 341, 353, 355, 357–360, 363–368, 370, 377, 382, 384, 395, 399, 414, 418, 420, 421, 423, 435, 436, 449, 455

**cephalic** relating to the head 213

**cheilitis** an abnormal condition of the lips characterized by inflammation and cracking of the skin 124, 410

**chemoembolization** injection of chemotherapeutic agent(s) and/or inert particles into tumour vessel(s) 81, 139

**chemotaxis** movement of an organism in response to a chemical stimulus 104

**cholagogue** agent that stimulates bile flow from the gallbladder into the duodenum 110, 111, 113, 245, 447

**cholestasis** a condition where bile cannot flow from the liver to the duodenum 359, 373

**cholesterol** a fatty substance known as a lipid and is vital for the normal functioning of the body 8, 22, 26, 62, 65–68, 70, 73, 74, 82, 134, 139, 143, 156, 194, 198, 233, 234, 236, 282, 286, 288, 289, 295, 308, 315, 316, 321–323, 357, 358, 363, 368, 370, 377, 384, 390, 391, 393, 394, 396, 428, 430, 433, 436, 437, 440, 447, 449, 450

**cholinergic** this refers to any compound that can increase levels of acetylcholine or choline in the brain 83, 84, 140, 141, 411

**chronic** constant 15, 21, 24, 26, 27, 43, 45–47, 63, 102, 105, 113, 115, 130, 132, 133, 164, 198, 226, 228, 266, 272, 273, 280, 314, 316–319, 321, 324, 325, 332, 340, 343, 356, 358, 359, 362, 364, 370, 391, 414, 415, 422, 433, 442

**climacteric** the syndrome of endocrine, somatic, and psychic changes occurring at menopause in women 384

**clinical trials** Studies to determine whether a treatment is safe and effective. It is carried out with a sample of patients, usually after laboratory studies and studies with healthy volunteers have been conducted 30, 32, 34, 50, 73, 79, 82–84, 86, 88, 90, 140–142, 145, 150, 152, 153, 157, 168, 179–181, 195, 204, 214–216, 220, 221, 240, 258, 261, 272, 289, 293, 307, 318, 319, 340, 341, 343, 353, 355, 360–362, 364, 365, 372, 378, 379, 384, 391, 397, 399, 406, 407, 410, 419, 420, 426, 435, 437, 439, 440, 443, 448, 449, 451, 453

**coadministration** administered along with something else 89, 146, 345

**cochrane review** A systematic, up-to-date summary of reliable evidence of healthcare benefits and risks of a particular procedure or intervention, derived from the parent database maintained by the Cochrane Collaboration 58, 196

**cognitive function** an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering 83, 87, 141

**cohort study** a cohort is any group of people who are linked in some way and followed over time. Researchers observe what happens to one group that's been exposed to a particular variable for example, the effect of company downsizing on the health of office workers. This group is then compared to a similar group that hasn't been exposed to the variable 88, 145, 436

**columnar** A type of cell that lines the internal and external surfaces of the body 187

**commercial** A product such as a drug or dietary supplement made in large quantities to be sold 66, 77, 80, 99, 118, 120, 136–138, 149, 162, 163, 171, 188, 192, 194, 198, 245, 257, 287, 291, 312, 315, 335, 360, 381, 387, 393, 397, 416, 442, 448, 449, 451

**complaints** In medicine, a disorder, disease, or symptom 114, 115, 172, 181, 292, 317, 354, 356, 358, 390, 402, 405, 433, 438, 442

**complementary** A group of diverse medical and health care systems, practices, and products that are used together with conventional medicine 26, 28–30, 32, 37, 39, 50, 51, 57, 151, 180, 183, 187, 222, 238, 293

**complications** In medicine, an illness or condition that occurs while a patient has a disease. The complication is not a part of the disease, but may be a result of the disease or may be unrelated 35, 46, 86, 181, 279, 281, 361, 417, 423

**compound** in pharmacy, a substance that contains more than one ingredient 51, 57, 58, 63, 112, 185

**concentration-dependent** A drug that shows optimum response in its effect when its concentration is either equal or greater than 10 times above the MIC (minimum inhibitory concentration) at the site of infection for certain target micro-organism 83, 140

**consensus** a general agreement 32, 80, 138, 188, 222, 352, 419

**constituents** A component, part, or ingredient of a larger whole. For example, valerenic acid and valepotriate are constituents of the dietary supplement valerian 99, 101, 102, 105, 111, 112, 116, 121, 126, 133, 134, 157, 168, 169, 182, 186, 214, 216, 222, 257, 258, 260, 261, 269, 278, 279, 293, 300, 306, 358, 368, 390, 398, 403, 413, 416, 420, 433, 448

**contact dermatitis** any skin inflammation that occurs when the skin's surface comes in contact with a substance originating outside the body 130, 282, 283

**control groups** In a research study or clinical trial, the group that does not receive the new treatment being studied. This group is compared with the group that receives the new treatment, to see whether the new treatment works 183, 372

**cornification** The changing of cells that line the internal and external surfaces of the body into an outer layer of flat cells that look like fish scales under a microscope). Also called keritinization 170, 187, 384

**cross-over study** a type of clinical trial in which the study participants receive each treatment in a random order 103, 172, 237, 280, 341

**cultivars** a variety of plant that originated and persisted under cultivation 61, 67, 381

**cyanogenetic** potentially poisonous cyanide radicals are found in plants in the form of cyanogenetic glycosides, in which form they are not poisonous. The glycosides may be broken down by plant enzymes or by rumen microorganisms and the material then releases its cyanide 247

**cytology** The study of cells using a microscope 172, 186

**cytotoxic** relating to, or producing a toxic effect on cells 81, 138, 216, 269, 303, 353, 366, 382

**D**

**data** facts and information 19, 29, 40, 42, 46, 53, 81, 83–85, 89, 114, 121, 122, 128, 135, 139, 141, 142, 145, 157, 171, 178, 183, 184, 187, 214, 215, 229, 230, 238, 246, 255, 257, 259, 269, 278–281, 288, 290, 291, 303, 313, 326, 340–342, 347, 352, 362, 365, 372–374, 378, 386, 393–395, 430, 432, 434–440, 442, 449, 452

**decoction** decoction is a method of extraction by boiling of dissolved chemicals from herbal or plant material, which may include stems, roots, bark and rhizomes 59, 60, 90, 108, 117, 118, 152, 153, 220, 224, 256, 267, 270, 272, 299, 310, 324, 333, 338, 401, 404

**deleterious** damaging or harmful 68, 434

**demulcent** any of several oily substances used for soothing and reducing irritation of surfaces that have been abraded or irritated, especially mucosal surfaces 137, 287, 314, 316

**deoxymiroestrol** Deoxymiroestrol is a highly active phytoestrogen derived from the tuberous roots of Pueraria candollei var. mirifica 381, 382

**diaphoretic** able to increase perspiration 112, 113, 119, 168, 198, 257, 277, 310, 447

**dietary supplement** A product that is intended to supplement the diet. A dietary supplement contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their components; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is identified on the front label of the product as being a dietary supplement 32, 34, 37–40, 42, 55, 56, 75, 91, 92, 148, 157, 166, 187, 199, 218, 226, 242, 354, 428, 441

**diuretic** a substance that promotes the production of urine 15, 16, 62, 64, 67, 91, 112, 113, 119, 120, 147, 148, 156, 163, 166, 213, 228, 244, 245, 257, 277, 281, 288, 298, 300, 328, 331, 389, 415, 416, 447

**Doctrine of Signatures** This was an important aspect of folk medicine from the Middle Ages until the early modern period. Often associated with the work of herbalists and wise women, it drew upon the belief that natural objects that looked like a part of the body could cure diseases that would arise there. Folk healers in Christian and Muslim countries claimed that God, or Allah, deliberately made plants resemble the parts of the body they could cure. For example,

eyebright, a plant whose flower looks like bright blue eyes, was used to treat eye diseases. The use of eyebright for this purpose was still common in the 1700s. This belief became known as the "doctrine of signatures" after the appearance of a book by the German mystic Jakob Boehme called The Signature of All Things (1621). The Swiss physician Paracelsus, an important advocate of the doctrine of signatures, stated that "Nature marks each growth according to its curative benefit." Similarly, the English botanist William Cole (1626-62) believed that "the mercy of God... maketh Herbes for the use of men, and hath given them particular Signatures, whereby a man may read the use of them." (Museum, 2015) 78, 113, 135

**dopaminergic** related to dopamine 84, 141, 214

**dose-dependent** effects change when the dose of the treatment is changed 131, 224, 289, 291, 292, 319, 343, 365, 367, 382–384, 386, 407, 418, 435

**dose-related** If the effects change when the dose of the drug is changed, the effects are said to be dose-dependent 290, 373

**double-blind** Describes a clinical trial in which neither the researcher nor the patient knows which of several possible therapies the patient is receiving 29, 103, 104, 143, 171, 172, 183, 184, 186, 195, 220, 259, 341, 384, 419, 420, 449

**drugs** Any substance (other than food) that is used to prevent, diagnose, treat, or relieve symptoms of a disease or abnormal condition. Also, a substance that alters mood or body function or that can be habit-forming or addictive, especially a narcotic 27, 28, 30, 34, 37–42, 48, 50, 55, 56, 63, 69, 76, 87, 89, 108, 134, 145, 147, 150, 174, 182, 187, 203, 210, 219, 222, 223, 238, 247, 264, 294, 311, 312, 317, 320, 349, 351–354, 357, 368, 374–376, 379, 382, 398, 399, 403, 411, 424, 427

**dysmenorrhoea** painful menstrual periods 17, 23, 168, 175, 220, 255, 257, 258, 272, 273, 277, 279, 338, 402–405, 446

**dyspareunia** pain in the pelvic area during or after sexual intercourse 384

**dyspepsia** painful, difficult, or disturbed digestion, which may be accompanied by symptoms such as nausea and vomiting, heartburn, bloating, and stomach discomfort 13, 18, 23, 66, 113, 115, 125, 130, 133, 168, 207, 246, 249, 250, 292, 293, 300, 322, 358, 368, 373, 378, 405

**dyspnoea** shortness of breath 105

**E**

**Eclectic medical movement** a branch of American medicine which made use of botanical remedies along with other substances and physical therapy practices, popular in the latter half of the 19th and first half of the 20th centuries 162, 446

**eczema** Eczema is a term for a group of medical conditions that cause the skin to become inflamed or irritated 13, 191, 196–200, 205, 286, 292, 314, 318, 321, 322, 372, 389–391, 397, 406

**EDCs** These are defined as substances that *"interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism)"* (Crisp and Clegg, 1998) 51

**efficacy** capacity for producing a desired result or effect 31, 32, 37–39, 41–43, 48, 59, 80, 85, 107, 124, 138, 142, 149, 157, 166, 167, 175, 196, 215, 216, 222, 233, 234, 238, 248, 261, 266, 272, 279, 282, 295, 304, 318, 319, 341, 343, 344, 347, 349, 350, 353, 355, 361, 365, 366, 368, 374, 396, 407, 411, 419–421, 424, 437, 439–442, 451

**elixir** a sweetened, aromatic solution of alcohol and water containing, or used as a vehicle for, medicinal substances 224, 245

**emetic** causing vomiting 20, 48, 137, 339, 350, 351

**emmenagogue** An agent that induces or hastens menstrual flow 67, 115, 116, 130, 213, 245, 276, 283, 402, 405

**emollient** a moisturising treatment applied directly to the skin 124, 291, 316

**endogenous** from within the body 62, 166, 262, 340, 345, 434

**endometrial hyperplasia** a thickening of the lining of the uterus that can lead to cancer 441

**epidemiological** the associative relationships between the frequency of occurrence of a disease and its determinants, its predisposing and precipitating causes 52, 59, 81, 139, 352

**epileptiform** resembling epilepsy or its manifestations 283

**ER-negative** Oestrogen receptor negative (ER-). Having to do with breast cancer cells that do not have a protein (a receptor molecule) to which oestrogen will attach. Breast cancer cells that are ER- do not need the hormone oestrogen to grow and usually do not respond to hormone (antioestrogen) therapy that blocks these receptor sites 186

**ER-positive** Oestrogen receptor positive (ER+). Having to do with breast cancer cells that have a protein (a receptor molecule) to which oestrogen will attach. Breast cancer cells that are ER+ need the hormone oestrogen to grow and will usually respond to hormone (antioestrogen) therapy that blocks these receptor sites 186, 187

**ergogenic** a tendency to increase work output 79, 84, 141

**estriol** Estriol is one of the three main oestrogens produced by the human body 166, 171, 184, 382

**estrone** Estrone is an oestrogenic hormone secreted by the ovary as well as adipose tissue 259, 382, 439, 449

**ethanol** A type of alcohol. Also called ethyl alcohol or grain alcohol 102, 106, 184, 188, 189, 216, 270, 271, 291, 292, 307, 308, 382, 387, 404, 407, 408, 412, 433

**euphoric** having the ability to induce a state of happiness and confident well-being 246

**evidence** Information used to support the use of a particular screening procedure, treatment, or preventive measure. In medicine, evidence needed to determine effectiveness is provided by laboratory research, clinical trials, and other studies 29, 30, 32, 34, 38, 39, 41–44, 48, 49, 51,

**exogenous** outside the body 99, 340

**expectorant** promoting or facilitating the secretion or expulsion of phlegm, mucus, or other matter from the respiratory tract 10, 113, 119, 121, 122, 129, 137, 156, 159, 198, 199, 213, 257, 276, 287, 314–316, 389, 398, 415

**expert opinion** In medicine, the judgment of a respected healthcare professional, based on clinical experience or reports of expert committees. Expert opinions are important when results of controlled clinical trials and other scientific studies are not available to provide health care recommendations 188

**extract** A substance made by soaking an herb in a liquid that removes specific types of chemicals. The liquid can be used as is or evaporated to make a concentrate or a dry extract for use in capsules or tablets 22, 60, 68, 73, 79, 80, 83, 90, 91, 93, 94, 100–106, 120, 137, 140, 149, 153, 163, 165, 167, 169–171, 174, 184, 188, 189, 205, 210, 215, 216, 220, 224, 226, 232, 235, 240, 242, 245, 248, 250, 259, 267–273, 278, 279, 281, 282, 285, 288–294, 296, 302, 304, 307–309, 312, 317, 320, 323, 324, 332, 333, 339, 344–346, 350, 356, 357, 359, 360, 362, 363, 368, 369, 372, 377, 378, 380, 382–384, 387, 391, 392, 395–398, 402, 403, 407, 408, 410, 412–414, 418–421, 426, 427, 431, 433, 449–452

**F**

**febrifuge** serving to dispel or reduce fever 213

**flatulence** flatulence is passing gas from the digestive system out of the back passage. It's more commonly known as "passing wind", or "farting" 9, 17, 25, 109, 113–115, 119, 123, 156, 208, 249, 292, 446, 447

**flatulent colic** severe abdominal pain caused by spasm, obstruction, or distension of any of the hollow viscera, such as the intestines 208

**fluidextract** a liquid preparation of a vegetable drug, containing alcohol as a solvent or preservative, or both, of such strength that each milliliter contains the therapeutic constituents of 1 g of the standard drug it represents 116, 117

**Food and Drug Administration** FDA, Department of Health and Human Services. FDA is the Federal government agency responsible for ensuring that foods and dietary supplements are safe, wholesome and sanitary, and that drugs, medical devices, cosmetics, and food are honestly, accurately and informatively represented to the public. FDA regulates dietary supplements under a different set of regulations than those covering conventional foods and drug products (prescription and over-the-counter). The dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is

marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to get FDA approval before producing or selling dietary supplements 55, 157, 187

**free radicals** see Free radicals and antioxidants 143, 227, 232, 355, 408

**FSH** follicle-stimulating hormone - a hormone made by the pituitary gland (an organ at the base of the brain) that is used in reproduction and in making estrogen and sperm 170, 171, 185, 220, 223, 383, 384, 418, 439

**G**

**galactogogue** a substance that promotes lactation 130, 157, 327

**galactorrhoea** milky secretion from the breasts 23, 405

**galenical preparations** preparations of botanical drugs 116, 253, 284

**gastric** having to do with the stomach 102, 109–111, 113–115, 181, 216, 289, 292, 319, 332, 406, 408, 436

**gastrointestinal distress** is a broad category of symptoms including those of diarrhoea, indigestion/dyspepsia, and gastroenteritis. Other common gastrointestinal symptoms include heartburn, bloating and constipation 179

**genotoxicity** describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer 387

**ginsenosides** the presumed active component in ginseng, from the chemical class of saponins 75–77, 79–84, 88, 90, 93, 95, 96, 98–102, 104, 134, 136–141, 144, 145, 149, 153

**gruit** a herb mixture used for bittering and flavouring beer 298

**H**

**half-life** the amount of time required for the amount of something to fall to half its initial value 169, 340, 432

**hallucinogen** a psychoactive agent which can cause hallucinations, perception anomalies, and other substantial subjective changes in thoughts 246, 351

**hamilton anxiety scale** a rating system that is used to measure the severity of the symptoms of anxiety (including worrying, restlessness, fearfulness, trouble sleeping, poor concentration or memory, depression, aches and pains, shortness of breath, nausea, sweating, and impotence) 167, 184

**HDL** High-density lipoprotein - carries cholesterol away from the cells and back to the liver, where it's either broken down or passed out of the body as a waste product. For this reason, HDL is referred to as "good cholesterol" and higher levels are better 65, 79, 143, 233, 234, 282, 289, 295, 308, 363, 393, 396, 437, 450

**head-to-head** in direct confrontation, opposition, or competition 419

**heartburn** a burning sensation in the chest that can extend to the neck, throat, and face 14, 18, 206–209, 211, 250, 251, 275, 277, 314–317, 322, 358, 368, 372, 628

**hepatitis** A group of diseases in which the liver becomes enlarged and inflamed, causing fever, nausea, vomiting, abdominal pain, and dark urine 11, 21, 26, 42, 136, 180, 181, 273, 311, 316, 318, 319, 322–324, 332, 353, 355, 357–364, 368–370, 433, 442

**hepatocarcinogenic** producing or tending to produce cancer of the liver 131

**hepatoprotective** has the ability to prevent damage to the liver 113, 308, 357, 433, 450

**hepatotoxic** damaging to the liver 21, 34, 89, 102, 105, 132, 146, 182, 189, 190, 201, 203, 205, 270, 282, 291, 320, 359, 360, 413, 450

**hives** an allergic skin reaction causing localised redness, swelling, and itching 166, 283

**homeostasis** a self-regulating process by which biological systems in the human body tend to maintain stability while adjusting to conditions that are optimal for survival 101

**hormones** a group of chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be manufactured 11, 36, 38, 51, 52, 156, 168, 171, 172, 185, 213, 217, 220, 224, 250, 251, 254, 262, 312, 315, 317, 370, 377, 384, 387, 417, 427, 432, 439, 448, 452

**hot flashes** A sudden, temporary onset of body warmth, flushing, and sweating (often associated with menopause) 22, 23, 64, 94, 160, 164, 165, 171, 173, 174, 183, 184, 187, 188, 254, 257, 261, 309, 369, 384, 385, 389–393, 405, 406, 438, 439, 441, 449

**hypercapnea** abnormally elevated carbon dioxide (CO2) levels in the blood 333

**hyperkalaemia** too much potassium in the blood 63, 332

**hyperoesterogenism** excessive oestrogen 63, 64

**hypertonia** reduced ability of muscles to stretch due to increased muscle tension 130, 273, 325, 327

**hypoestrogenism** insufficient oestrogen 63, 64

**hypokalaemia** low potassium in the blood 325, 327, 333

**I**

**immunomodulatory** capable of modifying or regulating one or more immune functions 79, 85, 100, 103, 142, 216

**in-vitro** outside the body 38, 58, 65, 67, 74, 81, 82, 88, 98, 100, 102, 107, 112, 127, 128, 131, 138, 139, 145, 153, 170, 173, 185, 186, 213, 214, 216, 229, 233, 259, 260, 270, 271, 281, 289, 291, 307, 308, 318, 319, 342, 360, 361, 365, 370, 386, 399, 402, 407, 408, 418, 435, 436, 444, 449

**in-vivo** within the living organism 102, 107, 175, 197, 258, 259, 271, 302, 408

**incidence** The number of new cases of a disease diagnosed in a specific group of people during a specific period of time. For example, the annual incidence of childhood cancer is 14.6 cases per 100,000 children aged birth to 14 years 52, 68, 86, 88, 132, 142, 150, 178, 179, 181, 190, 196, 231, 280, 292, 321, 341, 367, 372, 393, 395, 399, 432, 434, 435

**infusion** the process of extracting chemical compounds or flavours from plant material in a solvent such as water, oil or alcohol, by allowing the material to remain suspended in the solvent over time. An infusion is also the name for the resultant liquid 60, 90, 117, 125, 153, 161, 192, 208, 248, 284, 333, 390, 397, 402, 403, 414

**insecticide** a substance used to kill insects 21, 123, 130, 386

**insomnia** difficulty in going to sleep or in getting enough sleep 9, 11, 19, 43, 45, 77, 87, 88, 95–97, 105, 106, 133, 147, 151, 183, 220, 247, 250, 251, 300, 301, 304, 338

**isopropyl alcohol** A substance used to kill germs and as a solvent. Also called isopropanol and rubbing alcohol 188

**K**

**kupperman index** a rating scale that is used to measure the severity of the symptoms of menopause, including hot flashes, tingling or crawling skin, difficulty sleeping, nervousness, melancholy, dizziness, weakness, joint or muscle pain, headache, and abnormal heart beat 167, 172, 183, 184

**L**

**laboratory tests** A medical procedure that involves testing a sample of blood, urine, tissue, or other substance collected from the body. Tests can help determine a diagnosis, plan treatment, check to see whether treatment is working, or monitor a disease over time 94, 182, 255

**laxative** substances that loosen stools and increase bowel movements 16, 228, 244, 245, 255, 257, 282, 287, 315, 316, 328, 329, 331, 355, 371, 372

**LDL** Low-density lipoprotein - carries cholesterol to the cells that need it. If there's too much cholesterol for the cells to use, it can build up in the artery walls, leading to disease of the arteries. For this reason, LDL is known as "bad cholesterol" 65, 70, 143, 232, 234, 289, 308, 321–323, 368, 370, 393, 396, 437, 440

**LH** luteinizing hormone - a hormone made in the brain that is important for the release of an egg from an ovary during the menstrual cycle and in making the hormones testosterone and oestrogen 170–172, 185, 220, 223, 383, 418, 439

**liver** A large organ located in the right upper abdomen. It stores nutrients that come from food, makes chemicals needed by the body, and breaks down some medicines and harmful substances so they can be removed from the body 17, 21, 23, 67, 68, 80, 89, 102, 105, 130, 132, 138, 145, 146, 175–177, 179–182, 189, 190, 193, 194, 199, 201–203, 205, 226, 239, 240, 247, 254, 255, 270, 273, 275, 281, 291, 301, 310, 311, 314–320, 322–325, 327, 329, 330, 332, 353–365, 368–371, 375–378, 383, 384, 389, 398, 402, 405, 406, 423, 427, 433, 434, 442, 447

**lot** A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits 69, 187, 354

**Lydia Pinkham's Vegetable Compound** a commercially successful herbal-alcoholic "women's tonic" meant to relieve menstrual and menopausal pains. It contained Unicorn Root (Aletris farinosa L.) 8 ounces, Life Root (Senecio aureus L.) 6 ounces, Black Cohosh (Cimicifuga racemosa (L.) Nutt.) 6 ounces, Pleurisy Root (Asclepias tuberosa L.) 6 ounces, Fenugreek Seed (Trigonella foenum-graecum L.) 12 ounces, Alcohol (18%) to make 100 pints 163, 287

**lymphoedema** swelling of the lymph nodes 113

**M**

**mastalgia** breast pain 106, 150, 216, 220, 391

**mechanisms of action** the means by which a substance (such as a dietary supplement) is able to produce an effect in the body 32, 184, 216, 230, 319

**menstrual cramps** spasmodic contractions of the uterus, such as those occurring during menstruation, usually causing pain in the abdomen that may radiate to the lower back and thighs 14, 25, 119, 162, 164, 206, 208, 209, 217, 254, 257, 258, 445, 447

**menstruation** the periodic discharge from the vagina of blood and tissues from a nonpregnant uterus 17, 24, 115, 156, 164, 166, 206, 209, 255, 272, 273, 275, 277–279, 386, 415

**meta-analysis** a statistical technique for combining the findings from independent studies 86, 143, 420, 434–437, 439, 440, 442

**metastasis** transmission of pathogenic microorganisms or cancerous cells from an original site to one or more sites elsewhere in the body, usually by way of the blood vessels or lymphatics 81, 138, 139

**meteorism** drumlike distention of the abdomen due to air or gas in the intestine or peritoneal cavity 373

**methylxanthines** a chemical group of drugs derived from xanthine (a purine derivative); members of the group include theophylline, caffeine, and theobromine 80, 138

**MIC** the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation 127, 382, 475

**microscopically** Too small to be seen without a microscope 66, 186

**mitogenic** stimulating cell division, which division is known as "mitosis" 100

**mucilaginous** resembling mucilage; that is, adhesive, viscid, sticky 66, 291

**multicentre trial** controlled studies which are planned and carried out by several cooperating institutions to assess certain variables and outcomes in specific patient populations 342, 344, 350

**murine** pertaining to or affecting mice or rats 280, 281, 285, 339

**mutagenic** a mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level 98, 107, 130, 131, 153, 159, 263, 334, 379, 387, 444

**N**

**nephrolithiasis** kidney stones 233, 236, 237
**nephroprotective** has the ability to prevent damage to the kidneys 113
**nervine** acting on or relieving disorders of the nerves 137, 213, 245, 300
**neurodermatitis** Neurodermatitis is a chronic skin condition in which the skin becomes inflamed and is extremely itchy 13, 191
**neurotoxic** poisonous or destructive to nerve tissue 209, 386, 413
**neurovegetative** relating to the vegetative (autonomic) nervous system 167
**no-effect dosage** the amount of the drug that has no effect on the test animal over a specified period of time 444
**No-Observed Effects Level** An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control 332
**nutritive** of or relating to nutrition 64, 415

**O**

**observational study** it draws a conclusion by comparing subjects against a control group 145
**oestrogen receptor (ER) binding assays** A laboratory test to determine the presence of a protein found on cells of female reproductive tissue, some other tissues in the body, and some cancer cells. The hormone estrogen will attach (bind) to the receptors inside the cells and may cause the cells to grow 186
**oestrogenic** having the properties of, or properties similar to, an oestrogen 51, 52, 54, 63, 79, 88, 106, 119, 125, 129–131, 145, 150, 164, 165, 170, 171, 181, 185–187, 222, 255, 259, 278, 301, 302, 307, 316, 320, 322, 326, 357, 382–384, 392, 398, 399, 403, 405, 434, 435, 438, 441, 448, 450
**oestrogenic properties** have weak female hormone-like (oestrogenic) properties 57
**open study** a study with no exclusion criteria 105
**open-label studies** when both the researcher and the participant know the treatment the participant is receiving 89, 146
**outcome** A specific endpoint measured in a clinical trial. Examples include weight loss, cholesterol levels, severe toxicity, worsening of disease, and death 29, 33, 73, 181, 184, 196, 231, 342, 352, 360, 430, 435, 439, 442
**ovariectomized** To remove one or both ovaries (the female reproductive organs in which eggs are made and stored) 129, 170, 173, 175, 187
**oxalate** a salt of oxalic acid 228, 229, 234, 236, 237, 242, 286
**oxidation** a chemical process that can damage cells 194, 232, 301, 358, 364
**oxytocic** causing the stimulation of the involuntary muscle of the uterus 64

**P**

**peer-reviewed journals** A scholarly or scientific publication in which an article is reviewed by a board of experts before it is published. The board members determine the accuracy of the article and approve or reject it 32, 181

**perimenopausal** Referring to a period of a woman's life, age 45 to 55-ish, in which menstrual periods become irregular; perimenopause is immediately before, during and after menopause 185, 186, 384, 392, 394, 395, 437, 438

**phagocytic** causing waste material to be engulfed and absorbed, also harmful microorganisms, or other foreign bodies in the bloodstream and tissues to be absorbed 104, 137

**pharmacokinetics** involves the relationship between the dose of the drug and the concentration (amount) of the drug in the body. Pharmacokinetics observes how drug move around the body. The four key steps involved are - absorption, distribution, metabolism and elimination 89, 146, 169, 214, 328, 433

**photodermatitis** a form of allergic contact dermatitis in which the allergen must be activated by light to sensitise the allergic response, and to cause a rash or other systemic effects on subsequent exposure 263, 282, 283

**phthisis** a name for any disease that causes wasting of the body, but the term is especially applied to pulmonary tuberculosis 23, 402, 405

**physiological** relating to the action of a drug when given to a healthy person, as distinguished from its therapeutic action 80, 106, 138, 339, 351, 365

**phytoestrogens** Compounds found in plants that can mimic the effects of oestrogen in the body (medical-dictionary, 2014) 51, 52, 54, 57–59, 62, 63, 161, 169, 174, 214, 275, 314, 315, 322, 381–387, 390, 392, 398, 399, 430–432, 434, 439, 442

**placebo** An inactive substance or treatment that has no effect on the body and that ideally looks, smells, and tastes the same as, and is given the same way as, the active drug or treatment being tested. The effects of the active substance or treatment are compared to the effects of the placebo 29, 33, 41, 86, 103, 104, 143, 145, 149, 156, 165, 171–174, 183, 184, 195–197, 205, 215, 231, 232, 255, 259, 340, 342, 343, 346, 361, 364, 382, 385, 393, 395, 410, 416, 417, 419–421, 439

**placebo group** a group that is given a placebo in a research study 103, 104, 184

**placebo-controlled** Refers to a method of studying a drug or dietary supplement in which a placebo (an inactive ingredient) is given to one group of participants, and the drug or dietary supplement being tested is given to a second group of participants. Results from the two groups are compared to see if the drug or dietary supplement being tested works better than the placebo 29, 41, 103, 104, 143, 171, 172, 183, 184, 186, 195, 259, 272, 280, 372, 384, 449

**plaques** accumulations of blood cells, fats, and other substances that may build up in blood vessels, possibly reducing or blocking blood flow 22, 390, 391, 394

**postpartum** the period beginning immediately after the birth of a child and extending for about six weeks 158

**postprandial** after eating 86, 295, 361, 373

**poultice** a soft moist mass, often heated and medicated, that is spread on cloth over the skin to treat an aching, inflamed, or painful part of the body 65, 159, 208, 227, 286, 291, 294, 299, 390, 406

**preparations** a mixture made for medicinal use 8, 34, 59, 66, 68, 80, 85, 90, 96, 103, 108, 110, 113, 115, 116, 122, 128, 132, 137, 138, 142, 149, 153, 163, 170, 172, 181, 188, 198, 202, 207, 214, 215, 246, 248, 249, 254, 256, 267, 284, 290, 294, 312, 314, 316, 319, 324, 332, 335, 344, 350, 351, 356, 360, 362, 391, 396, 409, 416, 431, 437, 440, 442, 448–452

**procarcinogen** a chemical substance that becomes a carcinogen only after it is altered by metabolic processes 157

**Profile of Mood States** a standard validated psychological test formulated by McNair in 1971 167

**prolactin** A hormone made by the pituitary gland (an organ located at the base of the brain) and important for making breast milk and in ovulation (the release of an egg from an ovary during the menstrual cycle) 65, 104, 170, 185, 213, 214, 219, 220, 224, 324, 347, 418

**proliferation** Multiplying or increasing in number. In biology, cell proliferation occurs by a process called cell division 85, 142, 186, 195, 232, 271, 319, 366, 367, 399, 449

**promyelocytic** A cell containing a few granules formed in the transition from myeloblast to myelocyte during the development of a granulocyte; it is the predominant cell type seen in granulocytic leukaemia 81, 139

**prophylactic** a preventative measure 86, 105, 135, 142

**prophylaxis** a measure taken to maintain health and prevent the spread of disease 246, 364

**prospective** under observation, following over a period of time 52, 190, 340, 362, 434

**prudent** wise, using good judgement 116, 175

**pruritus** intense chronic itching in the anal region 221, 372

**psychotropic** affecting mental activity, behavior, or perception 137, 338

## Q

**quality of life** the overall enjoyment of life, a sense of well-being, and the ability to carry out routine activities 41, 44, 144, 172, 184, 340, 362, 364, 396, 435

## R

**randomisation** Method analogous to tossing a coin to assign patients to treatment groups (the experimental treatment is assigned if the coin lands heads and a conventional, control or placebo treatment is given if the coin lands tails). Usually done by using a computer that generates a list of random numbers, which can then be used to generate a treatment allocation list 439

**randomised** When referring to an experiment or clinical trial, the process by which animal or human subjects are assigned by chance to separate groups that compare different treatments or other therapies. Randomization gives each participant an equal chance of being assigned to any of the groups 41, 103, 171, 172, 183, 184, 195–197, 237, 259, 272, 280, 289, 340, 341, 372, 384, 420, 435, 438, 439, 442, 449

**randomised controlled trials** studies in which people are allocated at random (by chance alone) to receive one of several clinical interventions 58, 421

**refrigerant** cooling, possessing the ability to reduce slight fever 228

**regulated** To govern, make uniform, and bring under the control of a rule, principle, or legal system. In the United States, the FDA has the authority to regulate dietary supplements 187

**relaxant** something that helps you to relax 113, 129, 168, 255, 264, 403, 405

**restorative** Tending or having the power to restore 105, 135, 246, 257

**retrospective data** the investigator collects data from past records and does not follow the patients up 340

**rhizomes** A horizontal stem that grows shallowly underground. At nodes along the rhizome, below-ground roots and above-ground shoots grow into new plants 163, 165, 169, 188

**rigorous** accurate, precise, and without deviation from standards 38, 39, 49, 149, 175, 182, 188, 247, 364

**risk** The chance or probability that a harmful event will occur. In health, for example, the chance that someone will develop a disease or condition 24, 27, 34, 39, 41, 51, 52, 54–56, 58, 63, 69, 79, 81, 90, 92, 94, 96, 98, 116, 139, 143, 145, 147, 149, 167, 171, 174, 176, 177, 180, 181, 196, 202, 203, 205, 219, 226, 229, 231, 232, 234–239, 242, 247, 262–267, 305, 312, 321, 326–328, 331–333, 346, 348, 352, 361, 363, 369, 370, 385, 386, 392, 394–396, 398, 399, 421, 425, 427, 430, 432, 434–438, 441–443, 450

## S

**safety data** Information about unwanted symptoms or diseases related to the use of drugs, medical devices, dietary supplements, food, and cosmetics 188

**saponins** any of a group of glycosides widely distributed in plants, which form a durable foam when their watery solutions are shaken, and which even in high dilutions dissolve erythrocytes 64, 67, 74, 78–80, 82, 99, 104, 134, 136–140, 169, 188, 193, 287–289, 295, 306, 308, 390, 447, 448

**scientific study** A method of gaining knowledge by making observations, proposing educated guesses (hypotheses) to explain the observations, and testing the hypotheses in ways that have reproducible results 188

**scirrhous** a hard slow-growing malignant tumour having a preponderance of fibrous tissue 338

**seborrheic dermatitis** Seborrheic dermatitis, or seborrhea, is a common skin disease that causes a red, itchy rash with white scales 13, 191, 200

**sedative** a drug that calms a patient, easing agitation and permitting sleep 22, 114, 156, 164, 168, 191, 198, 298–300, 302, 304, 337–339, 348, 349, 391, 397, 411, 415, 416

**selective toxicity** of antibiotics means that they must be highly effective against the microbe but have minimal or no toxicity to humans 65

**sex-hormone-binding globulin** A protein made by the liver that carries a male hormone (testosterone) and a female hormone (estradiol, a form of oestrogen) through the blood to body tissues. Oestrogen causes levels of SHBG to increase; testosterone causes levels of SHBG to decrease 185, 449

**significantly** In medicine, a mathematical measure of difference between two or more groups receiving different treatments that is greater than what might be expected to happen by chance alone 32, 58, 103, 129, 156, 165, 171, 184, 185, 208, 220, 282, 363, 365, 367, 369, 387, 392, 396

**single-blinded** describes a study in which either the investigator or the participant, but not both of them, is unaware of the nature of the treatment the participant is receiving 280

**sitz baths** a warm-water bath covering the hips and buttocks 220

**solution** A liquid in which another substance has been dissolved or mixed 41, 60, 75, 188, 280, 318, 324

**somnogenic** promoting sleep 137

**spasmolytic** having the ability to relieve spasms or convulsions 112, 405, 419

**squamous** A type of cell that covers the inside and outside surfaces of the body. Squamous cells are flat cells that look like fish scales under a microscope. They are found in tissues that form the surface of the skin, the lining of hollow organs (such as the uterus), and passages of the respiratory tract (nose, throat, windpipe, and lungs) and digestive tract (mouth, esophagus, and rectum) 187

**standardised** A process manufacturers may use to ensure batch-to-batch consistency of their products and to provide a measure of quality control. Dietary supplements are not required to be standardised in the United States. Some manufacturers use the term incorrectly or to mean different things and the presence of the word "standardised" on a supplement label does not necessarily indicate a level of product quality 31, 33, 39, 85, 88, 90, 91, 103, 104, 106, 142, 150, 153, 161, 163, 167, 170, 172, 188, 189, 224, 259, 267, 333, 346, 354, 358, 360, 362, 369, 372, 377, 378, 396, 397, 416, 426, 427

**statistical difference** A mathematical measure of variation between groups that is greater than what might be expected to happen by chance alone 183

**stepwise fashion** showing a gradual progression as if step by step 80, 138

**stimulant** temporarily increase alertness and energy 18, 20, 21, 25, 64, 76, 78, 89, 90, 128, 133, 135, 137, 145, 147, 149, 222, 245, 246, 264, 277, 278, 284, 292, 293, 329, 331, 339, 340, 359, 402, 447

**stomachic** serves to tone the stomach, improving its function and increasing appetite 13, 137, 207, 277, 287, 300, 338

**stomatic** relating to the mouth 113

**stomatitis** an inflammation of the lining of any of the soft-tissue structures of the mouth. Stomatitis is usually a painful condition, associated with redness, swelling, and occasional bleeding from the affected area 23, 124, 404, 405, 410

**sub-astringent** mildly astringent, causing contraction or arresting discharges 228

**subacute** This means that the symptom or illness is not yet chronic but has passed the acute phase 282, 379

**subchronic** Of intermediate duration, usually used to describe studies or periods of exposure lasting between 5 and 90 days 305

**substrates** a substrate is a drug that is metabolized by an enzyme system (Nursinglink, 2015) 240, 284, 330, 375, 376, 379, 398

**sympathomimetic-type** mimicking stimulation of the sympathetic nervous system 121

**synergistic** enhancing the effect of another force or agent 116, 171, 268, 363

**syrup** a concentrated sugar solution that contains medication 119, 212, 224, 284, 287, 293

**systematic literature review** provides a coherent, persuasive and updated synthesis of studies in a particular area of scientific inquiry. A critical consideration of studies is an integral part of the reviewing process. This would include an appropriate critique of methodological issues relating to the work reviewed, although these are discussed mainly with regard to the area of inquiry in general. Ultimately, systematic literature reviews should lead to new levels of understanding, conclusions and recommendations in the chosen area 238

**systematic review** collects and looks at multiple studies 58, 83, 141, 215, 231, 280, 289, 343, 346, 352, 393

**T**

**teratogenic** able to disturb the growth and development of an embryo or foetus 88, 98, 107, 131, 145, 153, 204, 285, 334, 444

**testosteromimetic** mimics the action of testosterone 246

**THC** tetrahydrocannabinol, see THC - Tetrahydrocannabinol for further specific information 335–341, 343–348, 350–352, 475

**thelarche** the onset of secondary (postnatal) breast development 283

**therapeutic index** The ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment. The larger the therapeutic index, the safer the drug is 34, 116, 374

**thymoleptic** having the ability to modify a patient's mood 246

**time-dependent** the time that serum concentrations remain above the MIC during the dosing interval 382, 386

**tincture** an alcohol or water-alcohol solution, usually referring to a preparation from herbal materials 59, 60, 63, 91, 116–118, 159, 161, 188, 189, 205, 211, 224, 245, 256, 268, 284, 333, 350, 358, 377, 396, 397, 402–404, 409, 412, 426, 452

**tissues** A group or layer of cells in a living organism that work together to perform a specific function 36, 37, 47, 63, 83, 134, 140, 186, 194, 332, 344, 383, 392, 408, 418

**tonic** patent medicine that claims to have tonic properties 22, 24, 25, 64, 76, 78, 108, 113, 135, 137, 163, 198, 213, 243–245, 254, 255, 261, 299, 300, 324, 338, 391, 402–404, 415, 447

**toxic** capable of causing death or serious debilitation 34, 36, 41, 50, 67, 68, 74, 98, 105, 109, 116, 121, 125, 129–131, 135, 153, 166, 176, 182, 189, 193, 195, 203, 222, 225, 247, 248, 256, 263, 264, 270, 276, 278, 281, 285, 291, 296, 305, 310, 313, 328, 334, 340, 352, 355, 357, 360, 362–366, 368, 369, 373, 379, 387, 406, 411, 413, 427, 433, 442, 444, 450, 452, 455

**transplant** The replacement of tissue with tissue from the person's own body or from another person 69, 73, 147, 181, 336, 345

**tumour load** Refers to the number of cancer cells, the size of a tumour, or the amount of cancer in the body 99

**U**

**uncontrolled study** A clinical study that lacks a comparison (i.e., a control) group 88

**unguent** a soothing preparation spread on wounds, etc 338

**upregulate** to increase the responsiveness of a cell or organ to a stimulus 303

**urethra** the organ that carries the urine out of the bladder and outside your body 16, 229, 231, 244, 246, 415, 417, 419, 421

**uterine stimulant** having the ability to cause, or increase the frequency and intensity of, uterine contractions 113

**V**

**vasodilator** causing dilation of blood vessels 101, 228, 232

**vasomotor symptoms** having to do with the narrowing and widening of blood vessels 24, 48, 58, 172, 173, 175, 188, 432, 435, 438, 439

**vermifuge** an agent that destroys or expels parasitic worms 207, 213, 300, 403, 405

**vesiculation** blistering 124

**viral load** the term used to describe the amount of virus in a body fluid 362, 363

**W**

**well-being** The state of feeling healthy, happy, and content. Well-being is affected by things such as physical and mental health, income, education, social support, attitude, values, stress, security, and other qualities of life 11, 27, 136, 144, 145, 171, 184

# Acronyms

**A**
**ACE** angiotensin converting enzyme 146, 328
**ACOG** American College of Obstetricians and Gynaecologists 173
**ALP** alkaline phosphatase 282
**ALT** alanineaminotransferase 282, 365, 372
**AST** aspartateaminotransferase 282, 365

**B**
**BMD** bone mineral density 396, 440
**BPH** benign prostatic hyperplasia 14, 22, 24, 218, 235, 390, 391, 396, 414, 415, 417–422, 424, 426, 427
**bw** body weight 128–132, 444

**C**
**CAHC** complementary and alternative health care 28
**CAM** complementary and alternative medicine 26–28, 32–35, 40
**CHD** Coronary Heart Disease 308
**CHF** Congestive Heart Failure 325
**CNS** Central Nervous System 79, 83, 140, 336, 340, 348, 349

**D**
**DGL** deglycyrrhizinated liquorice 320, 321, 332, 333
**DHT** dihydrotestosterone 417–420

**F**
**FDA** Food and Drug Administration 8, 32, 34, 37–39, 41, 42, 55, 56, 68, 69, 187, 205, 219, 305, 335, 336, 341, 346, 347, 349, 354, 411, 429

**G**
**GABA** gamma-aminobutyric acid 140, 141, 260
**GLA** gamma-linolenic acid 192–196, 198, 204, 205, 301

**H**
**HIV** human immunodeficiency virus 76, 142, 169, 175, 262, 314, 340, 343, 344, 351
**HRT** Hormone Replacement Therapy 52, 59, 167, 169, 171, 173, 215, 255, 439

**I**

**IV** intravenous 308–310, 318, 319, 323, 324, 328, 344, 368, 369, 444

**L**

**LD-50** oral lethal dose, 50% 125, 132, 269, 278, 285, 296, 339, 388

**M**

**mg** A measure of weight. It is a metric unit of mass equal to 0.001 gram (it weighs 28,000 times less than an ounce) 68, 74, 89, 91, 125, 128–132, 143, 145, 158, 167, 172, 180, 183–186, 188, 189, 204, 211, 224, 228, 237, 241, 267–271, 274, 279, 281, 282, 285, 290, 291, 294, 304–306, 309, 319, 321, 322, 328, 332, 333, 339–341, 343, 344, 350, 355, 365, 366, 372, 373, 377, 378, 383–385, 387, 388, 394, 396–399, 403, 407, 412, 413, 420, 421, 426, 427, 431, 435, 441–444

**N**

**NF** nuclear factor 128

**NSAID** Nonsteroidal anti-inflammatory drugs 204

**O**

**OTC** over-the-counter 55, 56, 245, 319

**P**

**PMDD** Premenstrual Dysphoric Disorder 216, 224

**PMS** Premenstrual Syndrome 12–14, 17, 22, 64, 119, 164, 165, 167, 168, 175, 191, 198–200, 215–220, 224, 254, 255, 258, 286, 292, 322, 390–392

**PSA** Prostate-specific antigen 370, 396, 418, 421, 435

**S**

**SHBG** see sex-hormone-binding globulin 442

**SLE** systemic lupus erythematosus 19, 69, 73, 74, 317, 318, 320, 386

**T**

**TNF** tumour necrosis factor 128

**U**

**UTI** urinary tract infection 15, 16, 38, 198, 226–231, 234–237, 240, 241, 244, 250, 336, 337, 446

**V**

**V/V** its concentration in volume/volume percent 224

# Bibliography


[ABC, 2000] ABC (2000). *Herbal Medicine: Expanded Commission E Monographs*. American Botanical Council. URL: http://cms.herbalgram.org/expandedE/index.html?ts=1432822161&signature=e8bca9e2f86583bcde73692bb2599af2&ts=1432824272&signature=855d8d76f14fc66826e62876c0589907 (cit. on pp. 9, 112, 114–115).

[ACOG, 2001] ACOG, ed. (2001). *ACOG Practice Bulletin. Use of botanicals for management of menopausal symptoms.* 28. American College of Obstetricians and Gynecologists, pp. 1–11 (cit. on p. 184).

[Adams et al., 2006] L. S. Adams et al. (2006). "Analysis of the interactions of botanical extract combinations against the viability of prostate cancer cell lines". *Evidence-Based Complementary and Alternative Medicine* 3.1, pp. 117–124 (cit. on p. 319).

[Adamska and Lutomski, 1971] M. Adamska and J. Lutomski (1971). "C-flavonoid glycosides in the seeds of Trigonella foenum graecum [in German]". *Planta Medica* 20, pp. 224–229 (cit. on p. 288).

[Administration, 2007] Therapeutic Goods Administration (2007). *Black cohosh (Cimicifuga racemosa): new labelling requirements and consumer information for medicines containing black cohosh*. Woden, Australia: Department of Health and Ageing (cit. on p. 176).

[R. Agarwal, C. Agarwal, et al., 2006] R. Agarwal, C. Agarwal, et al. (2006). "Anticancer potential of silymarin: from bench to bed side". *Anticancer Research* 26.6B, pp. 4457–4498 (cit. on p. 360).

[R. Agarwal, S. K. Gupta, et al., 2008] R. Agarwal, S. K. Gupta, et al. (2008). "Oculohypotensive effects of Foeniculum vulgare in experimental models of glaucoma". *Indian Journal of Physiology and Pharmacology* 52.1, pp. 72–83 (cit. on p. 280).

[E. M. Agency, 2006] European Medicines Agency (2006). *EMEA public statement on herbal medicinal products containing Cimicifugae racemosae rhizoma (black cohosh, root) - serious hepatic reactions*. London, UK: European Medicines Agency (cit. on p. 176).

[T. Agency, 2006] The Agency (2006). *Black cohosh (Cimicifuga racemosa) - risk of liver problems*. London, UK: Medicines and Healthcare products Regulatory Agency (cit. on p. 176).

[Aggarwal et al., 2008] B. B. Aggarwal et al. (2008). "Potential of spice-derived phytochemicals for cancer prevention". *Planta Medica* 74.13, pp. 1560–1569 (cit. on p. 280).

[Aherne, Kerry, and O'Brien, 2007] S. A. Aherne, J. P. Kerry, and N. M. O'Brien (2007). "Effects of plant extracts on antioxidant status and oxidant-induced stress in Caco-2 cells". *British Journal of Nutrition* 97.2, pp. 321–328 (cit. on pp. 408, 413).

[B. Ahmad et al., 2010] B. Ahmad et al. (2010). "Anti-inflammatory and enzyme inhibitory activities of a crude extract and a pterocarpan isolated from the aerial parts of Vitex agnus-castus". *Biotechnology Journal* 5.11, pp. 1207–1215 (cit. on pp. 213, 216).

[I. U. Ahmad, Forman, and Sarkar, 2010] I. U. Ahmad, J. D. Forman, and F. H. Sarkar (2010). "Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer". *Nutrition and Cancer* 62.7, pp. 996–1000 (cit. on p. 435).

[Ahuja, Kaack, and J. Roberts, 1998] S. Ahuja, B. Kaack, and J. Roberts (1998). "Loss of fimbrial adhesion with the addition of Vaccinium macrocarpon to the growth medium of P-fimbriated Escherichia coli". *Journal of Urology* 159.2, pp. 559–662 (cit. on p. 230).

[Ajabnoor and Tilmisany, 1988] M. A. Ajabnoor and A. K. Tilmisany (1988). "Effect of Trigonella foenum graceum on blood glucose levels in normal and alloxan-diabetic mice". *Journal of Ethnopharmacology* 22, pp. 45–49 (cit. on p. 289).

[Akhondzadeh and Abbasi, 2006] S. Akhondzadeh and S. H. Abbasi (2006). "Herbal medicine in the treatment of Alzheimer's disease". *American Journal of Alzheimer's Disease and Other Dementias* 21.2, pp. 113–118 (cit. on pp. 407, 410–411).

[Akhondzadeh, Noroozian, et al., 2003] S. Akhondzadeh, M. Noroozian, et al. (2003). "Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial". *Journal of Clinical Pharmacy and Therapeutics* 28.1, pp. 53–59 (cit. on pp. 407, 410, 412).

[Akita et al., 2003] H. Akita et al. (2003). "Maculopapular drug eruption due to the Japanese herbal medicine Kakkonto (kudzu or arrowroot decoction)". *Contact Dermatitis* 48.6, pp. 348–349 (cit. on p. 310).

[Albert-Puleo, 1980a] M. Albert-Puleo (1980a). "Fennel and anise as estrogenic agents". *Journal of Ethnopharmacology* 2, pp. 337–344 (cit. on pp. 121, 278).

[Albert-Puleo, 1980b] — (1980b). "Fennel and anise as estrogenic agents". *Journal of Ethnopharmacology* 2, pp. 337–344 (cit. on pp. 129, 132).

[Albrecht, H. Frerick, and Kuhn, 1992a] M. Albrecht, H. Frerick, and U. Kuhn (1992a). "Die Therapie toxischer Leberschaden mit Legalon". *Zeitschrift Fur Klinische Medizin-Zkm* 47, pp. 87–92 (cit. on p. 355).

[Albrecht, H. Frerick, and Kuhn, 1992b] — (1992b). "Die Therapie toxischer Leberschaden mit Legalon". *Zeitschrift Fur Klinische Medizin-Zkm* 47, pp. 87–92 (cit. on p. 364).

[Albuquerque, Sorenson, and Leal-Cardoso, 1995] A. A. Albuquerque, A. L. Sorenson, and J. H. Leal-Cardoso (1995). "Effects of essential oil of Croton zehntneri, and of anethole and estragole on skeletal muscles". *Journal of Ethnopharmacology* 49, pp. 41–49 (cit. on p. 128).

[Alekel, Van Loan, and Koehler, 2010] D. L. Alekel, M. D. Van Loan, and K. J. Koehler (2010). "The soy isoflavones for reducing bone loss (SIRBL) study: a 3-y randomized controlled trial in postmenopausal women". *American Journal of Clinical Nutrition* 91.1, pp. 218–230 (cit. on p. 440).

[Alves, S. M. Lima, and Silva, 2008] D. L. Alves, S. M. Lima, C. R. da Silva, et al. (2008). "Effects of Trifolium pratense and Cimicifuga racemosa on the endometrium of Wistar rats". *Maturitas* 61.4, pp. 364–370 (cit. on p. 170).

[A. S. Andrade, Hendrix, and T. L. Parsons, 2008] A. S. Andrade, C. Hendrix, and T. L. Parsons (2008). "Pharmacokinetic and metabolic effects of American ginseng (Panax quinquefolius) in healthy volunteers receiving the HIV protease inhibitor indinavir". *BMC Complementary and Alternative Medicine* 8.50 (cit. on pp. 89, 146).

[E. d. Andrade, Mesquita, and Claro Jde, 2007] E. de Andrade, A. A. de Mesquita, and A. Claro Jde (2007). "Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction". *Asian Journal of Andrology* 9.2, pp. 241–244 (cit. on pp. 84, 141).

[R. J. Andrade, Lucena, and De la Cruz, 1998a] R. J. Andrade, M. I. Lucena, and J. P. De la Cruz (1998a). "Effects of silymarin on the oxidative stress in patients with alcoholic liver cirrhosis. Results from a controlled, double blind, randomized pilot clinical trial". *Hepatology* 28, 629a (cit. on p. 355).

[R. J. Andrade, Lucena, and De la Cruz, 1998b] — (1998b). "Effects of silymarin on the oxidative stress in patients with alcoholic liver cirrhosis. Results from a controlled, double blind, randomized pilot clinical trial". *Hepatology* 28, 629a (cit. on p. 364).

[Andrews, Rooyackers, and B. R. Walker, 2003] R. C. Andrews, O. Rooyackers, and B. R. Walker (2003). "Effects of the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes". *Journal of Clinical Endocrinology & Metabolism* 88.1, pp. 285–291 (cit. on p. 320).

[Anon, 1999] Anon (1999). "Adverse reaction: milk thistle-associated toxicity". *Nurse Drug Alert* 23, p. 51 (cit. on p. 355).

[Anthony, Clarkson, and J. K. Williams, 1998] M. S. Anthony, T. B. Clarkson, and J. K. Williams (1998). "Effects of soy isoflavones on atherosclerosis: potential mechanisms". *American Journal of Clinical Nutrition* 68.6 supplement, 1390s–1393S (cit. on p. 436).

[Arao, Udayama, Kinjo, and Nohara, 1998] T. Arao, M. Udayama, J. Kinjo, and T. Nohara (1998). "Preventive effects of saponins from the Pueraria lobata root on in vitro immunological liver injury of rat primary hepatocyte cultures". *Planta Medica* 64.15, pp. 413–416 (cit. on p. 308).

[Arao, Udayama, Kinjo, Nohara, et al., 1997] T. Arao, M. Udayama, J. Kinjo, T. Nohara, et al. (1997). "Preventive effects of saponins from Puerariae radix (the root of Pueraria lobata Ohwi) on in vitro immunological injury of rat primary hepatocyte cultures". *Biological and Pharmaceutical Bulletin* 20.9, pp. 988–991 (cit. on p. 308).

[Arao et al., 1995] T. Arao et al. (1995). "Oleanene-type triterpene glycosides from Puerariae radix . II. Isolation of saponins and the application of tandem mass spectrometry to their structure determination". *Chemical and Pharmaceutical Bulletin* 43.7, pp. 1176–1179 (cit. on pp. 202, 306).

[Arao et al., 1997] — (1997). "Oleanene-type triterpene glycosides from Puerariae radix . IV. Six new saponins from Pueraria lobata". *Chemical and Pharmaceutical Bulletin* 45.2, pp. 362–366 (cit. on pp. 283, 306).

[Arimanini, Mattarello, and Fiore, 2004] D. Arimanini, M. J. Mattarello, and C. Fiore (2004). "Licorice reduces serum testosterone in healthy women". *Steroids* 69.11-12, pp. 763–766 (cit. on p. 320).

[Arimoto-Kobayashi et al., 1999] S. Arimoto-Kobayashi et al. (1999). "Inhibitory effects of beer and other alcoholic beverages on mutagenesis and DNA adduct formation induced by several carcinogens". *Journal of Agricultural and Food Chemistry* 47, pp. 221–230 (cit. on p. 303).

[Armanini, Castello, and Scaroni, 2007] D. Armanini, R. Castello, and C. Scaroni (2007). "Treatment of polycystic ovary syndrome with spironolactone plus licorice". *European Journal of Obstetrics & Gynecology and Reproductive Biology* 131.1, pp. 61–67 (cit. on p. 320).

[Association, 2010] American Medical Association (2010). *Use of cannabis for medicinal purposes*. Report 3. Council on Science and Public Health. URL: http://www.ama-assn.org/ama1/pub/upload/mm/443/csaph-report3-i09.pdf (cit. on p. 340).

[C. Atkinson, Compston, et al., 2004] C. Atkinson, J. E. Compston, et al. (2004). "The effects of phytoestrogen isoflavones on bone density in women: a double-blind randomized, placebo-controlled trial". *American Journal of Clinical Nutrition* 79, pp. 326–333 (cit. on p. 395).

[C. Atkinson, Oosthuizen, et al., 2004] C. Atkinson, W. Oosthuizen, et al. (2004). "Modest protective effects of isolflavones from red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49-65 year-old women". *Journal of Nutrition* 134, pp. 1759–1764 (cit. on p. 394).

[C. Atkinson, Warren, and Sala, 2004] C. Atkinson, R. M. Warren, and E. Sala (2004). "Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]". *Breast Cancer Research* 6, R170–179 (cit. on p. 399).

[Atmaca, Kumru, and Tezcan, 2003] M. Atmaca, S. Kumru, and E. Tezcan (2003). "Fluoxetine versus Vitex agnus castus extract in the treatment of premenstrual dysphoric disorder". *Human Psychopharmacology* 18.3, pp. 191–195 (cit. on p. 215).

[Attele, J. A. Wu, and C. S. Yuan, 1999] A. S. Attele, J. A. Wu, and C. S. Yuan (1999). "Ginseng pharmacology, multiple constituents and multiple actions". *Biochemical Pharmacology* 58.11, pp. 1685–1693 (cit. on pp. 83, 85, 140, 142).

[Avakian, 1984] E. V. Avakian (1984). "Effect of Panax ginseng on energy metabolism during exercise in rats". *Planta Medica* 50, pp. 151–154 (cit. on pp. 100–101).

[Avula et al., 2009] B. Avula et al. (2009). "Quantitative determination of triterpenoids and formononetin in rhizomes of black cohosh ( Actaea racemosa ) and dietary supplements by using UPLC-UV/ELS detection and identification by UPLC-MS". *Planta Medica* 75.4, pp. 381–386 (cit. on p. 169).

[Awang, 1990] D. V. C. Awang (1990). "Herbal medicine borage". *Canadian Pharmacists Journal* 123, pp. 121–126 (cit. on p. 192).

[Baba, Matsuyama, and Kozama, 1982] K. Baba, Y. Matsuyama, and M. Kozama (1982). "Studies on coumarins from the root of Angelica pubescens Maxim. IV. Structures of angelol-type prenylcoumarins". *Chemical and Pharmaceutical Bulletin* 30.6, pp. 2025–2035 (cit. on p. 257).

[Bach, 1996] D. Bach (1996). "Long-term drug treatment of benign prostatic hyperplasia. Results of a prospective 3-year multicenter study using Sabal extract IDS 89". *Phytomedicine* 3, p. 105 (cit. on p. 419).

[Baek, E, and Jun, 2003] D. H. Baek, S. J. E, and G. C. Jun (2003). "Composition comprising alcohol extract of pueraria sp. Roots [in Korean]". *Kongkae Taeho Kongbo*. US patent application KR 2003-089396 (cit. on p. 382).

[Bahrke and W. R. Morgan, 2000] M. S. Bahrke and W. R. Morgan (2000). "Evaluation of the ergogenic properties of ginseng: an update". *Sports Medicine* 29.2, pp. 113–133 (cit. on pp. 83, 140).

[Bailly et al., 2005] F. Bailly et al. (2005). "Synthesis and HIV-1 integrase inhibitory activities of caffeic acid dimers derived from Salvia officinalis". *Bioorganic & Medicinal Chemistry Letters* 15.22, pp. 5053–5056 (cit. on p. 408).

[Baker and Pryce, 2003a] D. Baker and G. Pryce (2003a). "The therapeutic potential of cannabis in multiple sclerosis". *Expert Opinion on Investigational Drugs* 12.4, pp. 561–567 (cit. on p. 342).

[Baker and Pryce, 2003b] — (2003b). "The therapeutic potential of cannabis in multiple sclerosis". *Expert Opinion on Investigational Drugs* 12.4, pp. 561–567 (cit. on p. 342).

[Baker, Pryce, et al., 2003] D. Baker, G. Pryce, et al. (2003). "The therapeutic potential of cannabis". *The Lancet Neurology* 2.5, pp. 291–298 (cit. on pp. 338, 340, 342–343).

[Balentine, 2015] J. R. Balentine (2015). *Sage*. MedicineNet. URL: http://www.medicinenet.com/script/main/mobileart.asp?articlekey=45495 (cit. on p. 412).

[Bamford, 2013] J. T. M. Bamford (2013). *Oral evening primrose oil and borage oil for eczema*. Cochrane Database of Systematic Reviews. Version Issue 4. Cochrane Database. DOI: 10.1002/14651858 (cit. on p. 205).

[Bamforth, 1998] C. W. Bamforth (1998). *Beer: tap into the art and science of brewing*. Plenum Press, p. 245. ISBN: 0-306-45797-0 (cit. on p. 299).

[Bandoniene and Murkovic, 2002] D. Bandoniene and M. Murkovic (2002). "The detection of radical scavenging compounds in crude extract of borage ( Borago officinalis L.) by using an on-line HPLC-DPPH method". *Journal of Biochemical and Biophysical Methods* 53, pp. 45–49 (cit. on p. 193).

[Banerjee and Izquierdo, 1982] U. Banerjee and J. A. Izquierdo (1982). "Anti-stress and antifatigue properties of Panax ginseng: Comparison with piracetam". *Acta Physiologica, Pharmacologica et Therapeutica Latinoamericana* 32, pp. 277–285 (cit. on p. 100).

[Bar-El, 2010] D. S. Bar-El (2010). "Soy as an endocrine disruptor: cause for caution?" *Journal of Pediatric Endocrinololgy Metabolism* 23.9, pp. 855–61 (cit. on p. 52).

[Bari et al., 2006] M. Bari et al. (2006). "New insights into endocannabinoid degradation and its therapeutic potential". *Mini Reviews in Medicinal Chemistry* 6.3, pp. 257–268 (cit. on p. 340).

[Baricevic, Sosa, and Della Loggia, 2001] D. Baricevic, S. Sosa, and R. Della Loggia (2001). "Topical anti-inflammatory activity of Salvia officinalis L. leaves: the relevance of ursolic acid". *Journal of Ethnopharmacology* 75.2-3, pp. 125–132 (cit. on p. 408).

[Barnes et al., 1998] S. Barnes et al. (1998). "HPLC-mass spectrometry analysis of isoflavones". *Proceedings of the Society for Experimental Biology and Medicine* 217.3, pp. 254–262 (cit. on p. 432).

[Barre and Holub, 1992] D. E. Barre and B. J. Holub (1992). "The effect of borage oil consumption on the composition of individual phospholipids in human platelets". *Lipids* 27, pp. 315–320 (cit. on p. 195).

[B. Barrett and D. J. Brown, 2007] B. Barrett and D. J. Brown (2007). *Proprietary Phytomedicinal Product Therapeutic Monograph. CVT-E002 ( Cold-fX ).* Austin, TX: American Botanical Council (cit. on pp. 88, 150).

[Bartley et al., 1981] G. B. Bartley et al. (1981). "Maple-syrup urine odor due to fenugreek ingestion". *New England Journal of Medicine* 305, p. 467 (cit. on p. 293).

[Barton, Soori, and B. A. Bauer, 2010] D. L. Barton, G. S. Soori, and B. A. Bauer (2010). "Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation. NCCTG trial N03CA". *Support Care Cancer* 18.2, pp. 179–187 (cit. on pp. 81, 139).

[Basaga et al., 1997] H. Basaga et al. (1997). "Free radical scavenging and antioxidative properties of 'silibin' complexes on microsomal lipid peroxidation". *Cell Biochemistry and Function* 15, pp. 27–33 (cit. on p. 366).

[Bayne et al., 1999] C. Bayne et al. (1999). "Serenoa repens ( Permixon ): a 5-alpha reductase types I and II inhibitor-new evidence in a coculture model of BPH". *Prostate* 40.4, pp. 232–246 (cit. on p. 418).

[Beaton et al., 2010] L. K. Beaton et al. (2010). "Soy protein isolates of varying isoflavone content do not adversely affect semen quality in healthy young men". *Fertility and Sterility* 94.5, pp. 1717–1722 (cit. on p. 442).

[Beavers et al., 2010] K. M. Beavers et al. (2010). "The lipid-lowering effects of 4 weeks of daily soymilk or dairy milk ingestion in a postmenopausal female population". *Journal of Medicinal Food* 13.3, pp. 650–656 (cit. on p. 437).

[Bebenek et al., 2010] M. Bebenek et al. (2010). "Effect of exercise and Cimicifuga racemosa (CR BNO 1055) on bone mineral density, 10-year coronary heart disease risk, and menopausal complaints: the randomized controlled Training and Cimicifuga racemosa Erlangen (TRACE) study". *Menopause* 17.4, pp. 791–800 (cit. on p. 173).

[Beck et al., 2003] V. Beck et al. (2003). "Comparison of hormonal activity (estrogen, androgen and progestin) of standardized plant extracts for large scale use in hormone replacement therapy". *The Journal of Steroid Biochemistry and Molecular Biology* 74, pp. 259–268 (cit. on p. 399).

[Beckert et al., 2007] B. W. Beckert et al. (2007). "The effect of herbal medicines on platelet function: an in vivo experiment and review of the literature". *Plastic and Reconstructive Surgery* 120.7, pp. 2044–2050 (cit. on p. 423).

[Ben Hameda, Gajdoová, and Havel, 2006] A. Ben Hameda, D. Gajdoová, and J. Havel (2006). "Analysis of Salvia officinalis plant extracts by capillary electrophoresis". *Journal of Separation Science* 29.8, pp. 1188–1192 (cit. on p. 406).

[Bennett and Hicklin, 1998] B. C. Bennett and J. R. Hicklin (1998). "Uses of saw palmetto ( Serenoa repens , Arecaceae) in Florida". *Economic Botany* 52.4, pp. 381–393 (cit. on p. 414).

[Bent, Kane, and Shinohara, 2006] S. Bent, C. Kane, and K. Shinohara (2006). "Saw Palmetto for benign prostatic hyperplasia". *New England Journal of Medicine* 354.6, pp. 557–566 (cit. on p. 419).

[Beral, Bull, and Reeves, 2005] V. Beral, D. Bull, and G. Reeves (2005). "Endometrial cancer and hormone-replacement therapy in the Million Women Study". *Lancet* 365.9470, pp. 1543–1551 (cit. on p. 59).

[Berardesca et al., 2008] E. Berardesca et al. (2008). "Combined effects of silymarin and methylsulfonylmethane in the management of rosacea: clinical and instrumental evaluation". *Journal of Cosmetic Dermatology* 7.1, pp. 8–14 (cit. on p. 359).

[Bergendorff, Dekermendjian, and M. Nielsen, 1997] O. Bergendorff, K. Dekermendjian, and M. Nielsen (1997). "Furanocoumarins with affinity to brain benzodiazepine receptors in vitro". *Phytochemistry* 44.6, pp. 1121–1124 (cit. on p. 260).

[D. Berger et al., 2000] D. Berger et al. (2000). "Efficacy of Vitex agnus castus L. extract Ze 440 in patients with pre-menstrual syndrome (PMS)". *Archives of Gynecology and Obstetrics* 264.3, pp. 150–153 (cit. on p. 215).

[S. Berger, Junior, and Kopanski, 1988] S. Berger, P. Junior, and L. Kopanski (1988). "27-deoxyactein: a new polycyclic triterpenoid glycoside from Actaea racemosa". *Planta Medica* 54.6, pp. 579–580 (cit. on p. 168).

[Berges et al., 1995] R. Berges et al. (1995). "Randomised, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia". *Lancet* 345.8964, pp. 1529–1532 (cit. on p. 420).

[J. S. Berman, Symonds, and Birch, 2004] J. S. Berman, C. Symonds, and R. Birch (2004). "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial". *Pain* 112.3, pp. 299–306 (cit. on p. 344).

[Betz, L. Anderson, and Avigan, 2009] J. M. Betz, L. Anderson, M. I. Avigan, et al. (2009). "Black cohosh: considerations of safety and benefit". *Nutrition Today* 44.4, pp. 155–162 (cit. on p. 179).

[Beuscher, 1995] N. Beuscher (1995). "Cimicifuga racemosa L. Black Cohosh". *Z Phytotherapie* 16, pp. 301–310 (cit. on p. 167).

[Bhattacharyya, Fusar-Poli, and Borgwardt, 2009] S. Bhattacharyya, P. Fusar-Poli, and S. Borgwardt (2009). "Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis". *Archives of General Psychiatry* 66.4, pp. 442–451 (cit. on p. 344).

[BHP, 1983] BHP (1983). *British Herbal Pharmacopoeia*. Keighley, U.K: British Herbal Medicine Association (cit. on pp. 117–118).

[BHP, 1990] — (1990). *British Herbal Pharmacopoeia*. London: British Herbal Medicine Association (cit. on p. 108).

[BHP, 1996] — (1996). *British Herbal Pharmacopoeia*. Exeter, UK: British Herbal Medicine Association (cit. on pp. 109, 112, 130).

[Bialecka, 1997] M. Bialecka (1997). "The effect of bioflavonoids and lecithin on the course of experimental atherosclerosis in rabbits". *Annales Academiae Medicae Stetinensis* 43, pp. 41–56 (cit. on p. 365).

[Bielenberg, 1989] J. Bielenberg (1989). *Pharmazeutische Zeitung* 134.12, pp. 9–12 (cit. on p. 334).

[Bilgi et al., 2010] N. Bilgi et al. (2010). "Imatinib and Panax ginseng : a potential interaction resulting in liver toxicity". *Annals of Pharmacotherapy* 44.5, pp. 926–928 (cit. on pp. 89, 146).

[Biondo et al., 2008] P. D. Biondo et al. (2008). "A randomized controlled crossover trial of the effect of ginseng consumption on the immune response to moderate exercise in healthy sedentary men". *Applied Physiology, Nutrition, and Metabolism* 33.5, pp. 966–975 (cit. on pp. 85, 142).

[N. G. Bisset, 1994] N. G. Bisset (1994). *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL: CRC Press (cit. on p. 131).

[Blakesmith et al., 2003] S. J. Blakesmith et al. (2003). "Effects of supplementation with purified red clover ( Trifolium pratense ) isoflavones: on plasma lipids and insulin resistance in healthy premenopausal women". *British Journal of Nutrition* 89, pp. 467–474 (cit. on p. 394).

[Blatherwick, 1923] N. Blatherwick (1923). "Studies of urinary acidity II: The increased acidity produced by eating prunes and cranberries". *Journal of Biological Chemistry* 57, p. 815 (cit. on p. 230).

[Blázquez, Carracedo, and Salazar, 2008] C. Blázquez, A. Carracedo, and M. Salazar (2008). "Down-regulation of tissue inhibitor of metalloproteinases-1 in gliomas: a new marker of cannabinoid antitumoral activity?" *Neuropharmacology* 54.1, pp. 235–243 (cit. on p. 340).

[Bluck and Bingham, 1997] L. J. Bluck and S. A. Bingham (1997). "Isoflavone content of breast milk and soy formulas: benefits and risk". *Clinical Chemistry* 43.5, pp. 851–852 (cit. on p. 442).

[Blumenthal, 1997] M. Blumenthal (1997). *Popular Herbs in the U.S. Market*. Austin, TX: American Botanical Council. Chap. Ginseng root (Asian), pp. 37–38 (cit. on pp. 78, 136).

[Blumenthal, Busse, et al., 1998] M. Blumenthal, W. R. Busse, et al., eds. (1998). *The Complete German Commission E Monographs. Therapeutic Guide to Herbal Medicines*. Integrative Medicine Communications. Boston: American Botanical Council (cit. on pp. 117–118, 130, 132).

[Blumenthal, Goldberg, and Brinckmann, 2000] M. Blumenthal, A. Goldberg, and J. Brinckmann, eds. (2000). *Herbal Medicine: Expanded Commission E Monographs*. Newton, MA: Integrative Medicine Communications (cit. on pp. 214–215, 404, 408).

[Blumenthal, Gruenwald, et al., 1997] M. Blumenthal, J. Gruenwald, et al. (1997). *The Complete German Commission E Monographs: Therapeutic Monographs on Medicinal Plants for Human Use*. Austin, TX: American Botanical Council (cit. on pp. 80, 90, 138, 153).

[Bode, U. Schmidt, and Durr, 1977] J. C. Bode, U. Schmidt, and H. K. Durr (1977). "Silymarin for the treatment of acute viral hepatitis? Report of a controlled trial (author's transl)". *Medizinische Klinik* 72, pp. 513–518 (cit. on p. 367).

[Bodinet and Freudenstein, 2004] C. Bodinet and J. Freudenstein (2004). "Influence of marketed herbal menopause preparations on MCF -7 cell proliferation". *Menopause* 11, pp. 281–289 (cit. on p. 399).

[Bokemeyer et al., 1996] C. Bokemeyer et al. (1996). "Silibinin protects against cisplatin-induced nephrotoxicity without compromising cisplatin or ifosfamide anti-tumour activity". *British Journal of Cancer* 74, pp. 2036–2041 (cit. on p. 366).

[Bolaños, Del Castillo, and Francia, 2010] R. Bolaños, A. Del Castillo, and J. Francia (2010). "Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: systematic review and meta-analysis". *Menopause* 17.3, pp. 660–666 (cit. on p. 439).

[Bolca, Urpi-Sarda, and Blondeel, 2010] S. Bolca, M. Urpi-Sarda, and P. Blondeel (2010). "Disposition of soy isoflavones in normal human breast tissue". *American Journal of Clinical Nutrition* 91.4, pp. 976–984 (cit. on p. 434).

[Bombardelli, Cristoni, and Lietti, 1980] E. Bombardelli, A. Cristoni, and A. Lietti, eds. (1980). *The effect of acute and chronic ginseng saponins treatment on adrenals function: biochemistry and pharmacological aspects*. Proceedings of the third International Ginseng Symposium. Seoul: Korean Ginseng Research Institute, pp. 9–16 (cit. on p. 100).

[Booth, Nikolic, and Breeman, 2004] N. L. Booth, D. Nikolic, and R. B. van Breeman (2004). "Confusion regarding anticoagulant coumarins in dietary supplements". *Clinical Pharmacology & Toxicology* 76, pp. 511–516 (cit. on p. 398).

[Borrelli and Ernst, 2008a] F. Borrelli and E. Ernst (2008a). "Black cohosh (Cimicifuga racemosa): a systematic review of adverse events". *American Journal of Obstetrics & Gynecology* 199.5, pp. 455–466 (cit. on p. 190).

[Borrelli and Ernst, 2008b] — (2008b). "Black cohosh ( Cimicifuga racemosa ) for menopausal symptoms: a systematic review of its efficacy". *Pharmacological Research* 58.1, pp. 8–14 (cit. on p. 172).

[Borrelli, Izzo, and Ernst, 2003] F. Borrelli, A. A. Izzo, and E. Ernst (2003). "Pharmacological effects of Cimicifuga racemosa". *Life Sciences* 73.10, pp. 1215–1229 (cit. on p. 160).

[Borukh, Kirbaba, and Senchuk, 1972] I. F. Borukh, V. I. Kirbaba, and G. V. Senchuk (1972). "Antimicrobial properties of cranberry [in Russian]". *Voprosy Pitaniia* 31.5, p. 82 (cit. on p. 228).

[Boskabady and Ramazani-Assari, 2001] M. H. Boskabady and M. Ramazani-Assari (2001). "Relaxant effect of Pimpinella anisum on isolated guinea pig tracheal chains and its possible mechanism(s)". *Journal of Ethnopharmacology* 74, pp. 83–88 (cit. on p. 129).

[Boué, Wiese, and Nehls, 2003] S. M. Boué, T. E. Wiese, and S. Nehls (2003). "Evaluation of the estrogenic effects of legume extracts containing phytoestrogens". *Journal of Agricultural and Food Chemistry* 51.8, pp. 2183–2199 (cit. on pp. 167, 306–307).

[Bout-van den Beukel et al., 2006] C. J. van den Bout-van den Beukel et al. (2006). "Possible drug-metabolism interactions of medicinal herbs with antiretroviral agents". *Drug Metabolism Reviews* 38.3, pp. 477–514 (cit. on p. 374).

[Boyd, 1970] E. M. Boyd (1970). "A review of studies on the pharmacology of the expectorants and inhalants". *International Journal of Clinical Pharmacology* 3, pp. 55–60 (cit. on p. 129).

[Boyd and Pearson, 1946] E. M. Boyd and G. L. Pearson (1946). "On the expectorant action of volatile oils". *American Journal of the Medical Sciences* 211, pp. 602–610 (cit. on p. 129).

[Boyd and Sheppard, 1968] E. M. Boyd and E. P. Sheppard (1968). "Effect of steam inhalation of volatile oils on the output and composition of respiratory tract fluid". *Journal of Pharmacology and Experimental Therapeutics* 163, pp. 250–256 (cit. on p. 129).

[Boyd and Sheppard, 1970] — (1970). "Inhaled anisaldehyde and respiratory tract fluid". *Pharmacology* 3, pp. 345–352 (cit. on p. 129).

[Bozin et al., 2007] B. Bozin et al. (2007). "Antimicrobial and antioxidant properties of rosemary and sage ( Rosmarinus officinalis L. and Salvia officinalis L., Lamiaceae) essential oils". *Journal of Agricultural and Food Chemistry* 55.19, pp. 7879–7885 (cit. on pp. 405, 408).

[Bradley, 1992] P. R. Bradley, ed. (1992). *British Herbal Compendium*. Vol. 1. Guildford, UK: British Herbal Medicine Association, pp. 115–118 (cit. on pp. 105, 108).

[Braeckman et al., 1997a] J. Braeckman et al. (1997a). "Efficacy and safety of the extract of Serenoa repens in the treatment of benign prostatic hyperplasia: Therapeutic equivalence between twice and once daily dosage forms". *Phytotherapy Research* 11, p. 558 (cit. on p. 419).

[Braeckman et al., 1997b] — (1997b). "Efficacy and safety of the extract of Serenoa repens in the treatment of benign prostatic hyperplasia: therapeutic equivalence between twice and once daily dosage forms". *Phytotherapy Research* 11, pp. 558–563 (cit. on pp. 420, 426).

[Brandenburg, 1983] D. Brandenburg (1983). "Alfalfa of the family Leguminosae". *Journal of the American Medical Association* 249, pp. 3303–3304 (cit. on p. 75).

[Braun, 1997] R. Braun (1997). *Standardzulassungen für Fertigarzneimittel—Text and Kommentar*. Stuttgart, Germany: Deutscher Apotheker Verlag (cit. on pp. 111, 115, 117).

[Breastfeeding Medicine Protocol Committee, 2011] "ABM clinical protocol - number 9 - use of galactogogues in initiating or augmenting the rate of maternal milk secretion" (2011). Version 1st. *Breastfeeding Medicine* 6. Ed. by The Academy of Breastfeeding Medicine Protocol Committee, pp. 41–9 (cit. on p. 157).

[Breemen, W. Liang, and Banuvar, 2010] R. B. van Breemen, W. Liang, S. Banuvar, et al. (2010). "Pharmacokinetics of 23-epi-26-deoxyactein in women after oral administration of a standardized extract of black cohosh". *Clinical Pharmacology & Toxicology* 87.2, pp. 219–225 (cit. on p. 169).

[Breitman, Fonseca, and W. E. Ward, 2005] P. L. Breitman, D. Fonseca, and W. E. Ward (2005). "Combinations of soy protein and high dietary calcium on bone biomechanics and bone mineral density in ovariectomized rats". *Menopause* 12.4, pp. 428–435 (cit. on p. 439).

[Brekhman and Dardymov, 1969] I. I. Brekhman and I. V. Dardymov (1969). "Pharmacological investigation of glycosides from ginseng and Eleutherococcus". *Journal of Natural Products* 32, pp. 46–51 (cit. on p. 100).

[F. Brinker, 1996] F. Brinker (1996). "A comparative review of Eclectic female regulators". *Journal of Natural Medicines* 7, pp. 11–26 (cit. on p. 446).

[F. J. Brinker, 1998a] F. J. Brinker (1998a). *Herb Contraindications and Drug Interactions*. 2nd. Sandy, OR: Eclectic Medical Publications (cit. on p. 72).

[F. J. Brinker, 1998b] — (1998b). *Herb Contraindications and Drug Interactions*. 2nd. Sandy, OR: Eclectic Medical Publications (cit. on p. 202).

[F. J. Brinker, 1998c] — (1998c). *Herb Contraindications and Drug Interactions*. 2nd ed. Sandy, OR: Eclectic Medical Publications (cit. on p. 222).

[F. J. Brinker, 1998d] F. J. Brinker (1998d). *Herb Contraindications and Drug Interactions*. 2nd ed. Sandy, OR: Eclectic Medical Publications (cit. on p. 264).

[F. J. Brinker, 1998e] — (1998e). *Herb Contraindications and Drug Interactions*. 2nd ed. Sandy, OR: Eclectic Medical Publications (cit. on p. 283).

[Brinkley et al., 1981] L. Brinkley et al. (1981). "Bioavailability of oxalate in foods". *Urology* 17.6, pp. 534–538 (cit. on p. 237).

[Brosche and Platt, 2000] T. Brosche and D. Platt (2000). "Effect of borage oil consumption on fatty acid metabolism, transepidermal water loss and skin parameters in elderly people". *Archives of Gerontology and Geriatrics* 30, pp. 139–150 (cit. on p. 196).

[C. H. Brown, 2002] C. H. Brown (2002). *Overview of drug interactions*. URL: http://uspharmacist.com/oldformat.asp?url=newlook/files/feat/mar00druginteractionshtml (cit. on p. 72).

[D. J. Brown, 1994] D. J. Brown (1994). "Herbal research review: Vitex agnus castus clinical monograph". *Quarterly Review of Natural Medicine* (Summer), pp. 111–121 (cit. on p. 222).

[Bruneton, 1995a] J. Bruneton (1995a). *Pharmacognosy, Phytochemistry, Medicinal Plants*. Paris, France: Lavoisier Publishing (cit. on p. 111).

[Bruneton, 1995b] — (1995b). *Pharmacognosy, Phytochemistry, Medicinal Plants*. Paris: Lavoisier Publishing (cit. on p. 306).

[Bruneton, 1995c] — (1995c). *Pharmacognosy, phytochemistry, medicinal plants*. Paris: Lavoisier (cit. on pp. 99, 105).

[Bucci, 2000] R. Bucci L (2000). "Selected herbals and human exercise performance". *American Journal of Clinical Nutrition* 72.2, 624S–636S (cit. on pp. 85, 142).

[Buchi and Jenny, 1984] K. Buchi and E. Jenny (1984). "On the interference of the standardized ginseng extract G115 and pure ginsenosides with agonists of the progesterone receptor of the human myometrium". *Phytopharm*, pp. 1–6 (cit. on p. 106).

[Buchner, 1842] L. Buchner (1842). "Justus Liebigs". *European Journal of Organic Chemistry* 42, p. 226. Previously known as 'Ann Chem' (cit. on p. 112).

[P. Buck, 1899] P. Buck (1899). "Un nouveau remède spécifique contre la dysmenorrhée: leumenol". *Belgique Médicale* 2, pp. 363–365 (cit. on pp. 272–273).

[Budavari, 1996] S. Budavari, ed. (1996). *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*. 12th ed. Whitehouse Station, N.J: Merck & Co, Inc, p. 109 (cit. on pp. 108, 111–112).

[Buggy et al., 2003] D. J. Buggy et al. (2003). "Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain". *Pain* 106.1-2, pp. 169–172 (cit. on p. 343).

[Bukowiecki and Michalska, 1972] H. Bukowiecki and Z. Michalska (1972). "Anatomical studies of the vegetable organs of Actaea L. genus". *Acta Poloniae Pharmaceutica* 29.4, pp. 432–438 (cit. on p. 175).

[Burke, Olson, and Cusack, 2002] B. E. Burke, R. D. Olson, and B. J. Cusack (2002). "Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine". *Biomedicine & Pharmacotherapy* 56.6, pp. 283–288 (cit. on pp. 258, 267).

[Burkhardt et al., 1986] G. Burkhardt et al. (1986). "Terpene hydrocarbons in Pimpinella anisum". *Pharmaceutisch Weekblad Scientific* 8, pp. 190–193 (cit. on p. 121).

[Burstein et al., 2004] S. H. Burstein et al. (2004). "Ajulemic acid: A novel cannabinoid produces analgesia without a high." *Life Sciences* 75.12, pp. 1513–1522 (cit. on pp. 338, 343).

[Busby, Jeffcoat, and Bloedon, 2002] M. G. Busby, A. R. Jeffcoat, and L. T. Bloedon (2002). "Clinical characteristics and pharmacokinetics of purified soy isoflavones: single-dose administration to healthy men". *American Journal of Clinical Nutrition* 75, pp. 126–136 (cit. on p. 399).

[Buttery and L. C. Ling, 1967] R. G. Buttery and L. C. Ling (1967). "Identification of hop varieties by gas chromatographic analysis of their essential oils". *Journal of Agricultural and Food Chemistry* 15.3, pp. 531–535 (cit. on p. 301).

[Caldwell and J. D. Sutton, 1988] J. Caldwell and J. D. Sutton (1988). "Influence of dose size on the disposition of trans-[methoxy-14C] anethole in human volunteers". *Food and Chemical Toxicology* 26, pp. 87–91 (cit. on p. 127).

[Cambria-Kiely, 2002] J. A. Cambria-Kiely (2002). "Effect of soy milk on warfarin efficacy". *Annals of Pharmacotherapy* 36.12, pp. 1893–1896 (cit. on p. 443).

[S. C. Campbell et al., 2010] S. C. Campbell et al. (2010). "One-year soy protein supplementation does not improve lipid profile in postmenopausal women". *Menopause* 17.3, pp. 587–593 (cit. on p. 437).

[Campos, Garrido, and Guerra, 1989a] R. Campos, A. Garrido, and R. Guerra (1989a). "Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver". *Planta Medica* 55, pp. 417–419 (cit. on p. 355).

[Campos, Garrido, and Guerra, 1989b] — (1989b). "Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver". *Planta Medica* 55, pp. 417–419 (cit. on pp. 364, 366).

[Canada, 2006] Health Canada (2006). "Health Canada is advising consumers about a possible link between black cohosh and liver damage". *Health Canada*. Ottowa, Ontario (cit. on p. 177).

[Canada, 2007] Health Canada (2007). "Black cohosh [fact sheet]". *Health Canada*. Ottowa, Ontario (cit. on p. 177).

[Canada, 2009] — (2009). "Black cohosh [monograph]". *Health Canada* (cit. on p. 179).

[Capek, 2008] P. Capek (2008). "An arabinogalactan containing 3-O-methyl-D-galactose residues isolated from the aerial parts of Salvia officinalis L." *Carbohydrate Research* 343.8, pp. 1390–1393 (cit. on p. 406).

[Capek and Hríbalová, 2004] P. Capek and V. Hríbalová (2004). "Water-soluble polysaccharides from Salvia officinalis L. possessing immunomodulatory activity". *Phytochemistry* 65.13, pp. 1983–1992 (cit. on p. 406).

[Capek, Hribalova, et al., 2003] P. Capek, V. Hribalova, et al. (2003). "Characterization of immunomodulatory polysaccharides from Salvia officinalis L". *International Journal of Biological Macromolecules* 33.1-3, pp. 113–119 (cit. on p. 405).

[Capek, Machová, and Turjan, 2009] P. Capek, E. Machová, and J. Turjan (2009). "Scavenging and antioxidant activities of immunomodulating polysaccharides isolated from Salvia officinalis". 44. *L. Int J Biol Macromol*. Ed. by 1, pp. 75–80 (cit. on p. 408).

[Carducci et al., 1996] R. Carducci et al. (1996). "Silibinin and acute poisoning with Amanita phalloides". *Minerva Anestesiologica* 62, pp. 187–193 (cit. on pp. 366–367).

[A. R. Carmichael, 2008] A. R. Carmichael (2008). "Can Vitex agnus castus be used for the treatment of mastalgia? What is the current evidence?" *Evidence-Based Complementary and Alternative Medicine* 5.3, pp. 247–250 (cit. on pp. 214, 216).

[Carmignani et al., 2010] L. O. Carmignani et al. (2010). "The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: a randomized controlled trial". *Maturitas* 67.3, pp. 262–269 (cit. on p. 439).

[C. B. Carroll, Bain, and Teare, 2004] C. B. Carroll, P. G. Bain, and L. Teare (2004). "Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study". *Neurology* 63.7, pp. 1245–1250 (cit. on p. 344).

[D. G. Carroll, 2006] D. G. Carroll (2006). "Nonhormonal therapies for hot flashes in menopause". *American Family Physician* 73.3, pp. 457–464 (cit. on p. 448).

[Carson, 1951] J. F. Carson (1951). "The structure of humulone and lupulone as revealed by ozonization". *Journal of the American Chemical Society* 73, pp. 4652–4654 (cit. on p. 300).

[Carson, 1952] — (1952). "The alkaline isomerization of humulone". *Journal of the American Chemical Society* 74, pp. 4615–4620 (cit. on p. 300).

[Casarosa, Cosci di Coscio, and Fratta, 1988] C. Casarosa, M. Cosci di Coscio, and M. Fratta (1988). "Lack of effects of a lyposterolic extract of Serenoa repens on plasma levels of testosterone, follicle-stimulating hormone, and luteinizing hormone". *Clinical Therapeutics* 10.5, pp. 585–588 (cit. on pp. 418, 426).

[Cassidy and Hooper, 2006] A. Cassidy and L. Hooper (2006). "Phytoestrogens and cardiovascular disease". *Journal of the British Menopause Society* 12.2, pp. 49–56 (cit. on p. 58).

[Castleman, 1991] M. Castleman (1991). *The Healing Herbs: The Ultimate Guide To The Curative Powers Of Nature's Medicine*. Emmaus, Pennsylvania: Rodale Press (cit. on p. 115).

[CATIE, 2011a] CATIE, ed. (2011a). *A Practical Guide to Complementary Therapies - Herbal Therapies*. URL: http://www.catie.ca/en/practical-guides/complementary-therapies/3-wellness-strategies/3-4 (cit. on p. 51).

[CATIE, 2011b] — ed. (2011b). *A Practical Guide to Complementary Therapies - Regulation of Natural Health Products*. URL: http://www.catie.ca/en/practical-guides/complementary-therapies/1-introduction/1-4 (cit. on p. 31).

[CATIE, 2011c] — ed. (2011c). *A Practical Guide to Complementary Therapies - Research and Complementary Therapies*. URL: http://www.catie.ca/en/practical-guides/complementary-therapies/1-introduction/1-2 (cit. on p. 30).

[CATIE, 2011d] — ed. (2011d). *A Practical Guide to Complementary Therapies - So, what are complementary therapies?* URL: http://www.catie.ca/en/practical-guides/complementary-therapies/1-introduction/1-1 (cit. on p. 28).

[Cavalieri, 1974a] S. Cavalieri (1974a). "A controlled clinical trial of Legalon in 40 patients". *Gazzetta Medica Italiana Archivio per le Scienze Mediche* 133, pp. 628–635 (cit. on p. 355).

[Cavalieri, 1974b] — (1974b). "A controlled clinical trial of Legalon in 40 patients". *Gazzetta Medica Italiana Archivio per le Scienze Mediche* 133, pp. 628–635 (cit. on p. 365).

[CDC, 1997] CDC (1997). "Outbreaks of Escherichia coli 0157:H7 infection associated with eating alfalfa sproutsMichigan and Virginia, June-July 1997". *Journal of the American Medical Association* 278, pp. 809–810 (cit. on pp. 8, 68–69).

[CDI, 2015] CDI (2015). *Ginseng*. Clinical Drug Information. URL: http://www.drugs.com/cdi/ginseng.html (cit. on pp. 95, 152).

[Celik and Isik, 2008] I. Celik and I. Isik (2008). "Determination of chemopreventive role of Foeniculum vulgare and Salvia officinalis infusion on trichloroacetic acid-induced increased serum marker enzymes lipid peroxidation and antioxidative defense systems in rats". *Natural Product Research* 22.1, pp. 66–75 (cit. on p. 408).

[Centonze, Mori, and Koch, 2009] D. Centonze, F. Mori, and G. Koch (2009). "Lack of effect of cannabis-based treatment on clinical and laboratory measures in multiple sclerosis". *Neurological Sciences* 30.6, pp. 531–534 (cit. on p. 343).

[Ceska, 1986] O. Ceska (1986). "Naturally occurring crystals of photocarcinogenic furocoumarins on the surface of parsnip roots sold as food". *Experientia* 42, pp. 1302–1304 (cit. on p. 116).

[Cetin, Ozer, and Cakir, 2010] B. Cetin, H. Ozer, and A. Cakir (2010). "Antimicrobial activities of essential oil and hexane extract of Florence fennel [ Foeniculum vulgare var. azoricum (Mill.) Thell.] against foodborne microorganisms". *Journal of Medicinal Food* 13.1, pp. 196–204 (cit. on p. 281).

[Cha, 1981] L. Cha (1981). "Effects of Angelica sinensis on experimental arrhythmias". *Chinese Pharmaceutical Bulletin* 16, p. 259 (cit. on p. 271).

[Cha, C. C. Chien, and F. H. Lu, 1981] L. Cha, C. C. Chien, and F. H. Lu (1981). "Antiarrhythmic effect of Angelica sinensis root, tetrandrine and Sophora flavescens root". *Chinese Pharmaceutical Bulletin* 16, pp. 53–54 (cit. on p. 271).

[Chae, K. M. Park, and G. Y. Lee, 2004] H. J. Chae, K. M. Park, and G. Y. Lee (2004). "Je-chun-jun induced apoptosis of human cervical carcinoma HeLa cells". *Acta Pharmacologica Sinica* 25.10, pp. 1372–1379 (cit. on p. 260).

[Chainy, 2000] G. B. N. Chainy et al. (2000). "Anethole blocks both early and late cellular responses transduced by tumor necrosis factor: effect on NF-B, AP-1, JNK, MAPKK and apoptosis". *Oncogene* 19, pp. 2943–2950 (cit. on p. 128).

[Chambers and Camire, 2003] B. K. Chambers and M. E. Camire (2003). "Can cranberry supplementation benefit adults with type 2 diabetes?" *Diabetes Care* 26.9, pp. 2695–2696 (cit. on p. 232).

[Chan et al., 2008] B. Y. Chan et al. (2008). "Ethanolic extract of Actaea racemosa (black cohosh) potentiates bone nodule formation in MC3T3-E1 preosteoblast cells". *Bone* 43.3, pp. 567–573 (cit. on p. 173).

[Chandeying and Sangthawan, 2007] V. Chandeying and M. Sangthawan (2007). "Efficacy comparison of Pueraria mirifica (PM) against conjugated equine estrogen (CEE) with/without medroxyprogesterone acetate (MPA) in the treatment of climacteric symptoms in perimenopausal women: phase III study". *Journal of the Medical Association of Thailand* 90.9, pp. 1720–1726 (cit. on p. 384).

[Chandler and Hawkes, 1984a] R. F. Chandler and D. Hawkes (1984a). "Aniseed a spice, a flavor, a drug". *Canadian Pharmaceutical Journal* 117, pp. 28–29 (cit. on p. 130).

[Chandler and Hawkes, 1984b] — (1984b). "Aniseed: spice, flavor, drug". *Canadian Pharmacists Journal* 117, pp. 28–29 (cit. on pp. 120–121, 123).

[H. M. Chang and But, 1986] H. M. Chang and P. P. H. But, eds. (1986). *Pharmacology and applications of Chinese materia medica*. Vol. 1. Philadelphia, PA: World Scientific Publishing (cit. on pp. 272–273).

[Chansakaow, Ishikawa, and Seki, 2000] S. Chansakaow, T. Ishikawa, and H. Seki (2000). "Rejuvenating principles of Pueraria mirifica". *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* 42, pp. 49–54 (cit. on pp. 381, 387).

[Chansakaow, Ishikawa, Seki, et al., 2000] S. Chansakaow, T. Ishikawa, H. Seki, et al. (2000). "Identification of deoxymiroestrol as the actual rejuvenating principle of "Kwao Keur", Pueraria mirifica . The known miroestrol may be an artifact". *Journal of Natural Products* 63.2, pp. 173–175 (cit. on p. 381).

[Chansakaow, Ishikawa, Sekine, et al., 2000] S. Chansakaow, T. Ishikawa, K. Sekine, et al. (2000). "Isoflavonoids from Pueraria mirifica and their estrogenic activity". *Planta Medica* 66.6, pp. 572–575 (cit. on p. 382).

[Chapkin and S. L. Carmichael, 1990] R. S. Chapkin and S. L. Carmichael (1990). "Effects of dietary n-3 and n-6 polyunsaturated fatty acids on macrophage phospholipid classes and subclasses". *Lipids* 25, pp. 827–834 (cit. on p. 194).

[Chapkin, Somers, and Erickson, 1988] R. S. Chapkin, S. D. Somers, and K. L. Erickson (1988). "Dietary manipulation of macrophage phospholipid classes: selective increase of dihomogammalinolenic acid". *Lipids* 23, pp. 766–770 (cit. on p. 194).

[Chapkin, Somers, Schumacher, et al., 1988] R. S. Chapkin, S. D. Somers, L. Schumacher, et al. (1988). "Fatty acid composition of macrophage phospholipids in mice fed fish or borage oil". *Lipids* 23, pp. 380–383 (cit. on p. 194).

[Chappel, S. Y. Smith, and Chagnon, 1998] C. I. Chappel, S. Y. Smith, and M. Chagnon (1998). "Subchronic toxicity study of tetrahydroisohumulone and hexahydroisohumulone in the beagle dog". *Food and Chemical Toxicology* 36, pp. 915–922 (cit. on p. 305).

[Charnock, 2000] J. S. Charnock (2000). "Gamma-linolenic acid provides additional protection against ventricular fibrillation in aged rats fed linoleic acid rich diets". *Prostaglandins, Leukotrienes and Essential Fatty Acids* 62, pp. 129–134 (cit. on p. 195).

[D. Cheema, Coomarasamy, and El-Toukhy, 2007] D. Cheema, A. Coomarasamy, and T. El-Toukhy (2007). "Non-hormonal therapy of post-menopausal vasomotor symptoms: a structured evidence-based review". *Archives of Gynecology and Obstetrics* 276.5, pp. 463–469 (cit. on p. 259).

[P. Cheema, El-Mefty, and Jazieh, 2001] P. Cheema, O. El-Mefty, and A. R. Jazieh (2001). "Intraoperative haemorrhage associated with the use of extract of Saw Palmetto herb: a case report and review of literature". *Journal of Internal Medicine* 250.2, pp. 167–169 (cit. on p. 423).

[C. F. Chen, Chiou, and J. T. Zhang, 2008] C. F. Chen, W. F. Chiou, and J. T. Zhang (2008). "Comparison of the pharmacological effects of Panax ginseng and Panax quinquefolium". *Acta Pharmacologica Sinica* 29.9, pp. 1103–1108 (cit. on pp. 80, 138).

[M. F. Chen et al., 1990] M. F. Chen et al. (1990). "Effect of glycyrrhizin on the pharmacokinetics of prednisolone following low dosage of prednisolone hemisuccinate". *Endocrinologia Japonica* 37.3, pp. 331–341 (cit. on p. 328).

[M. F. Chen et al., 1991] — (1991). "Effect of oral administration of glycyrrhizin on the pharmacokinetics of prednisolone". *Endocrinologia Japonica* 38.2, pp. 167–174 (cit. on p. 328).

[M. H. Chen, 1985] M. H. Chen (1985). "Studies on the chemical constituents of Pueraria lobata [in Chinese]". *Zhong Yao Tung Bao* 10.6, pp. 34–36 (cit. on pp. 183, 306).

[Q. C. Chen, J. Lee, and W. Jin, 2007] Q. C. Chen, J. Lee, and W. Jin (2007). "Cytotoxic constituents from Angelicae sinensis radix". *Archives of Pharmacal Research* 30.5, pp. 565–569 (cit. on pp. 257, 260).

[R. Chen and C. Yuan, 1991] R. Chen and C. Yuan (1991). *China Journal of Chinese Materia Medica* 16.10, pp. 617–619 (cit. on p. 320).

[S. G. Chen, 1995] S. G. Chen (1995). "Protective effects of Angelica sinensis on myocardial ischemia/ reperfusion injury in rabbits". *Chung-kuo Chung His I Chieh Ho Tsa Chih* 15, pp. 486–488 (cit. on p. 271).

[S. N. Chen, Fabricant, Z. Z. Lu, et al., 2002] S. N. Chen, D. S. Fabricant, Z. Z. Lu, et al. (2002). "Cimiracemates A-D, phenylpropanoid esters from the rhizomes of Cimicifuga racemosa". *Phytochemistry* 61.4, pp. 409–413 (cit. on p. 168).

[S. N. Chen, Fabricant, Z., et al., 2002] S. N. Chen, D. S. Fabricant, Lu Z. Z., et al. (2002). "Cimiracemosides I-P, new 9,19-cyclolanostane triterpene glycosides from Cimicifuga racemosa". *Journal of Natural Products* 65.10, pp. 1391–1397 (cit. on p. 168).

[S. N. Chen, Friesen, and D. Webster, 2011] S. N. Chen, J. B. Friesen, and D. Webster (2011). "Phytoconstituents from Vitex agnus-castus fruits". *Fitoterapia* 82.4, pp. 528–533 (cit. on pp. 213, 216).

[S. N. Chen, W. Li, et al., 2001] S. N. Chen, W. Li, et al. (2001). "Isolation, structure elucidation, and absolute configuration of 26-deoxyactein from Cimicifuga racemosa and clarification of nomenclature associated with 27-deoxyactein." *Journal of Natural Products* 65, pp. 601–605. URL: http://www.ncbi.nlm.nih.gov/pubmed/11975513 (cit. on p. 188).

[X. Chen, 1987] X. Chen (1987). "Protective effects of ginsenosides on anoxia/reoxygenation of cultured rat monocytes and on reperfusion injuries against lipid peroxidation". *Biomedica Biochimica Acta* 46, pp. 646–649 (cit. on p. 100).

[X. Chen, 1996] — (1996). "Cardiovascular protection by ginsenosides and their nitric oxide releasing action". *Clinical and experimental pharmacology & physiology* 23.8, pp. 728–732 (cit. on pp. 82, 139).

[X. Chen, M. Zhou, and Q. Li, 2008] X. Chen, M. Zhou, and Q. Li (2008). "Sanchi for acute ischaemic stroke". *Cochrane Database of Systematic Reviews* 4 (CD006305) (cit. on pp. 82, 140).

[Y. Chen, 1984] Y. Chen (1984). "Analysis of the composition of Angelica sinensis determination of the essential oil composition by capillary column GC/MS". *Gaodeng Xuexiao Huaxue Xuebao* 5, p. 125 (cit. on p. 257).

[Y. C. Chen and Gao, 1994] Y. C. Chen and Y. Q. Gao (1994). "Research on the mechanism of blood-tonifying effect of danggui buxue decoction". *Chung Kuo Chung Yao Tsa Chih* 19, pp. 43–45, 63 (cit. on p. 271).

[Y. Chen, H. Y. Tsai, and T. S. Wu, 1995] Y. Chen, H. Y. Tsai, and T. S. Wu (1995). "Anti-inflammatory and analgesic activities from roots of Angelica pubescens". *Planta Medica* 61.1, pp. 2–8 (cit. on p. 260).

[W. Y. Cheng, Kuo, and C. J. Huang, 2007] W. Y. Cheng, Y. H. Kuo, and C. J. Huang (2007). "Isolation and identification of novel estrogenic compounds in yam tuber ( Dioscorea alata Cv. Tainung No. 2)". *Journal of Agricultural and Food Chemistry* 55.18, pp. 7350–7358 (cit. on p. 448).

[X. J. Cheng, 1987] X. J. Cheng (1987). "Protective effects of ginsenosides on anoxia/reoxygenation of cultured rat myocytes and on reperfusion injuries against lipid peroxidation". *Biomedica Biochimica Acta* 46, pp. 646–649 (cit. on p. 100).

[Cherdshewasart, 2003] W. Cherdshewasart (2003). "Toxicity tests of phytoestrogen-rich herb, Pueraria mirifica". *Journal of Scientific Research Chulalongkorn University* 28.1, pp. 1–12 (cit. on p. 388).

[Cherdshewasart, Cheewasopit, and Picha, 2004a] W. Cherdshewasart, W. Cheewasopit, and P. Picha (2004a). "The differential anti-proliferation effect of white ( Pueraria mirifica ), red ( Butea superba ), and black ( Mucuna collettii ) Kwao Krua plants on the growth of MCF-7 cells". *Journal of Ethnopharmacology* 93.2-3, pp. 255–260 (cit. on pp. 222, 306–307).

[Cherdshewasart, Cheewasopit, and Picha, 2004b] — (2004b). "The differential anti-proliferation effect of white ( Pueraria mirifica ), red ( Butea superba ), and black ( Mucuna collettii ) Kwao Krua plants on the growth of MCF-7 cells". *Journal of Ethnopharmacology* 93.2-3, pp. 255–260 (cit. on p. 382).

[Cherdshewasart, Kitsamai, and Malaivijitnond, 2007] W. Cherdshewasart, Y. Kitsamai, and S. Malaivijitnond (2007). "Evaluation of the estrogenic activity of the wild Pueraria mirifica by vaginal cornification assay". *Journal of Reproduction and Development* 53.2, pp. 385–393 (cit. on p. 384).

[Cherdshewasart, Panriansaen, and Picha, 2007] W. Cherdshewasart, R. Panriansaen, and P. Picha (2007). "Pretreatment with phytoestrogen-rich plant decreases breast tumor incidence and exhibits lower profile of mammary ERalpha and ERbeta". *Maturitas* 58.2, pp. 174–181 (cit. on p. 383).

[Cherdshewasart and Sriwatcharakul, 2007] W. Cherdshewasart and S. Sriwatcharakul (2007). "Major isoflavonoid contents of the 1-year-cultivated phytoestrogen-rich herb, Pueraria mirifica". *Bioscience, Biotechnology, and Biochemistry* 71.10, pp. 2527–2533 (cit. on p. 382).

[Cherdshewasart and Sriwatcharakul, 2008] — (2008). "Metabolic activation promotes estrogenic activity of the phytoestrogen-rich plant". *Maturitas* 59.2, pp. 128–136 (cit. on p. 383).

[Cherdshewasart, Subtang, and Dahlan, 2007] W. Cherdshewasart, S. Subtang, and W. Dahlan (2007). "Major isoflavonoid contents of the phytoestrogen rich-herb Pueraria mirifica in comparison with Pueraria lobata". *Journal of Pharmaceutical and Biomedical Analysis* 43.2, pp. 428–434 (cit. on p. 381).

[Cherdshewasart and Sutjit, 2008] W. Cherdshewasart and W. Sutjit (2008). "Correlation of antioxidant activity and major isoflavonoid contents of the phytoestrogen-rich Pueraria mirifica and Pueraria lobata tubers". *Phytomedicine* 15.1-2, pp. 38–43 (cit. on p. 386).

[Cherdshewasart, Traisup, and Picha, 2008] W. Cherdshewasart, V. Traisup, and P. Picha (2008). "Determination of the estrogenic activity of wild phytoestrogen-rich Pueraria mirifica by MCF-7 proliferation assay". *Journal of Reproduction and Development* 54.1, pp. 63–67 (cit. on p. 382).

[Chevalier et al., 1997] G. Chevalier et al. (1997). "Distribution study of radioactivity in rats after oral administration of the lipido/sterolic extract of Serenoa repens ( Permixon ) supplemented with [1-14C]-lauric acid, [1-14C]-oleic acid or [4-14C]-beta-sitosterol". *European Journal of Drug Metabolism and Pharmacokinetics* 22.1, pp. 73–83 (cit. on p. 418).

[Chevallier, 1996] A. Chevallier (1996). *Encyclopedia of Medicinal Plants*. New York, NY: DK Publishing, pp. 246–247 (cit. on pp. 120–121, 123–124, 212, 306, 404).

[Chilton-Lopez et al., 1996] S. M. E. Chilton-Lopez et al. (1996). "Metabolism of gammalinolenic acid in human neutrophils". *Journal of Immunology* 156, pp. 2941–2947 (cit. on p. 195).

[Chin, H. A. Jung, and Y. Liu, 2007] Y. W. Chin, H. A. Jung, and Y. Liu (2007). "Anti-oxidant constituents of the roots and stolons of licorice ( G. glabra ) ." *Journal of Agricultural and Food Chemistry* 55.12, pp. 4691–4697 (cit. on p. 317).

[Chindewa et al., 2008] R. Chindewa et al. (2008). "Pueraria mirifica , phytoestrogen-induced change in synaptophysin expression via estrogen receptor in rat hippocampal neuron". *Journal of the Medical Association of Thailand* 91.2, pp. 208–214 (cit. on p. 386).

[Chintharlapalli, Papineni, and Jutooru, 2007] S. Chintharlapalli, S. Papineni, and I. Jutooru (2007). "Structure-dependent activity of glycyrrhetinic acid derivatives as peroxisome proliferator-activated receptor [gamma] agonists in colon cancer cells". *Molecular Cancer Therapeutics* 6.5, pp. 1588–1598 (cit. on p. 319).

[C. W. Choi, S. I. Lee, and Huk, 1984] C. W. Choi, S. I. Lee, and K. Huk (1984). "Effect of ginseng on hepatic alcohol metabolizing enzyme system activity in chronic alcohol-treated mouse". *Korean Journal of Pharmacognosy* 20, pp. 13–21 (cit. on p. 100).

[E. M. Choi and J. K. Hwang, 2004] E. M. Choi and J. K. Hwang (2004). "Antiinflammatory, analgesic and antioxidant activities of the fruit of Foeniculum vulgare". *Fitoterapia* 75.6, pp. 557–565 (cit. on p. 279).

[H. K. Choi and Seong, 1995] H. K. Choi and D. W. Seong (1995). "Effectiveness for erectile dysfunction after the administration of Korean red ginseng". *Korean Journal of Ginseng Science*, 19, pp. 17–21 (cit. on p. 104).

[Chopin Lucks, 2003] B. Chopin Lucks (2003). "Vitex agnus castus essential oil and menopausal balance: a research update". *Complementary Therapies in Nursing and Midwifery* 9.3, pp. 157–160 (cit. on p. 214).

[Chou, 1979] Y. P. Chou (1979). "The effect of Angelica sinensis on hemodynamics and myocardiac oxygen consumption in dogs". *Acta Pharmaceutica Sinica* 14, pp. 156–160 (cit. on p. 270).

[Choudhary and Jalil, 2009] M. I. Choudhary and S. Jalil (2009). "Antiinflammatory and lipoxygenase inhibitory compounds from Vitex agnus-castus". *Phytotherapy Research* 23.9, pp. 1336–1339 (cit. on pp. 213, 216).

[Choy et al., 1994] Y. Choy et al. (1994). "Immunopharmacological studies of low molecular weight polysaccharide from Angelica sinensis". *American Journal of Chinese Medicine* 22.2, pp. 137–145 (cit. on p. 257).

[L. P. Christensen, 2009] L. P. Christensen (2009). "Ginsenosides chemistry, biosynthesis, analysis, and potential health effects". *Advances in Food and Nutrition Research* 55, pp. 1–99 (cit. on pp. 79–83, 137–140).

[R. Christensen et al., 2008] R. Christensen et al. (2008). "Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials". *Osteoarthritis and Cartilage* 16.4, pp. 399–408 (cit. on pp. 440, 443).

[D. R. Christie et al., 2010] D. R. Christie et al. (2010). "Metabolic effects of soy supplementation in postmenopausal Caucasian and African American women: a randomized, placebo-controlled trial". *American Journal of Obstetrics & Gynecology* 203.2, 153.e1–153.e9 (cit. on p. 438).

[S. Christie and A. Walker, 1998] S. Christie and A. Walker (1998). "Vitex agnus-castus L." *European Journal of Herbal Medicine* 3, pp. 29–45. (1) a review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners. (Cit. on pp. 212, 224).

[Christy, 1999] C. Christy (1999). "Foodborne diseases: fruits and vegetables." *Pediatric Infectious Disease Journal* 18, pp. 911–912 (cit. on pp. 8, 68–69).

[Chrzan, 2007] B. G. Chrzan (2007). "Phytoestrogens activate estrogen receptor beta1 and estrogenic responses in human breast and bone cancer cell lines". *Molecular Nutrition & Food Research* 51.2, pp. 171–7 (cit. on p. 52).

[Chuang et al., 1995] W. C. Chuang et al. (1995). "A comparative study on commercial samples of ginseng radix". *Planta Medica* 61.5, pp. 459–465 (cit. on pp. 80, 137–138).

[Cicek et al., 2010] S. S. Cicek et al. (2010). "Development of a fast and convenient method for the isolation of triterpene saponins from Actaea racemosa by high-speed countercurrent chromatography coupled with evaporative light scattering detection". *Planta Medica* 76.5, pp. 467–473 (cit. on p. 169).

[Cinatl, Morgenstern, and G. Bauer, 2003] J. Cinatl, B. Morgenstern, and G. Bauer (2003). "Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus". *Lancet* 361.9374, pp. 2045–2046 (cit. on p. 318).

[Clarkson, Anthony, and T. M. Morgan, 2001] T. B. Clarkson, M. S. Anthony, and T. M. Morgan (2001). "Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens". *Journal of Clinical Endocrinology & Metabolism* 86.1, pp. 41–47 (cit. on p. 436).

[Codina et al., 1997] R. M. Codina et al. (1997). "Specific immunoglobulins to soybean hull allergens in soybean asthma". *Chest* 111.1, pp. 75–80 (cit. on p. 442).

[B. I. Cohen et al., 1990] B. I. Cohen et al. (1990). "The effect of alfalfa-corn diets on cholesterol metabolism and gallstones in prairie dogs". *Lipids* (25), pp. 143–148 (cit. on pp. 67–68).

[J. I. Cohen, 2005] J. I. Cohen (2005). "Licking latency with licorice". *Journal of Clinical Investigation* 115.3, pp. 591–593 (cit. on p. 318).

[P. J. Cohen, 2009a] P. J. Cohen (2009a). "Medical marijuana: the conflict between scientific evidence and political ideology - Part one of two". *Journal of Pain & Palliative Care Pharmacotherapy* 23.1, pp. 4–25 (cit. on pp. 337, 346).

[P. J. Cohen, 2009b] — (2009b). "Medical marijuana: the conflict between scientific evidence and political ideology - Part two of two". *Journal of Pain & Palliative Care Pharmacotherapy* 23.2, pp. 120–140 (cit. on p. 339).

[Coldham and Sauer, 2001] N. G. Coldham and M. J. Sauer (2001). "Identification, quantitation and biological activity of phytoestrogens in a dietary supplement for breast enhancement". *Food and Chemical Toxicology* 39, pp. 1211–1224 (cit. on p. 302).

[F. Comelli et al., 2008] F. Comelli et al. (2008). "Antihyperalgesic effect of a Cannabis sativa extract in a rat model of neuropathic pain: mechanisms involved". *Phytotherapy Research* 22.8, pp. 1017–1024 (cit. on pp. 343, 348).

[M. C. Comelli et al., 2007] M. C. Comelli et al. (2007). "Toward the definition of the mechanism of action of silymarin: activities related to cellular protection from toxic damage induced by chemotherapy". *Integrative Cancer Therapies* 6.2, pp. 120–129 (cit. on p. 360).

[Committee, 2006] Economic Committee (2006). *Summary of Reports: Nürnberg, Germany*. INTERNATIONAL HOP GROWERS CONVENTION. Economic Committee (cit. on p. 299).

[Corcilius, 1956] F. Corcilius (1956). "Isolation of a new coumarin". *Archiv der Pharmazie - Chemistry in Life Sciences* 289, pp. 81–86 (cit. on p. 112).

[Corey and L. I. Wu, 1993] E. J. Corey and L. I. Wu (1993). "Enantioselective total synthesis of miroestrol". *Journal of the American Chemical Society* 115.20, pp. 9327–9328 (cit. on p. 382).

[Corran, 1975] H. S. Corran (1975). *A History of Brewing*. Vermont Canada: David and Charles PLC, p. 303. ISBN: 0-7153-6735-8 (cit. on p. 298).

[B. Costa et al., 2007] B. Costa et al. (2007). "The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain". *European Journal of Pharmacology* 556.1-3, pp. 75–83 (cit. on p. 343).

[S. Craig, Haigh, and Harrar, 1997] S. Craig, J. Haigh, and S. Harrar (1997). *The Complete Book of Alternative Nutrition*. Emmaus, PA: Rodale Press, pp. 278–279 (cit. on p. 431).

[Crisp and Clegg, 1998] T. M. Crisp and E. D. Clegg (1998). "Environmental endocrine disruption: an effects assessment and analysis." *Environmental Health Perspectives* 106 (Supplement 1), pp. 11–56. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1533291/ (cit. on pp. 51, 464).

[CSIR, 1948–1976] CSIR (1948–1976). *The wealth of India*. Vol. 11 vols. New Delhi: Council of Scientific and Industrial Research (cit. on pp. 301, 338–339, 352).

[csmmhpra, 2004] csmmhpra (2004). *Interaction between warfarin and cranberry juice: new advice*. 30. Committee on Safety of Medicines, Medicines and Healthcare Products Regulatory Agency., p. 10 (cit. on p. 238).

[J. F. Cui, 1995] J. F. Cui (1995). "Identification and quantification of ginsenosides in various commercial ginseng preparations". *European journal of pharmaceutical sciences* 3, pp. 77–85 (cit. on p. 99).

[Curreli, Friedman-Kien, and Flore, 2005] F. Curreli, A. E. Friedman-Kien, and O. Flore (2005). "Glycyrrhizic acid alters Kaposi sarcoma-associated herpesvirus latency, triggering p53-mediated apoptosis in transformed B lymphocytes". *Journal of Clinical Investigation* 115.3, pp. 642–652 (cit. on p. 318).

[Cuzzolin, Zaffani, and Benoni, 2006] L. Cuzzolin, S. Zaffani, and G. Benoni (2006). "Safety implications regarding use of phytomedicines". *European Journal of Clinical Pharmacology* 62.1, pp. 37–42 (cit. on p. 283).

[DAB-DDR, 1983] DAB-DDR (1983). *Deutsches Arzneibuch der Deutsche Demokratische Republik*. Berlin, Germany: Akademie Verlag (cit. on p. 111).

[Dang and Lowik, 2005] Z. C. Dang and C. Lowik (2005). "Dose-dependent effects of phytoestrogens on bone". *Trends in Endocrinology & Metabolism* 16.5, pp. 207–213 (cit. on p. 58).

[D'Angelo, 1986] L. D'Angelo (1986). "Double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers". *Journal of ethnopharmacology* 16, pp. 15–22 (cit. on pp. 104–105, 108).

[Daniele et al., 2005] C. Daniele et al. (2005). "Vitex agnus castus : asystematic review of adverse events". *Drug Safety* 28.4, pp. 319–332 (cit. on pp. 221, 223).

[Dante and Facchinetti, 2011] G. Dante and F. Facchinetti (2011). "Herbal treatments for alleviating premenstrual symptoms: a systematic review". *Journal of Psychosomatic Obstetrics & Gynecology* 32.1, pp. 42–51 (cit. on p. 215).

[Darling et al., 2009] A. L. Darling et al. (2009). "Dietary protein and bone health: a systematic review and meta-analysis". *American Journal of Clinical Nutrition* 90.6, pp. 1674–1692 (cit. on pp. 440, 443).

[M. K. Das, Bhattacharya, and Ghosal, 2006] M. K. Das, A. Bhattacharya, and S. K. Ghosal (2006). "Effect of different terpene-containing essential oils on percutaneous absorption of trazodone hydrochloride through mouse epidermis". *Drug Delivery* 13.6, pp. 425–431 (cit. on p. 280).

[Davies and Bledsoe, 2005] J. K. Davies and J. M. Bledsoe (2005). "Prenatal alcohol and drug exposures in adoption". *Pediatric Clinics of North America* 52.5, pp. 1369–1393, vii (cit. on p. 347).

[Davis, Jayo, and A. Ho, 2008] V. L. Davis, M. J. Jayo, and A. Ho (2008). "Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2". *Cancer Research* 68.20, pp. 8377–8383 (cit. on p. 190).

[Davydov, Molokovsky, and Limarenko, 1990] V. V. Davydov, A. Molokovsky, and A. Y. Limarenko (1990). "Efficacy of ginseng drugs in experimental insulin-dependent diabetes and toxic hepatitis". *Patologichezkaia Fiziologiia I Eksperimentalkaia Terapiia* 5, pp. 49–52 (cit. on p. 102).

[De Cooman, Everaert, and De Keukeleire, 1998] L. De Cooman, E. Everaert, and D. De Keukeleire (1998). "Quantitative analysis of hop acids, essential oils, and flavonoids as a clue to the identification of hop varieties". *Phytochemical Analysis* 9, pp. 145–150 (cit. on p. 300).

[De Swaef, 1996a] S. De Swaef (1996a). "Simultaneous quantitation of lauric acid and ethyl laureate in Sabal serrulata by capillary gas chromatography and derivatisation with trimethyl sulphoniumhydroxide". *Journal of Chromatography* 719, p. 479 (cit. on p. 416).

[De Swaef, 1996b] — (1996b). "Supercritical fluid chromatography of free fatty acids and ethyl esters in ethanolic extracts of Sabal serrulata". *Phytochemical Analysis* 7, p. 223 (cit. on p. 416).

[Debruyne et al., 1994] D. Debruyne et al. (1994). "Comparison of three advanced chromatographic techniques for cannabis identification". *Bulletin on Narcotics* 46.2, pp. 109–121 (cit. on p. 339).

[Deep and R. Agarwal, 2007] G. Deep and R. Agarwal (2007). "Chemopreventive efficacy of silymarin in skin and prostate cancer". *Integrative Cancer Therapies* 6.2, pp. 130–145 (cit. on pp. 360, 374).

[Degenhardt and W. D. Hall, 2008] L. Degenhardt and W. D. Hall (2008). "The adverse effects of cannabinoids: implications for use of medical marijuana". *Canadian Medical Association Journal* 178.13, pp. 1685–1686 (cit. on p. 352).

[Dehmlow, Erhard, and Groot, 1996] C. Dehmlow, J. Erhard, and H. de Groot (1996). "Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin". *Hepatology* 23, pp. 749–754 (cit. on p. 367).

[Dehmlow, Murawski, and Groot, 1996] C. Dehmlow, N. Murawski, and H. de Groot (1996). "Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells". *Life Sciences* 58, pp. 1591–1600 (cit. on p. 367).

[Dekermendjian, Ai, and M. Nielsen, 1996] K. Dekermendjian, J. Ai, and M. Nielsen (1996). "Characterisation of the furanocoumarin phellopterin as a rat brain benzodiazepine receptor partial agonist in vitro". *Neuroscience Letters* 219, pp. 151–154 (cit. on p. 260).

[Délos et al., 1995] S. Délos et al. (1995). "Testosterone metabolism in primary cultures of human prostate epithelial cells and fibroblasts". *The Journal of Steroid Biochemistry and Molecular Biology* 55.3-4, pp. 375–383 (cit. on p. 418).

[Dewey, 2001] D. Dewey, ed. (2001). *NuPharma*: *Cholestaid* (cit. on p. 68).

[Dhar, 1995] S. K. Dhar (1995). "Anti-fertility activity and hormonal profile of trans-anethole in rats". *Indian Journal of Physiology and Pharmacology* 39, pp. 63–67 (cit. on p. 131).

[Di Carlo and Izzo, 2003] G. Di Carlo and A. A. Izzo (2003). "Cannabinoids for gastrointestinal diseases: potential therapeutic applications". *Expert Opinion on Investigational Drugs* 12.1, pp. 39–49 (cit. on p. 341).

[Di Marzo and Petrocellis, 2006] V. Di Marzo and L. D. Petrocellis (2006). "Plant, synthetic, and endogenous cannabinoids in medicine". *Annual Review of Medicine* 57, pp. 553–574 (cit. on pp. 338, 340–341).

[Di Pierro et al., 2008] F. Di Pierro et al. (2008). "Clinical efficacy, safety and tolerability of BIO-C (micronized Silymarin) as a galactagogue". *Acta Biomed* 79.3, pp. 205–210 (cit. on p. 374).

[Di Silverio, Monti, and Sciarra, 1998] F. Di Silverio, S. Monti, and A. Sciarra (1998). "Effects of long-term treatment with Serenoa repens ( Permixon ) on the concentrations and regional distribution of androgens and epidermal growth factor in benign prostatic hyperplasia". *Prostate* 37.4, pp. 77–83 (cit. on p. 419).

[DiCenzo, Shelton, and K. Jordan, 2003] R. DiCenzo, M. Shelton, and K. Jordan (2003). "Coadministration of milk thistle and indinavir in healthy subjects". *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 23.7, pp. 866–870 (cit. on p. 374).

[Die et al., 2009] M. D. van Die et al. (2009). "Vitex agnus-castus (Chaste-Tree/Berry) in the treatment of menopause-related complaints". *Journal of Alternative and Complementary Medicine* 15.8, pp. 853–862 (cit. on pp. 214–216).

[Dixon-Shanies and Shaikh, 1999] D. Dixon-Shanies and N. Shaikh (1999). "Growth inhibition of human breast cancer cells by herbs and phytoestrogens." *Oncology Reports* 6, pp. 1383–1387. eprint: http://www.ncbi.nlm.nih.gov/pubmed/10523716 (cit. on pp. 185–186).

[Djavan, Fong, and Chaudry, 2005] B. Djavan, Y. K. Fong, and A. Chaudry (2005). "Progression delay in men with mild symptoms of bladder outlet obstruction: a comparative study of phytotherapy and watchful waiting". *World Journal of Urology* 23.4, pp. 253–256 (cit. on p. 419).

[I. Dobelis, 1986] I. Dobelis (1986). *Magic and Medicine of Plants*. Pleasantville, NY: Reader's Digest Association (cit. on pp. 227, 276).

[I. N. Dobelis, 1986] I. N. Dobelis, ed. (1986). *Magic and Medicine of Plants*. Pleasantville, NY: Reader's Digest Association (cit. on pp. 161, 181).

[Dodson and Stermitz, 1986] C. D. Dodson and F. R. Stermitz (1986). "Pyrrolizidine alkaloids from borage (Borago officinalis) seeds and flowers". *Journal of Natural Products* 49, pp. 727–728 (cit. on pp. 193, 205).

[Dominquez and Hinojosa, 1976] X. A. Dominquez and M. Hinojosa (1976). "Mexican medicinal plants. 28. Isolation of 5hydroxy-7,34-trimethoxyflavone from Turnera diffusa". *Planta Medica* 30, p. 68 (cit. on p. 245).

[Donabedian, 2006] H. Donabedian (2006). "Nutritional therapy and infectious diseases: a two-edged sword". *Nutrition Journal* 5, p. 21 (cit. on p. 231).

[J. Y. Dong and Qin, 2011] J. Y. Dong and L. Q. Qin (2011). "Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies". *Breast Cancer Research and Treatment* 125.2, pp. 315–323 (cit. on pp. 434, 443).

[S. Dong, Inoue, and Y. Zhu, 2007] S. Dong, A. Inoue, and Y. Zhu (2007). "Activation of rapid signaling pathways and the subsequent transcriptional regulation for the proliferation of breast cancer MCF-7 cells by the treatment with an extract of Glycyrrhiza glabra root". *Food and Chemical Toxicology* 45.12, pp. 2470–2478 (cit. on p. 319).

[W. G. Dong, S. P. Liu, and H. H. Zhu, 2004] W. G. Dong, S. P. Liu, and H. H. Zhu (2004). "Abnormal function of platelets and role of angelica sinensis in patients with ulcerative colitis". *World Journal of Gastroenterology* 10.4, pp. 606–609 (cit. on p. 264).

[Drugs.com, 2009] Drugs.com (2009). *Alfalfa*. URL: http://www.drugs.com/npc/alfalfa.html (cit. on pp. 8, 68, 74).

[Drugs.com, 2014] — (2014). *Fennel*. URL: http://www.drugs.com/mtm/fennel.html (cit. on pp. 18, 283).

[drugs.com, 2009a] drugs.com (2009a). *Alfalfa*. Wolters Kluwer Health. URL: http://www.drugs.com/npp/alfalfa.html (cit. on pp. 62, 73).

[drugs.com, 2009b] — (2009b). *Angelica*. Wolters Kluwer Health. URL: http://www.drugs.com/npp/angelica.html (cit. on pp. 109, 112–114, 116, 118).

[drugs.com, 2009c] — (2009c). *Borage*. Wolters Kluwer Health. URL: http://www.drugs.com/npc/borage.html (cit. on pp. 198, 201, 204).

[drugs.com, 2009d] — (2009d). *Chaste-Tree*. Wolters Kluwer Health. URL: http://www.drugs.com/npp/chaste-tree.html (cit. on p. 225).

[drugs.com, 2009e] — (2009e). *Cranberry*. Wolters Kluwer Health. URL: http://www.drugs.com/npp/cranberry.html (cit. on pp. 237–240, 242).

[drugs.com, 2009f] — (2009f). *Damiana*. Wolters Kluwer Health. URL: http://www.drugs.com/npp/damiana.html (cit. on pp. 243–244, 246–248).

[drugs.com, 2009g] — (2009g). *Dong-Quai*. Wolters Kluwer Health. URL: http://www.drugs.com/npp/dong-quai.html (cit. on pp. 261–262, 264, 267, 269).

[drugs.com, 2014a] — ed. (2014a). *Fennel*. Drugs.com. URL: http://www.drugs.com/npp/fennel.html (cit. on pp. 277, 282).

[drugs.com, 2014b] — ed. (2014b). *Fenugreek*. Drugs.com. URL: http://www.drugs.com/mtm/fenugreek.html (cit. on pp. 287, 292–293).

[drugs.com, 2015a] — (2015a). *Black Cohosh*. URL: http://www.drugs.com/npp/black-cohosh.html (cit. on pp. 161, 163, 166, 169).

[drugs.com, 2015b] drugs.com (2015b). *Borage*. Clinical Drug Information, LLC. URL: http://www.drugs.com/cdi/borage.html (cit. on pp. 198, 205).

[drugs.com, 2015c] — (2015c). *Chaste-tree*. Clinical Drug Information. URL: http://www.drugs.com/cdi/chaste-tree.html (cit. on pp. 217–219, 222–223).

[drugs.com, 2015d] — (2015d). *Cranberry*. Wolters Kluwer. URL: http://www.drugs.com/sfx/cranberry-side-effects.html (cit. on pp. 15, 237).

[D'Souza et al., 2009] D. C. D'Souza et al. (2009). "Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans". *Psychopharmacology* 202.4, pp. 569–578 (cit. on p. 343).

[Dugoua, Seely, Perri, Millis, et al., 2008] J. J. Dugoua, D. Seely, D. Perri, E. Millis, et al. (2008). "Safety and efficacy of cranberry (vaccinium macrocarpon) during pregnancy and lactation". *Canadian Journal of Clinical Pharmacology* 15.1, pp. 80–86 (cit. on pp. 227, 238).

[Dugoua et al., 2006] J. J. Dugoua et al. (2006). "Safety and efficacy of black cohosh ( Cimicifuga racemosa ) during pregnancy and lactation". *Canadian Journal of Clinical Pharmacology* 13.3, e257–e261 (cit. on p. 181).

[Dugoua et al., 2008] — (2008). "Safety and efficacy of chastetree (Vitex agnus-castus) during pregnancy and lactation". *Canadian Journal of Clinical Pharmacology* 15.1, e74–e79 (cit. on p. 222).

[J. Duke, 1985] J. Duke (1985). *Handbook of Medicinal Herbs*. Boca Raton, FL: CRC Press (cit. on pp. 66–67, 166, 276, 283, 337, 404, 410).

[J. Duke, 2001] — (2001). *Handbook of Medicinal Herbs*. Boca Raton, FL: CRC Press, pp. 120–121 (cit. on p. 188).

[J. A. Duke, 1972] J. A. Duke (1972). *Isthmian ethnobotanical dictionary*. Published by the author. Baltimore: Harrod & Co (cit. on p. 300).

[J. A. Duke, 1983a] — (1983a). *Handbook of Energy Crops*. URL: http://www.hort.purdue.edu/newcrop/duke_energy/Cannabis_sativa.html (cit. on pp. 337–338).

[J. A. Duke, 1983b] — (1983b). *Humulus lupulus*. URL: http://www.hort.purdue.edu/newcrop/duke_energy/Humulus_lupulus.html (cit. on p. 304).

[J. A. Duke and Ayensu, 1985] J. A. Duke and E. S. Ayensu (1985). *Medicinal plants of China*. Vol. 1. Algonac, MI: Reference Publications (cit. on p. 273).

[J. A. Duke and Wain, 1981] J. A. Duke and K. K. Wain (1981). *Medicinal plants of the world. Computer index with more than 85,000 entries*. Vol. 3 vols (cit. on p. 300).

[E. M. Düker and Kopanski, 1989] E. M. Düker and L. Kopanski (1989). "Inhibition of 5-reductase activity by extracts from Sabal serrulata". *Planta Medica* 55, p. 587 (cit. on p. 418).

[E. M. Düker et al., 1991a] E. M. Düker et al. (1991a). "Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats". *Planta Medica* 57, pp. 420–424. eprint: http://www.ncbi.nlm.nih.gov/pubmed/1798794 (cit. on p. 185).

[E. M. Düker et al., 1991b] — (1991b). "Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats". *Planta Medica* 57.5, pp. 420–424 (cit. on p. 171).

[Duncan, Hare, and W. B. Buck, 1997] K. L. Duncan, W. R. Hare, and W. B. Buck (1997). "Malignant hyperthermia-like reaction secondary to ingestion of hops in five dogs". *Journal of the American Veterinary Medical Association* 210, pp. 51–54 (cit. on p. 305).

[Duthie, Jenkinson, and Crozier, 2006] S. J. Duthie, A. M. Jenkinson, and A. Crozier (2006). "The effects of cranberry juice consumption on antioxidant status and biomarkers relating to heart disease and cancer in healthy human volunteers". *European Journal of Nutrition* 45.2, pp. 113–122 (cit. on p. 232).

[E., J. Liu, and Lantvit, 2002] Burdette. J. E., J. Liu, and D. Lantvit (2002). "Trifolium pratense (red clover) exhibits estrogenic effects in vivo in ovariectomized Sprague-Dawley rats". *Journal of Nutrition* 132, pp. 27–30 (cit. on pp. 392, 397).

[M. Eidi, A. Eidi, and Bahar, 2006] M. Eidi, A. Eidi, and M. Bahar (2006). "Effects of Salvia officinalis L. (sage) leaves on memory retention and its interaction with the cholinergic system in rats". *Nutrition* 22.3, pp. 321–326 (cit. on pp. 407, 411, 413).

[M. Eidi, A. Eidi, and Zamanizadeh, 2005] M. Eidi, A. Eidi, and H. Zamanizadeh (2005). "Effect of Salvia officinalis L. leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats". *Journal of Ethnopharmacology* 100.3, pp. 310–313 (cit. on p. 408).

[Einbond, Shimizu, and D. Xiao, 2004] L. S. Einbond, M. Shimizu, D. Xiao, et al. (2004). "Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells". *Breast Cancer Research and Treatment* 83.3, pp. 221–231 (cit. on p. 174).

[Einer-Jensen, J. Zhao, Andersen, et al., 1996] N. Einer-Jensen, J. Zhao, K. P. Andersen, et al. (1996). "Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats". German. *Maturitas* 25.2, pp. 149–153 (cit. on p. 170).

[Einer-Jensen, J. Zhao, K. P. Anderson, et al., 1996] N. Einer-Jensen, J. Zhao, K. P. Anderson, et al. (1996). "Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats". *Maturitas* 25, pp. 149–153. eprint: http://www.ncbi.nlm.nih.gov/pubmed/8905606 (cit. on pp. 185, 187).

[Eldridge, 1975] J. Eldridge (1975). "Bush Medicine in the Exumas and Long Island Bahamas: A field study". *Economic Botany* 29.4, p. 307 (cit. on p. 245).

[Elghamry and Hänsel, 1969] M. Elghamry and R. Hänsel (1969). "Activity and isolated phytoestrogen of shrub palmetto fruits ( Serenoa repens Small), a new estrogenic plant". *Experientia* 25.8, pp. 828–829 (cit. on p. 416).

[Elisabetsky, 1995] E. Elisabetsky (1995). "Sedative properties of linalool". *Fitoterapia* 66, pp. 407–424 (cit. on p. 128).

[Elisabetsky, Silva Brum, and Souza, 1999] E. Elisabetsky, L. F. Silva Brum, and D. O. Souza (1999). "Anticonvulsant properties of linalool in glutamate-related seizure models". *Phytomedicine* 6, pp. 107–113 (cit. on p. 128).

[Ellis, Toperoff, and Vaida, 2009] R. J. Ellis, W. Toperoff, and F. Vaida (2009). "Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial". *Neuropsychopharmacology* 34.3, pp. 672–680 (cit. on p. 343).

[Elujoba and Hardman, 1987] A. A. Elujoba and R. Hardman (1987). "Saponin-hydrolyzing enzymes from fenugreek seed". *Fitoterapia* 58, pp. 197–199 (cit. on p. 287).

[Enderlin et al., 2009] C. A. Enderlin et al. (2009). "Dietary soy intake and breast cancer risk". *Oncology Nursing Forum* 36.5, pp. 531–539 (cit. on p. 434).

[Engelmann et al., 2006] U. Engelmann et al. (2006). "Efficacy and safety of a combination of sabal and urtica extract in lower urinary tract symptoms". *Arzneimittelforschung* 56.3, pp. 222–229 (cit. on p. 420).

[Engels et al., 2007] F. K. Engels et al. (2007). "Medicinal cannabis in oncology". *European Journal of Cancer* 43.18, pp. 2638–2644 (cit. on p. 341).

[Ensminger et al., 1994] A. H. Ensminger et al. (1994). *Foods & Nutrition Encyclopedia*. 2nd. Vol. 2. Boca Raton, FL: CRC Press, pp. 2017–2035 (cit. on pp. 430–431).

[Ercolani, 1976] G. L. Ercolani (1976). "Bacteriological quality assessment of fresh marketed lettuce and fennel". *Applied and Environmental Microbiology* 31.6, pp. 847–852 (cit. on p. 283).

[Eri et al., 2000] S. Eri et al. (2000). "Direct thermal desorption-gas chromatography and gas chromatography-mass spectrometry profiling of hop (Humulus lupulus L.) essential oils in support of varietal characterization". *Journal of Agricultural and Food Chemistry* 48, pp. 1140–1149 (cit. on pp. 300, 302).

[Ernst, 2002a] E. Ernst (2002a). "Herbal medicinal products during pregnancy: are they safe?" *International Journal of Obstetrics & Gynaecology* 109, pp. 227–235 (cit. on p. 326).

[Ernst, 2002b] — (2002b). "Herbal medicinal products during pregnancy: are they safe?" *International Journal of Obstetrics & Gynaecology* 109.3, pp. 227–235 (cit. on pp. 88, 145).

[Ernst, 2003] E. Ernst (2003). "Avocado-soybean unsaponifiables (ASU) for osteoarthritisa systematic review". *Clinical Rheumatology* 22.4-5, pp. 285–288 (cit. on pp. 440, 443).

[Fallah Huseini et al., 2004a] H. Fallah Huseini et al. (2004a). "The clinical trial of Silybum Marianum seed extract (Silymarin) on type II diabetic patients with hyperlipidemia". *Iranian Journal of Diabetes and Lipid Disorders* 3, pp. 201–206 (cit. on p. 355).

[Fallah Huseini et al., 2004b] — (2004b). "The clinical trial of Silybum Marianum seed extract (Silymarin) on type II diabetic patients with hyperlipidemia". *Iranian Journal of Diabetes and Lipid Disorders* 3, pp. 201–206 (cit. on p. 365).

[familydoctor.org, 2015] familydoctor.org (2015). *Herbal Health Products and Supplements*. URL: http://familydoctor.org/familydoctor/en/drugs-procedures-devices/over-the-counter/herbal-products-and-supplements.html (cit. on p. 57).

[Fan and Chapkin, 1992] Y. Y. Fan and R. S. Chapkin (1992). "Mouse peritoneal macrophage prostaglandin E1 synthesis is altered by dietary gamma-linolenic acid". *Journal of Nutrition* 122, pp. 1600–1606 (cit. on p. 194).

[Fan and Chapkin, 1998] — (1998). "Importance of dietary gamma-linolenic acid in human health and nutrition". *Journal of Nutrition* 128, pp. 1411–1414 (cit. on pp. 193–194).

[Fan, Chapkin, and Ramos, 1996] Y. Y. Fan, R. S. Chapkin, and K. S. Ramos (1996). "Dietary lipid source alters murine macrophage/vascular smooth muscle cell interactions in vitro". *Journal of Nutrition* 126, pp. 2083–2088 (cit. on p. 193).

[Farber et al., 1990] J. M. Farber et al. (1990). "Listeriosis traced to the consumption of alfalfa tablets and soft cheese". *New England Journal of Medicine* 322, p. 338 (cit. on p. 75).

[Farese et al., 1991] R. V. Farese et al. (1991). "Licorice-induced hypermineralocorticoidism". *New England Journal of Medicine* 325.17, pp. 1223–1227 (cit. on p. 334).

[Farnsworth, 2001] N. R. Farnsworth, ed. (2001). *NAPRALERT database*. an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services. Chicago, IL: University of Illinois at Chicago (cit. on pp. 126, 130).

[Fecka and Turek, 2007] I. Fecka and S. Turek (2007). "Determination of water-soluble polyphenolic compounds in commercial herbal teas from Lamiaceae: peppermint, melissa, and sage". *Journal of Agricultural and Food Chemistry* 55.26, pp. 10908–10917 (cit. on p. 406).

[Fehr, 1983] K. Fehr (1983). *Cannabis and Health Hazards*. Toronto, Canada: Addiction Research Foundation (cit. on p. 337).

[Felter, 1900] H. W. Felter, ed. (1900). *American Medicinal Plants*. Sandy, OR: Eclectic Medical Journal Publications. Eclectic Medical (cit. on p. 162).

[Felter, 1922] H. W. Felter (1922). *The Eclectic Materia Medica, Pharmacology and Therapeutics*. Cincinnati, OH: Eclectic Medical Publications (cit. on pp. 119, 166).

[Ferenci, Scherzer, and Kerschner, 2008] P. Ferenci, T. M. Scherzer, and H. Kerschner (2008). "Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy". *Gastroenterology* 135.5, pp. 1561–1567 (cit. on p. 362).

[Fewtrell, Abbott, and K. Kennedy, 2004] M. S. Fewtrell, R. A. Abbott, and K. Kennedy (2004). "Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants". *Journal of Pediatrics* 144, pp. 471–479 (cit. on p. 197).

[Filaretov, 1986] A. A. Filaretov (1986). "Effect of adaptogens on the activity of the pituitary-adrenocortical system in rats". *Bulletin of Experimental Biology and Medicine* 101, pp. 627–629 (cit. on p. 100).

[Finkle and Zarlengo, 2004] R. S. Finkle and K. M. Zarlengo (2004). "Blue cohosh and perinatal stroke". *New England Journal of Medicine* 351, pp. 302–303 (cit. on p. 181).

[Fintelmann, 1970a] V. Fintelmann (1970a). "Zur Therapie der Fettleber mit Silymarin". *Die Therapiewoche* 20, pp. 1055–2064 (cit. on p. 355).

[Fintelmann, 1970b] — (1970b). "Zur Therapie der Fettleber mit Silymarin". *Die Therapiewoche* 20, pp. 1055–2064 (cit. on pp. 364, 367).

[Fintelmann and Albert, 1980a] V. Fintelmann and A. Albert (1980a). "Nachweis der therapeutischen Wirksamkeit von Legalon bei toxischen Lebererkrankungen im Doppelblindversuch". *Die Therapiewoche* 30, pp. 5589–5594 (cit. on pp. 354–355).

[Fintelmann and Albert, 1980b] — (1980b). "Nachweis der therapeutischen Wirksamkeit von Legalon bei toxischen Lebererkrankungen im Doppelblindversuch". German. *Die Therapiewoche* 30, pp. 5589–5594 (cit. on pp. 364, 367, 373).

[Fitzpatrick, 2000] M. Fitzpatrick (2000). "Soy formulas and the effects of isoflavones on the thyroid". *New Zealand Medical Journal* 113.1103, pp. 24–26 (cit. on p. 442).

[Flach, 2002] A. J. Flach (2002). "Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma". *Transactions of the American Ophthalmological Society Journal* 100, pp. 215–222 (cit. on p. 341).

[Flaig, Gustafson, and L. J. Su, 2007] T. W. Flaig, D. L. Gustafson, and L. J. Su (2007). "A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients". *Investigational New Drugs* 25.2, pp. 139–146 (cit. on pp. 360, 378).

[Flisiak and Prokopowicz, 1997] R. Flisiak and D. Prokopowicz (1997). "Effect of misoprostol on the course of viral hepatitis B". *Hepatogastroenterology* 44, pp. 1419–1425 (cit. on p. 366).

[Forgo, 1983] I. Forgo (1983). "Effect of drugs on physical performance and hormone system of sportsmen". *Münchener Medizinische Wochenschrift* 125, pp. 822–824 (cit. on pp. 103, 105).

[Forgo, Kayasseh, and Staub, 1981] I. Forgo, L. Kayasseh, and J. J. Staub (1981). "Effect of a standardized ginseng extract on general well-being, reaction capacity, pulmonary function and gonadal hormones". *Medizinische Welt* 19, pp. 751–756 (cit. on p. 106).

[Forgo and Kirchdorfer, 1981] I. Forgo and A. M. Kirchdorfer (1981). "On the question of influencing the performance of top sportsmen by means of biologically active substances". *Ärztliche Praxis* 33, pp. 1784–1786 (cit. on pp. 103, 105).

[Forgo and Kirchdorfer, 1982] — (1982). "The effect of different ginsenoside concentrations on physical work capacity". *Notabene medici* 12, pp. 721–727 (cit. on pp. 103, 105).

[Forgo and Schimert, 1985] I. Forgo and G. Schimert (1985). "The duration of effect of the standardized ginseng extract in healthy competitive athletes". *Notabene Medici* 15, pp. 636–640 (cit. on pp. 103, 105).

[S. Foster, 1991] S. Foster (1991). *Milk thistle- Silybum marianum*. American Botanical Council. Austin, TX. Chap. 305, pp. 3–7 (cit. on p. 357).

[S. Foster, 1999] — (1999). "Black cohosh: Cimicifuga racemosa: a literature review." *HerbalGram* 45, pp. 35–49 (cit. on pp. 166–167).

[S. Foster, 2009] — (2009). *Ginseng*. URL: http://www.stevenfoster.com/education/monograph/ginseng.html (cit. on pp. 78, 135).

[S Foster, 2012] S Foster (2012). *Sage*. URL: https://nccih.nih.gov/health/sage (cit. on pp. 410–411).

[S. Foster, 2014] S. Foster (2014). *Black Cohosh*. URL: http://www.stevenfoster.com/education/monograph/actaea.html (cit. on p. 166).

[Fox et al., 2004] P. Fox et al. (2004). "The effect of cannabis on tremor in patients with multiple sclerosis". *Neurology* 62.7, pp. 1105–1109 (cit. on p. 342).

[Fraj, 1996] J. Fraj et al. (1996). "Occupational asthma induced by aniseed". *Allergy* 51, pp. 337–349 (cit. on p. 130).

[Franco, 2005] A. V. Franco (2005). "Recurrent urinary tract infections. Best practice & research". *Clinical Obstetrics and Gynecology* 19.6, pp. 861–873 (cit. on p. 231).

[E. W. Freeman, 2010] E. W. Freeman (2010). "Therapeutic management of premenstrual syndrome". *Expert Opinion on Pharmacotherapy* 11.17, pp. 2879–2889 (cit. on p. 215).

[R. M. Freeman et al., 2006] R. M. Freeman et al. (2006). "The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS)". *International Urogynecology Journal and Pelvic Floor Dysfunction* 17.6, pp. 636–641 (cit. on p. 342).

[Frei-Kleiner et al., 2005] S. Frei-Kleiner et al. (2005). "Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial". *Maturitas* 51.4, pp. 397–404 (cit. on p. 172).

[F. Frerick, Kuhn, and Strenge-Hesse, 1990a] F. Frerick, U. Kuhn, and A. Strenge-Hesse (1990a). "Silymarin–ein Phytopharmakon zur Behandlung toxischen Leberschaden: Anwendungsbeobachtung bei 2169 Patienten". *Kassenarzt* 33, pp. 36–41 (cit. on p. 355).

[F. Frerick, Kuhn, and Strenge-Hesse, 1990b] — (1990b). "Silymarin–ein Phytopharmakon zur Behandlung toxischen Leberschaden: Anwendungsbeobachtung bei 2169 Patienten". *Kassenarzt* 33, pp. 36–41 (cit. on p. 364).

[Freudenstein, Dasenbrock, and Nisslein, 2002] J. Freudenstein, C. Dasenbrock, and T. Nisslein (2002). "Lack of promotion of estrogen-dependent mammary gland tumors in vivo by an isopropanolic Cimicifuga racemosa extract." *Cancer Research* 62, pp. 3448–3452 (cit. on p. 185).

[Fugh-Berman, 2003] A. Fugh-Berman (2003). "Bust enhancing herbal products". *Obstetrics & Gynecology* 101.6, pp. 1345–1349 (cit. on p. 263).

[Fukushima, Ohhashi, and Ohno, 2001] M. Fukushima, T. Ohhashi, and S. Ohno (2001). "Effects of diets enriched in n-6 or n-3 fatty acids on cholesterol metabolism in older rats chronically fed a cholesterol-enriched diet". *Lipids* 36, pp. 261–266 (cit. on p. 194).

[Fulder, 1977] S. Fulder (1977). "The growth of cultured human fibroblasts treated with hydrocortisone and extracts of the medicinal plant Panax ginseng". *Experimental Gerontology* 12, pp. 125–131 (cit. on p. 100).

[Fussel, Wolf, and Brattsröm, 2000] A. Fussel, A. Wolf, and A. Brattsröm (2000). "Effect of a fixed valerian-Hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study". *European Journal of Medical Research* 5, pp. 385–390 (cit. on p. 302).

[Fussel, Wolf, and Brattstrom, 2000] A. Fussel, A. Wolf, and A. Brattstrom (2000). "Effect of a fixed valerian-hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study". *European Journal of Medical Research* 5, pp. 385–390 (cit. on p. 304).

[Gadek, DeMichele, and Karlstad, 1999] J. E. Gadek, S. J. DeMichele, and M. D. Karlstad (1999). "Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome". *Critical Care Medicine* 27, pp. 1409–1420 (cit. on p. 196).

[Gaedeke et al., 1996] J. Gaedeke et al. (1996). "Cisplatin nephrotoxicity and protection by silibinin". *Nephrology Dialysis Transplantation* 11, pp. 55–62 (cit. on p. 367).

[Gallo, Zannoni, and Apollonio, 2005] D. Gallo, G. F. Zannoni, and P. Apollonio (2005). "Characterization of the pharmacologic profile of a standardized soy extract in the ovariectomized rat model of menopause: effects on bone, uterus, and lipid profile". *Menopause* 12.5, pp. 589–600 (cit. on p. 439).

[H. Gangrade, Mishra, and Kanshal, 1979] H. Gangrade, S. H. Mishra, and R. Kanshal (1979). "Antimicrobial activity of the oil and unsaponifiable matter of red rosette". *Indian Drugs* 16, pp. 147–148 (cit. on p. 287).

[S. K. Gangrade, 1991] S. K. Gangrade (1991). "In vitro antifungal effect of the essential oils". *Indian Perfumer* 35, pp. 46–48 (cit. on p. 127).

[Garcia et al., 1997] M. C. Garcia et al. (1997). "Composition and characterization of soyabean and related products". *Critical Reviews in Food Science and Nutrition* 37.4, pp. 361–391 (cit. on p. 431).

[Garcia-Bravo, 1997] B. Garcia-Bravo et al. (1997). "Occupational contact dermatitis from anethole in food handlers". *Contact Dermatitis* 37, pp. 38–39 (cit. on p. 130).

[Garcia-Pérez et al., 2009] M. A. Garcia-Pérez et al. (2009). "Isopropanolic Cimicifuga racemosa is favorable on bone markers but neutral on an osteoblastic cell line". *Fertility and Sterility* 91.4, pp. 1347–1350 (cit. on p. 173).

[Gazák, Walterová, and Kren, 2007] R. Gazák, D. Walterová, and V. Kren (2007). "Silybin and silymarinnew and emerging applications in medicine". *Current Medicinal Chemistry* 14.3, pp. 315–338 (cit. on pp. 359–360).

[Geller, Shulman, and Breemen, 2009] S. E. Geller, L. P. Shulman, R. B. van Breemen, et al. (2009). "Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial". *Menopause* 16.6, pp. 1156–1166 (cit. on p. 172).

[Genazzani and Sorrentino, 1962] E. Genazzani and L. Sorrentino (1962). "Vascular action of acteina: active constituent of Actaea racemosa L". *Nature* 194, pp. 544–545 (cit. on p. 175).

[Gerard, 1597] J. Gerard (1597). *The Herball, or Generall Historie of Plantes*, p. 880. side 903 (cit. on p. 119).

[Gerber et al., 1998] G. S. Gerber et al. (1998). "Saw palmetto ( Serenoa repens ) in men with lower urinary tract symptoms: effects on urodynamic parameters and voiding symptoms". *Urology* 51, pp. 1003–1007 (cit. on p. 426).

[Gerhard et al., 1998] I. Gerhard et al. (1998). "Mastodynon bei weiblicher Sterilität". *Forsch Komplementarmed Klass Naturheilkd* 5.6, pp. 272–278 (cit. on p. 216).

[Gerhauser, Alt, and Heiss, 2002] C. Gerhauser, A. Alt, and E. Heiss (2002). "Cancer chemopreventive activity of xanthohumol, a natural product derived from hop". *Molecular Cancer Therapeutics* 1, pp. 959–969 (cit. on p. 303).

[Gershbein, 1977a] L. L. Gershbein (1977a). "Regeneration of rat liver in the presence of essential oils and their components". *Food and Cosmetics Toxicology* 15, pp. 173–181 (cit. on p. 130).

[Gershbein, 1977b] — (1977b). "Regeneration of rat liver in the presence of essential oils and their components". *Food and Cosmetics Toxicology* 15.3, pp. 173–181 (cit. on p. 281).

[Geuenich, Goffinet, and Venzke, 2008] S. Geuenich, C. Goffinet, and S. Venzke (2008). "Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density". *Retrovirology* 5, p. 27 (cit. on p. 408).

[Gharagozloo, Moayedi, and Zakerinia, 2009] M. Gharagozloo, B. Moayedi, and M. Zakerinia (2009). "Combined therapy of silymarin and desferrioxamine in patients with beta-thalassemia major: a randomized double-blind clinical trial". *Fundamental & Clinical Pharmacology* 23.3, pp. 359–365 (cit. on p. 359).

[Gibson, Lines, and Neumann, 1992] R. A. Gibson, D. R. Lines, and M. A. Neumann (1992). "Gamma linolenic acid (GLA) content of encapsulated evening primrose oil products". *Lipids* 27, pp. 82–84 (cit. on p. 192).

[Gillan et al., 1995] R. Gillan et al. (1995). "Comparison of Cannabis sativa by random amplification of polymorphic DNA (RAPD) and HPLC of cannabinoids: a preliminary study". *Journal of Science and Technology* 35.3, pp. 169–177 (cit. on p. 339).

[1991], "Ginseng radix" (1991). *German Commission E Monograph* 11. Bundesanzeiger (cit. on pp. 105, 108).

[Gödecke, Lankin, and Nikolic, 2009a] T. Gödecke, D. C. Lankin, D. Nikolic, et al. (2009a). "Guanidine alkaloids and Pictet-Spengler adducts from black cohosh ( Cimicifuga racemosa )". *Journal of Natural Products* 72.3, pp. 433–437 (cit. on p. 168).

[Gödecke, Nikolic, and Lankin, 2009b] T. Gödecke, D. Nikolic, D. C. Lankin, et al. (2009b). "Phytochemistry of cimicifugic acids and associated bases in Cimicifuga racemosa root extracts". *Phytochemical Analysis* 20.2, pp. 120–133 (cit. on p. 168).

[D. P. Goel et al., 2004] D. P. Goel et al. (2004). "Doping-control urinalysis of a ginseng extract, Cold-fX , in athletes". *International Journal of Sport Nutrition and Exercise Metabolism* 14.4, pp. 473–480 (cit. on pp. 98, 153).

[Goepel et al., 1999] M. Goepel et al. (1999). "Saw palmetto extracts potently and noncompetitively inhibit human alpha1-adrenoceptors in vitro". *Prostate* 38.3, pp. 208–215 (cit. on p. 419).

[Goh and Loh, 2001] S. Y. Goh and K. C. Loh (2001). "Gynaecomastia and the herbal tonic Dong Quai". *Singapore Medical Journal* 42.3, pp. 115–116 (cit. on p. 263).

[Gool, Thijs, and Henquet, 2003] C. J. van Gool, C. Thijs, and C. J. Henquet (2003). "Gamma-linolenic acid supplementation for prophylaxis of atopic dermatitisa randomized controlled trial in infants at high familial risk". *American Journal of Clinical Nutrition* 77, pp. 943–951 (cit. on p. 196).

[Gorelick, 1995] N. J. Gorelick (1995). "Genotoxicity of trans-anethole in vitro". *Mutation Research* 326, pp. 199–209 (cit. on pp. 130–131).

[Green, Kearse, and McIntyre, 2001] K. Green, E. C. Kearse, and O. L. McIntyre (2001). "Interaction between delta-9-tetrahydrocannabinol and indomethacin". *Ophthalmic Research* 33.4, pp. 217–220 (cit. on pp. 341, 344).

[Greenblatt, Moltke, and Perloff, 2006] D. J. Greenblatt, L. L. von Moltke, and E. S. Perloff (2006). "Interaction of flurbiprofen with cranberry juice, grape juice, tea, and fluconazole: in vitro and clinical studies". *Clinical Pharmacology & Toxicology* 79.1, pp. 125–133 (cit. on p. 238).

[Greenlee et al., 2007] H. Greenlee et al. (2007). "Clinical applications of Silybum marianum in oncology". *Integrative Cancer Therapies* 6.2, pp. 158–165 (cit. on pp. 361, 374, 378).

[Grieve, 1971] M. Grieve (1971). *A Modern Herbal*. Vol. 1. New York, NY: Dover Publications, Inc (cit. on p. 110).

[Grieve, 1979] — (1979). *A Modern Herbal*. New York: Dover Publications, Inc. (cit. on p. 108).

[Griffin, 2006] J. Griffin (2006). *Beer & Brewing, The Brewing Process. Understanding Beer - A Broad Overview of Brewing, Tasting and Analyzing Beer*. URL: Jongriffin.com (cit. on p. 298).

[Gruenwald, 1998] J. Gruenwald (1998). "Standardized black cohosh (Cimicifuga) extract clinical monograph". *Quarterly Review of Natural Medicine Summer*, pp. 117–125 (cit. on p. 181).

[Grungreiff, Albrecht, and Strenge-Hesse, 1995a] K. Grungreiff, M. Albrecht, and A. Strenge-Hesse (1995a). "Benefit of medicinal liver therapy in general practice". *Die Medizinische Welt* 46, pp. 222–227 (cit. on p. 355).

[Grungreiff, Albrecht, and Strenge-Hesse, 1995b] — (1995b). "Benefit of medicinal liver therapy in general practice". *Die Medizinische Welt* 46, pp. 222–227 (cit. on p. 364).

[Guh et al., 1996] J. Guh et al. (1996). "Antiproliferative effect in rat vascular smooth muscle cells by osthole, isolated from Angelica pubescens". *European Journal of Pharmacology* 298.2, pp. 191–197 (cit. on p. 260).

[J. W. C. Gunn, 1920] J. W. C. Gunn (1920). "The carminative action of volatile oils". *Journal of Pharmacology and Experimental Therapeutics* 16, pp. 39–47 (cit. on p. 128).

[T. R. Gunn and I. M. Wright, 1996] T. R. Gunn and I. M. Wright (1996). "The use of black and blue cohosh in labour". *New Zealand Medical Journal* 109, pp. 410–411. eprint: http://www.ncbi.nlm.nih.gov/pubmed/8937396 (cit. on p. 181).

[A. Gupta, R. Gupta, and B. Lal, 2001] A. Gupta, R. Gupta, and B. Lal (2001). "Effect of Trigonella foenum graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double-blind placebo controlled study". *Journal of the Association of Physicians of India* 49, pp. 1057–1061 (cit. on pp. 289–290, 293–294).

[R. K. Gupta, Jain, and Thakur, 1986] R. K. Gupta, D. C. Jain, and R. S. Thakur (1986). "Minor steroidal sapogenins from fenugreek seeds, Trigonella foenum-graecum". *Journal of Natural Products* 49, p. 1153 (cit. on p. 288).

[S. Gupta, 1980] S. Gupta (1980). "A new mitogen and interferon inducer". *Clinical Research* 28, 504A (cit. on p. 100).

[Gutiérrez, Hidalgo, and Cantabrana, 1996] M. Gutiérrez, A. Hidalgo, and B. Cantabrana (1996). "Spasmolytic activity of a lipidic extract from Sabal serrulata fruits. Further study of the mechanisms underlying this activity". *Planta Medica* 62.6, pp. 507–511 (cit. on pp. 419, 426).

[C. C. d. Guzman and Siemonsma, 1999] C. C. de Guzman and J. S. Siemonsma, eds. (1999). *Plant resources of South-East Asia, No. 13. Spices*. Bogor, PROSEA (cit. on pp. 126, 130).

[G. Guzman, Kallwitz, and Wojewoda, 2009] G. Guzman, E. R. Kallwitz, and C. Wojewoda (2009). "Liver injury with features mimicking autoimmune hepatitis following the use of black cohosh". *Journal of Medical Case Reports*. DOI: 2009.918156 (cit. on p. 189).

[Haddad et al., 2005] P. S. Haddad et al. (2005). "Natural health products, modulation of immune function and prevention of chronic diseases". *Evidence-Based Complementary and Alternative Medicine* 2.4, pp. 513–520 (cit. on pp. 85, 142).

[Haimov-Kochman, Brzezinski, and Hochner-Celnikier, 2008] R. Haimov-Kochman, A. Brzezinski, and D. Hochner-Celnikier (2008). "Herbal remedies for menopausal symptoms: are we cautious enough?" *European Journal of Contraception and Reproductive Health Care* 13.2, pp. 133–137 (cit. on p. 259).

[Haimov-Kochman and Hochner-Celnikier, 2005a] R. Haimov-Kochman and D. Hochner-Celnikier (2005a). "Hot flashes revisited: pharmacological and herbal options for hot flashes management. What does the evidence tell us?" *Acta Obstetricia et Gynecologica Scandinavica* 84.10, pp. 972–979 (cit. on pp. 259, 263, 267).

[Haimov-Kochman and Hochner-Celnikier, 2005b] — (2005b). "Hot flashes revisited: pharmacological and herbal options for hot flashes management. What does the evidence tell us?" *Acta Obstetricia et Gynecologica Scandinavica* 84.10, pp. 972–979 (cit. on p. 448).

[Haines et al., 2008] C. J. Haines et al. (2008). "A randomized, double-blind, placebo-controlled study of the effect of a Chinese herbal medicine preparation (Dang Gui Buxue Tang) on menopausal symptoms in Hong Kong Chinese women". *Climacteric* 11.3, pp. 244–251 (cit. on pp. 256, 259).

[Halbach and Görler, 1971] G. Halbach and K. Görler (1971). "Separation of flavonoids from the fruits of St Mary's distel ( Silybum marianum ) [in German]". *Planta Medica* 19.4, pp. 293–298 (cit. on p. 359).

[W. Hall and Degenhardt, 2003] W. Hall and L. Degenhardt (2003). "Medical marijuana initiatives: are they justified? How successful are they likely to be?" *CNS Drugs* 17.10, pp. 689–697 (cit. on pp. 346–347, 352).

[Hallstrom, Fulder, and Carruthers, 1982] C. Hallstrom, S. Fulder, and M. Carruthers (1982). "Effect of ginseng on the performance of nurses on night duty". *Comparative medicine East and West* 6, pp. 277–282 (cit. on pp. 103, 105).

[Halmai and Novak, 1963] J. Halmai and I. Novak (1963). *Farmakognózia [Pharmacognosy]*. Budapest: Medicina Könyvhiadó (cit. on p. 126).

[Hamilton-Reeves et al., 2010] J. M. Hamilton-Reeves et al. (2010). "Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: results of a meta-analysis". *Fertility and Sterility* 94.3, pp. 997–1007 (cit. on pp. 442–443).

[Hampton et al., 2002] R. Hampton et al. (2002). "Comparative chemical attributes of native North American hop, Humulus lupulus var. lupuloides E. Small". *Phytochemistry* 61, pp. 855–862 (cit. on p. 300).

[B. H. Han, Y. N. Han, and M. H. Park, 1985] B. H. Han, Y. N. Han, and M. H. Park (1985). *Advances in Chinese medicinal materials research. Chemical and biochemical studies on antioxidant components of ginseng*. Ed. by HM Chang, WW Tso, and A Koo. Singapore: World Scientific Publishing, pp. 485–498 (cit. on p. 101).

[G. Q. Han, 1991] G. Q. Han (1991). "The screening of Chinese traditional drugs by biological assay and the isolation of some active components". *International Journal of Chinese Medicine* 16, pp. 1–17 (cit. on p. 271).

[Y. Han et al., 2009] Y. Han et al. (2009). "Effect of silymarin on the pharmacokinetics of losartan and its active metabolite E-3174 in healthy Chinese volunteers". *European Journal of Clinical Pharmacology* 65.6, pp. 585–591 (cit. on p. 374).

[Hann et al., 1991] S. Hann et al. (1991). "Angelica-induced phytophotodermatitis". *Photodermatology, Photoimmunology & Photomedicine* 8.2, pp. 84–85 (cit. on p. 263).

[Hannan, Rokeya, and Faruque, 2003] J. M. Hannan, B. Rokeya, and O. Faruque (2003). “Effect of soluble dietary fiber fraction of Trigonella foenum graecum on glycemic, insulinemic, lipidemic and platelet aggregation status of Type 2 diabetic model rats”. *Journal of Ethnopharmacology* 88, pp. 73–77 (cit. on p. 289).

[Hänsel, 1994] R. Hänsel, ed. (1994). *Hagers Handbuch der pharmazeutischen Praxis. Drogen PZ*. German. 5th ed. Vol. 6. Berlin: Springer. Hagers handbook of pharmaceutical practice. Vol. 6, Drugs PZ, 5th ed. (Cit. on pp. 126, 130).

[M. Harada, M. Suzuki, and Y., 1984] M. Harada, M. Suzuki, and Ozaki. Y. (1984). “Effect of Japanese Angelica root and peony root on uterine contraction in the rabbit in situ”. *Journal of Pharmacobio-dynamics* 7.5, p. 304311 (cit. on p. 112).

[T. Harada et al., 2002] T. Harada et al. (2002). “Congestive heart failure caused by digitalis toxicity in an elderly man taking a licorice-containing Chinese herbal laxative”. *Cardiology* 98.4, p. 218 (cit. on p. 328).

[Harbige et al., 2000] L. S. Harbige et al. (2000). “The protective effects of omega-6 fatty acids in experimental autoimmune encephalomyelitis (EAE) in relation to transforming growth factor-beta 1 (TGF-beta1) up-regulation and increased prostaglandin E2 (PGE2) production”. *Clinical & Experimental Immunology* 122, pp. 445–452 (cit. on p. 194).

[Harborne, Heywood, and C. A. Williams, 1969] J. B. Harborne, V. H. Heywood, and C. A. Williams (1969). “Distribution of myristicin in seeds of the umbelliferae”. *Phytochemistry* 8, p. 1729 (cit. on p. 121).

[Harland and Haffner, 2008] J. I. Harland and T. A. Haffner (2008). “Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol”. *Atherosclerosis* 200.1, pp. 13–27 (cit. on p. 437).

[Härmälä, 1992] P. Härmälä (1992). “A furanocoumarin from Angelica archangelica”. *Planta Medica* 58, pp. 287–289 (cit. on p. 112).

[Härmälä et al., 1992] P. Härmälä et al. (1992). “Choice of solvent in the extraction of Angelica archangelica roots with reference to calcium blocking activity”. *Planta Medica* 58.2, p. 176183 (cit. on pp. 112–113).

[Hartwell, 1967-1971] J. L. Hartwell (1967-1971). “Plants used against cancer. A survey”. *Lloydia*. Now published as "Journal of Natural Products" since 1979, pp. 30–34 (cit. on p. 299).

[Hasegawa, 2004] H. Hasegawa (2004). “Proof of the mysterious efficacy of ginseng: basic and clinical trials: metabolic activation of ginsenoside: deglycosylation by intestinal bacteria and esterification with fatty acid”. *Journal of Pharmacological Sciences* 95.2, pp. 153–157 (cit. on pp. 80, 138).

[Hassan Samira, 1985] M. M. Hassan Samira (1985). “Effect of the standardized ginseng extract G 115 on the metabolism and electrical activity of the rabbit’s brain”. *Journal of International Medical Research* 13, pp. 342–348 (cit. on p. 100).

[Hata, Kozawa, and Ikeshiro, 1967] K. Hata, M. Kozawa, and Y. Ikeshiro (1967). “On the coumarins of the roots of Angelica polymorpha Maxim. [in Japanese]”. *Yakugaku Zasshi* 87.4, pp. 464–465 (cit. on p. 257).

[Hayashino, 2005] Y. Hayashino (2005). “Is herbal "root" effective for reducing alcohol drinking?” *Alcoholism: Clinical and Experimental Research* 29.10, p. 1913 (cit. on pp. 72, 306, 308).

[Hayouni el, Chraief, and Abedrabba, 2008] A. Hayouni el, I. Chraief, and M. Abedrabba (2008). “Tunisian Salvia officinalis L. and Schinus molle L. essential oils: their chemical compositions and their preservative effects against Salmonella inoculated in minced beef meat”. *International Journal of Food Microbiology* 125.3, pp. 242–251 (cit. on p. 408).

[Z. He, R. Chen, and Y. Zhou, 2009] Z. He, R. Chen, and Y. Zhou (2009). “Treatment for premenstrual syndrome with Vitex agnus castus : a prospective, randomized, multi-center placebo controlled study in China”. *Maturitas* 63.1, pp. 99–103 (cit. on p. 215).

[A. Heck, 2000] A. Heck (2000). “Potential interactions between alternative therapies and warfarin”. *American Journal of Health-System Pharmacy* 57, pp. 1221–1227 (cit. on p. 116).

[A. M. Heck, DeWitt, and Lukes, 2000] A. M. Heck, B. A. DeWitt, and A. L. Lukes (2000). “Potential interactions between alternative therapies and warfarin”. *American Journal of Health-System Pharmacy* 57, pp. 1221–1230 (cit. on p. 398).

[Hedelin et al., 2011] M. Hedelin et al. (2011). “Dietary phytoestrogens and the risk of ovarian cancer in the women’s lifestyle and health cohort study”. *Cancer Epidemiology, Biomarkers & Prevention* 20.2, pp. 308–317 (cit. on p. 436).

[Held, 1993a] C. Held (1993a). “Therapy of toxic hepatopathies: Mary’s thistle extract lowers the fibrosis activity”. *Die Therapiewoche* 43, pp. 2002–2009 (cit. on p. 355).

[Held, 1993b] — (1993b). “Therapy of toxic hepatopathies: Mary’s thistle extract lowers the fibrosis activity”. *Die Therapiewoche* 43, pp. 2002–2009 (cit. on p. 365).

[Henz, 2000] B. M. Henz (2000). “Efficacy of borage oil in patients with atopic eczema”. *British Journal of Dermatology* 143, p. 201 (cit. on p. 196).

[Henz, Jablonska, and Van de Kerkhof, 1999] B. M. Henz, S. Jablonska, and P. C. Van de Kerkhof (1999). “Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema”. *British Journal of Dermatology* 140, pp. 685–688 (cit. on p. 196).

[Heo, S. T. Lee, and Chu, 2008] J. H. Heo, S. T. Lee, and K. Chu (2008). "An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease". *European Journal of Neurology* 15.8, pp. 865–868 (cit. on pp. 84, 141).

[Hepler and Frank, 1971] R. S. Hepler and I. R. Frank (1971). "Marihuana smoking and intraocular pressure". *Journal of the American Medical Association* 217.10, p. 1392 (cit. on p. 341).

[herbalgram, 1987] herbalgram (1987). *Dill Weed*. The Commission E Monographs. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0085.html (cit. on p. 249).

[herbalgram, 1989] — (1989). *Damiana leaf and herb*. The Commission E Monographs. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0079.html?ts=1434389392&signature=19a669c14949f0f526fcfaad4b7cb312 (cit. on pp. 246, 248).

[herbalgram, 1990a] — (1990a). *Angelica root*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0004.html (cit. on pp. 9, 110, 114–116).

[herbalgram, 1990b] — (1990b). *Caraway*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0048.html (cit. on p. 211).

[herbalgram, 1990c] — (1990c). *Caraway oil*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0047.html (cit. on p. 211).

[herbalgram, 1990d] — (1990d). *Dill Seed*. The Commission E Monographs. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0084.html (cit. on p. 249).

[herbalgram, 1990e] — (1990e). *Fenugreek seed*. The Commission E Monographs. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0100.html (cit. on p. 294).

[herbalgram, 1991a] — (1991a). *Fennel. Fennel*. The Commission E Monographs. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0099.html (cit. on p. 284).

[herbalgram, 1991b] — (1991b). *Unapproved herbs - borage*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0033.html (cit. on p. 198).

[herbalgram, 1992a] — (1992a). *Basil herb*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0015.html (cit. on p. 159).

[herbalgram, 1992b] — (1992b). *Chaste Tree*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0057.html (cit. on pp. 214, 224–225).

[herbalgram, 1994] — (1994). *Soy Phospholipid*. URL: http://cms.herbalgram.org/commissione/Monographs/Monograph0343.html (cit. on pp. 433–434, 442–444).

[herbalgram, 2000] herbalgram (2000). *Chaste Tree. Chaste tree fruit*. Herbal Medicine: Expanded Commission E Monographs. American Botanical Council. URL: http://cms.herbalgram.org/expandedE/ChasteTreefruit.html (cit. on p. 220).

[herbsataglance, 2012] herbsataglance (2012). *Soy*. URL: https://nccih.nih.gov/health/soy/ataglance.htm (cit. on pp. 428, 441).

[herbwisdom, 2015a] herbwisdom (2015a). *Basil*. RFI Media Ltd. URL: http://www.herbwisdom.com/herb-basil.html (cit. on pp. 12, 155–157, 159).

[herbwisdom, 2015b] — (2015b). *Black cohosh*. URL: http://www.herbwisdom.com/herb-black-cohosh.html (cit. on pp. 165, 168–169).

[herbwisdom, 2015c] — (2015c). *Borage*. URL: http://www.herbwisdom.com/herb-borage.html (cit. on pp. 13, 202, 205).

[herbwisdom, 2015d] — (2015d). *Chaste Tree*. URL: http://www.herbwisdom.com/herb-agnus-castus.html (cit. on pp. 213, 217, 220, 222, 224).

[herbwisdom, 2015e] — (2015e). *Cranberry*. URL: http://www.herbwisdom.com/herb-cranberry.html (cit. on pp. 231–232).

[herbwisdom, 2015f] — (2015f). *Damiana*. URL: http://www.herbwisdom.com/herb-damiana.html (cit. on pp. 244–245, 247).

[herbwisdom, 2015g] — (2015g). *Dill*. URL: http://www.herbwisdom.com/herb-dill.html (cit. on pp. 111, 251–253).

[herbwisdom, 2015h] — (2015h). *Dong Quai*. Hallnet Ltd. URL: http://www.herbwisdom.com/herb-dong-quai.html (cit. on pp. 255, 257).

[herbwisdom, 2015i] — (2015i). *Fennel*. RFI Media Ltd. URL: http://www.herbwisdom.com/herb-fennel.html (cit. on pp. 276–277).

[herbwisdom, 2015j] — (2015j). *Fenugreek*. RFI Media Ltd. URL: http://www.herbwisdom.com/herb-fenugreek.htm (cit. on p. 286).

[herbwisdom, 2015k] — (2015k). *Licorice root*. URL: http://www.herbwisdom.com/herb-licorice-root.html (cit. on pp. 19, 315–316, 318, 321–322, 325, 327, 333).

[herbwisdom, 2015l] — (2015l). *Milk thistle*. RFI Media Ltd. URL: http://www.herbwisdom.com/herb-milk-thistle.html (cit. on pp. 357–358, 362–363).

[herbwisdom, 2015m] — (2015m). *Peuraria Mirifica*. URL: http://www.herbwisdom.com/herb-peuraria-mirifica.html (cit. on pp. 380, 385–386).

[herbwisdom, 2015n] — (2015n). *Red Clover*. URL: http://www.herbwisdom.com/herb-red-clover.html (cit. on pp. 22, 391–394, 396).

[herbwisdom, 2015o] — (2015o). *Sage*. RFI Media ltd. URL: http://www.herbwisdom.com/herb-sage.html (cit. on pp. 404–405).

[herbwisdom, 2015p] — (2015p). *Saw Palmetto*. URL: http://www.herbwisdom.com/herb-saw-palmetto.html (cit. on pp. 414–415, 417, 427).

[herbwisdom, 2015q] — (2015q). *Soy*. URL: http://www.herbwisdom.com/herb-soy-isoflavones.html (cit. on pp. 429, 432–433, 443).

[herbwisdom, 2015r] herbwisdom (2015r). *Wild Yam*. URL: http://www.herbwisdom.com/herb-wild-yam.html (cit. on pp. 25, 447–448, 450–451).

[M. Herrmann, Joppe, and Schmaus, 2002] M. Herrmann, H. Joppe, and G. Schmaus (2002). "Thesinine-4-O-beta-D-glucoside the first glycosylated plant pyrrolizidine alkaloid from Borago officinalis". *Phytochemistry* 60, pp. 399–402 (cit. on pp. 193, 202, 205).

[Heyland, Dhaliwal, and Drover, 2003] D. K. Heyland, R. Dhaliwal, and J. W. Drover (2003). "Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients". *Journal of Parenteral and Enteral Nutrition* 27, pp. 355–374 (cit. on p. 196).

[Hiai, 1979] S. Hiai (1979). "Stimulation of pituitary-adrenocortical system by ginseng saponin". *Endocrinology Japan* 26, p. 661 (cit. on p. 100).

[Hiai, Sasaki, and Oura, 1979] S. Hiai, S. Sasaki, and H. Oura (1979). "Effects of Ginseng saponin on rat adrenal cyclic AMP". *Planta Medica* 37, pp. 15–19 (cit. on p. 100).

[Hikino, 1985a] H. Hikino (1985a). "Antihepatotoxic actions of ginsenosides from Panax ginseng roots". *Planta Medica* 51, pp. 62–64 (cit. on p. 100).

[Hikino, 1985b] — (1985b). "Antihepatotoxic activity of crude drugs". *Yakugaku Zasshi* 105, pp. 109–118 (cit. on p. 102).

[Hindin et al., 1994] R. Hindin et al. (1994). "Radioimmunoassay of hair for determination of cocaine, heroin, and marijuana exposure: comparison with self-report". *International Journal of Mental Health & Addiction* 29.6, pp. 771–789 (cit. on p. 339).

[Hirata, 1997] J. D. Hirata (1997). "Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial". *Fertility and Sterility* 68, pp. 981–986 (cit. on pp. 272–273).

[Hirata et al., 1997] J. D. Hirata et al. (1997). "Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial". *Fertility and Sterility* 68.6, pp. 981–986 (cit. on pp. 259, 267).

[Hirobe et al., 1997] C. Hirobe et al. (1997). "Cytotoxic flavonoids from Vitex agnus-castus". *Phytochemistry* 46.3, pp. 521–524 (cit. on p. 213).

[Hizli and Uygur, 2007] F. Hizli and M. C. Uygur (2007). "A prospective study of the efficacy of Serenoa repens , tamsulosin, and Serenoa repens plus tamsulosin treatment for patients with benign prostate hyperplasia". *International Urology and Nephrology* 39.3, pp. 879–886 (cit. on p. 420).

[Hoare, Li Wan Po, and H. Williams, 2000] C. Hoare, A. Li Wan Po, and H. Williams (2000). "Systematic review of treatments for atopic eczema". *Health Technology Assessment* 4, pp. 1–191 (cit. on p. 196).

[Hobbs, 1991] C. Hobbs (1991). "The chaste tree: Vitex agnus castus". *Pharmacy in History* 33.1, pp. 19–24 (cit. on p. 212).

[Hoberg et al., 1999] E. Hoberg et al. (1999). "Diterpenoids from the fruits of Vitex agnus-castus". *Phytochemistry* 52.8, pp. 1555–1558 (cit. on p. 213).

[Hoek, Hermans-Lokkerbol, and Verpoorte, 2001] A. C. Hoek, A. C. J. Hermans-Lokkerbol, and R. Verpoorte (2001). "An improved NMR method for the quantification of alpha-acids in hops and hop products". *Phytochemical Analysis* 12, pp. 53–57 (cit. on p. 300).

[Hohmann et al., 2003] J. Hohmann et al. (2003). "Phenylpropanoid glycosides and diterpenoids from Salvia officinalis". *Biochemical Systematics and Ecology* 31.4, pp. 427–429 (cit. on p. 405).

[Holdcroft et al., 2006] A. Holdcroft et al. (2006). "A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract ( Cannador ) for postoperative pain management". *Anesthesiology* 104.5, pp. 1040–1046 (cit. on pp. 343, 346).

[Homma, Oka, and Ikeshima, 1995] M. Homma, K. Oka, and K. Ikeshima (1995). "Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics". *Journal of Pharmacy and Pharmacology* 47.8, pp. 687–692 (cit. on p. 328).

[Hon, 1990] P. M. Hon (1990). "A ligustilide dimer from Angelica sinensis". *Phytochemistry* 29, pp. 1189–1191 (cit. on p. 271).

[Hon et al., 1990] P. M. Hon et al. (1990). "A ligustilide dimer from Angelica sinensis". *Phytochemistry* 29.4, pp. 1189–1191 (cit. on p. 257).

[Hooper, Kroon, and Rimm, 2008] L. Hooper, P. A. Kroon, and E. B. Rimm (2008). "Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials". *American Journal of Clinical Nutrition* 88.1, pp. 38–50 (cit. on pp. 437, 443).

[Hooper, Madhavan, et al., 2010] L. Hooper, G. Madhavan, et al. (2010). "Effects of isoflavones on breast density in pre- and post-menopausal women: a systematic review and meta-analysis of randomized controlled trials". *Human Reproduction Update* 16.6, pp. 745–760 (cit. on p. 435).

[Hooper, Ryder, and Kurzer, 2009] L. Hooper, J. J. Ryder, and M. S. Kurzer (2009). "Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis". *Human Reproduction Update* 15.4, pp. 423–440 (cit. on p. 439).

[Horiuchi et al., 2007] K. Horiuchi et al. (2007). "Antimicrobial activity of oleanolic acid from Salvia officinali s and related compounds on vancomycin-resistant enterococci (VRE)". *Biological and Pharmaceutical Bulletin* 30.6, pp. 1147–1149 (cit. on p. 408).

[Hornsey, 2003] I. S. Hornsey (2003). *A History of Beer and Brewing*. Royal Society of Chemistry, p. 305. ISBN: 9780854046300 (cit. on p. 298).

[Hosking and J. P. Zajicek, 2008] R. D. Hosking and J. P. Zajicek (2008). "Therapeutic potential of cannabis in pain medicine". *British Journal of Anaesthesia* 101.1, pp. 59–68 (cit. on p. 342).

[Hosoyama, Kuwahata, and Suga, 2007] H. Hosoyama, R. Kuwahata, and M. Suga (2007). "Menopausal disorder or skin aging preventing agents and food containing Pueraria mirifica and soybean isoflavones". *Kokai Tokkyo Koho* 7 (cit. on p. 384).

[Hou et al., 2004] Y. Z. Hou et al. (2004). "Protective effect of Ligusticum chuanxiong and Angelica sinensis on endothelial cell damage induced by hydrogen peroxide". *Life Sciences* 75.14, pp. 1775–1786 (cit. on p. 260).

[Hoult and Payá, 1996] J. R. Hoult and M. l. Payá (1996). "Pharmacological and biochemical actions of simple coumarins: natural products with therapeutic potential". *General Pharmacology* 27.4, pp. 713–722 (cit. on p. 264).

[Howell et al., 1998] A. B. Howell et al. (1998). "Inhibition of the adherence of p-fimbriated Escherichia coli to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries". *New England Journal of Medicine* 339.19, pp. 1085–1086 (cit. on p. 230).

[Howes et al., 2004] J. B. Howes et al. (2004). "The effects of dietary supplementation with isoflavones from red clover on cognitive function in postmenopausal women". *Climacteric* 7, pp. 70–77 (cit. on p. 399).

[Hruby, Caomos, and Thaler, 1984a] K. Hruby, G. Caomos, and H. Thaler (1984a). "Silbinin in the treatment of deathcap fungus poisoning". *Forum* 6, pp. 23–26 (cit. on p. 355).

[Hruby, Caomos, and Thaler, 1984b] — (1984b). "Silbinin in the treatment of deathcap fungus poisoning". *Forum* 6, pp. 23–26 (cit. on pp. 365, 367).

[H. Y. Hsu, 1986] H. Y. Hsu (1986). *Oriental materia medica, a concise guide*. Long Beach, CA: Oriental Healing Arts Institute (cit. on pp. 269, 273).

[Y. J. Hsu, Y. F. Lin, and Chau, 2003] Y. J. Hsu, Y. F. Lin, and T. Chau (2003). "Electrocardiographic manifestations in patients with thyrotoxic periodic paralysis". *American Journal of the Medical Sciences* 326.3, pp. 128–132 (cit. on p. 334).

[Hu, X. Yang, and P. C. Ho, 2005] Z. Hu, X. Yang, and P. C. Ho (2005). "Herb-drug interactions: a literature review". *Drugs* 65.9, pp. 1239–1282 (cit. on p. 374).

[K. C. Huang, 1993] K. C. Huang (1993). *The pharmacology of Chinese herbs. Herbs with multiple actions*. Boca Raton, FL: CRC Press, pp. 21–48 (cit. on p. 101).

[Y. Huang, B. Jiang, and Nuntanakorn, 2010] Y. Huang, B. Jiang, and P. Nuntanakorn (2010). "Fukinolic acid derivatives and triterpene glycosides from black cohosh inhibit CYP isozymes, but are not cytotoxic to Hep-G2 cells in vitro." *Current Drug Safety* 5.2, pp. 118–124 (cit. on pp. 182, 190).

[Huber et al., 2011] M. Huber et al. (2011). *How should we define health?* Volume 343, Issue d4163. British Medical Journal. URL: http://savenhshomeopathy.org/wp-content/uploads/2012/09/Huber-Definition-Health-BMJ-21.pdf (cit. on p. 27).

[Huddleston and E. A. Jackson, 2001] M. Huddleston and E. A. Jackson (2001). "Is an extract of the fruit of agnus castus (chaste tree or chasteberry) effective for prevention of symptoms of premenstrual syndrome (PMS)?" *The Journal of Family Practice* 50.4, p. 298 (cit. on p. 224).

[Huertas-Ceballos, Macarthur, and Logan, 2002] A. Huertas-Ceballos, C. Macarthur, and S. Logan (2002). "Dietary interventions for recurrent abdominal pain (RAP) in childhood". *Cochrane Database of Systematic Reviews* 2.CD003019 (cit. on p. 440).

[Huggett et al., 1997] A. C. Huggett et al. (1997). "Phyto-oestrogens in soy-based infant formula". *Lancet* 350.9080, pp. 815–816 (cit. on p. 442).

[Huh, H. R. Yang, and D. S. Park, 2006] J. E. Huh, H. R. Yang, and D. S. Park (2006). "Puerariae radix promotes differentiation and mineralization in human osteoblast-like SaOS-2 cells". *Journal of Ethnopharmacology* 104.3, pp. 345–350 (cit. on p. 308).

[A. L. Huntley and Ernst, 2003] A. L. Huntley and E. Ernst (2003). "A systematic review of herbal medicinal products for the treatment of menopausal symptoms". *Menopause* 10, pp. 465–476 (cit. on p. 393).

[A. Huntley and Ernst, 2003a] A. Huntley and E. Ernst (2003a). "A systematic review of the safety of black cohosh". *Menopause* 10.1, pp. 58–64 (cit. on p. 168).

[A. Huntley and Ernst, 2003b] — (2003b). "A systematic review of the safety of black cohosh". *Menopause* 10.1, pp. 58–64 (cit. on pp. 189–190).

[Huseini, Larijani, and Heshmat, 2006] H. F. Huseini, B. Larijani, and R. Heshmat (2006). "The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial". *Phytotherapy Research* 20.12, pp. 1036–1039 (cit. on p. 361).

[Hussain, 2007] S. A. Hussain (2007). "Silymarin as an adjunct to glibenclamide therapy improves long-term and postprandial glycemic control and body mass index in type 2 diabetes". *Journal of Medicinal Food* 10.3, pp. 543–547 (cit. on p. 361).

[Y. W. Hwang et al., 2009] Y. W. Hwang et al. (2009). "Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies". *Nutrition and Cancer* 61.5, pp. 598–606 (cit. on p. 435).

[N. A. Ibrahim et al., 2008] N. A. Ibrahim et al. (2008). "Gynecological efficacy and chemical investigation of Vitex agnus-castus L. fruits growing in Egypt". *Natural Product Research* 22.6, pp. 537–546 (cit. on p. 213).

[Y. K. Ibrahim and Ogunmodede, 1991] Y. K. Ibrahim and M. S. Ogunmodede (1991). "Growth and survival of Pseudomonas aeruginosa in some aromatic waters". *Pharmaceutica Acta Helvetiae* 66, pp. 286–288 (cit. on p. 122).

[Ihara-Watanabe et al., 1999] M. Ihara-Watanabe et al. (1999). "Effects of dietary alpha- or gamma-linolenic acids on levels and fatty acid compositions of serum and hepatic lipids, and activity and mRNA abundance of 3-hydroxy-3-methylglutaryl CoA reductase in rats". *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology* 122, pp. 213–220 (cit. on p. 194).

[Ikeda, Arase, and Kobayashi, 2006] K. Ikeda, Y. Arase, and M. Kobayashi (2006). "A long-term glycyrrhizin injection therapy reduces hepatocellular carcinogenesis rate in patients with interferon-resistant active chronic hepatitis C: a cohort study of 1249 patients". *Digestive Diseases and Sciences* 51.3, pp. 603–609 (cit. on p. 319).

[Imai et al., 2009] M. Imai et al. (2009). "Cytotoxic effects of flavonoids against a human colon cancer derived cell line, COLO 201: a potential natural anti-cancer substance". *Cancer Letters* 276.1, pp. 74–80 (cit. on p. 216).

[Imanshahidi and Hosseinzadeh, 2006] M. Imanshahidi and H. Hosseinzadeh (2006). "The pharmacological effects of Salvia species on the central nervous system". *Phytotherapy Research* 20.6, pp. 427–437 (cit. on pp. 407–408).

[Ingham, Markham, et al., 1986] J. L. Ingham, K. R. Markham, et al. (1986). "Puerarin 6'-O-beta-apiofuranoside, a C-glycosylisoflavone O-glycoside from Pueraria mirifica". *Phytochemistry* 25.7, pp. 1772–1775 (cit. on p. 381).

[Ingham, Tahara, and Dziedzic, 1986] J. L. Ingham, S. Tahara, and S. Z. Dziedzic (1986). "A chemical investigation of Pueraria mirifica roots". *Journal of Biosciences* 41.4, pp. 403–408 (cit. on pp. 381–382).

[Ingham, Tahara, and Dziedzic, 1988] — (1988). "Coumestans from the roots of Pueraria mirifica". *Journal of Biosciences* 43.1-2, pp. 5–10 (cit. on p. 382).

[Ingham, Tahara, and Dziedzic, 1989] — (1989). "Minor isoflavones from the roots of Pueraria mirifica". *Journal of Biosciences* 44.9-10, pp. 724–726 (cit. on p. 382).

[Inomata et al., 2005] N. Inomata et al. (2005). "Late-onset anaphylaxis to fermented soybeans: the first confirmation of food-induced, late-onset anaphylaxis by provocation test". *Annals of Allergy, Asthma & Immunology* 94.3, pp. 402–406 (cit. on p. 442).

[International Cyber Business Services, 2000] Inc. International Cyber Business Services, ed. (2000). *Angelica*. URL: http://www.holistic-online.com/Herbal-Med/_Herbs/h4.htm (visited on 10/16/2015) (cit. on p. 113).

[Isbrucker and Burdock, 2006] R. A. Isbrucker and G. A. Burdock (2006). "Risk and safety assessment on the consumption of Licorice root ( Glycyrrhiza sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin". *Regulatory Toxicology and Pharmacology* 46.3, pp. 167–192 (cit. on pp. 315, 317–320, 325–326, 332, 334).

[Ishikawa and Higuchi, 2006] T. Ishikawa and Y. Higuchi (2006). "Manufacture of miroestrol from Pueraria mirifica [in Japanese]". *Kokai Tokkyo Koho*. US patent application JP 2006-290822 (cit. on p. 382).

[Ishikawa and Sekine, 2001] T. Ishikawa and K. Sekine (2001). "Deoxymiroestrol as estrogen agonist and their therapeutic use [in Japanese]". *Kokai Tokkyo Koho*. US patent application JP 2001-122871 (cit. on p. 382).

[Ishiwatari, 2003] S. Ishiwatari (2003). "Irritation-decreasing compositions containing plant extracts for cosmetics and pharmaceuticals [in Japanese]". *Kokai Tokkyo Koho*. US patent application JP 2003-155246 (cit. on pp. 381, 387).

[Iskedjian et al., 2007] M. Iskedjian et al. (2007). "Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain". *Current Medical Research and Opinion* 23.1, pp. 17–24 (cit. on p. 343).

[Iwata, Hotta, and Goto, 2009] E. Iwata, H. Hotta, and M. Goto (2009). "The screening method of a bifidogenic dietary fiber extracted from inedible parts of vegetables". *Journal of Nutritional Science and Vitaminology* 55.4, pp. 385–388 (cit. on p. 448).

[M. Jackson, 1988] M. Jackson (1988). *The New World World Guide to Beer*. Philadelphia, Pennsylvania: Running Press, p. 18. ISBN: 0-89471-884-3 (cit. on p. 298).

[J. S. Jacobson, Troxel, and Evans, 2001] J. S. Jacobson, A. B. Troxel, J. Evans, et al. (2001). "Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer". *Journal of Clinical Oncology* 19.10, pp. 2739–2745 (cit. on p. 171).

[M. Jacobson, 1987] M. Jacobson (1987). "Optical isomers of $\alpha$-copaene derived from several plant sources". *Journal of Agricultural and Food Chemistry* 35, pp. 798–800 (cit. on p. 112).

[JAMA, 2002] JAMA (2002). "Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial." *Journal of the American Medical Association* 288, pp. 321–333. eprint: http://www.ncbi.nlm.nih.gov/pubmed/12117397 (cit. on p. 181).

[Jang et al., 2008] D. J. Jang et al. (2008). "Red ginseng for treating erectile dysfunction: a systematic review". *British Journal of Clinical Pharmacology* 66.4, pp. 444–450 (cit. on pp. 86, 143).

[Jankowski, 1973] K. Jankowski (1973). "Alkaloids of cranberries". *Experientia* 29.11, pp. 1334–1335 (cit. on p. 228).

[Jankowski, 1983] — (1983). "Trace glycoside from cranberries (vaccinium oxicoccos)". *Journal of Natural Products* 46, p. 190 (cit. on p. 228).

[Janssen, 1986] A. M. Janssen (1986). "Screening for antimicrobial activity of some essential oils by the agar overlay technique". *Pharmazeutisch Weekblad (Scientific Edition)* 8, pp. 289–292 (cit. on p. 127).

[Jaroenporn, Malaivijitnond, Wattanasirmkit, Trisomboon, et al., 2006] S. Jaroenporn, S. Malaivijitnond, K. Wattanasirmkit, H. Trisomboon, et al. (2006). "Effects of Pueraria mirifica , an herb containing phytoestrogens, on reproductive organs and fertility of adult male mice". *Endocrine* 30.1, pp. 93–101 (cit. on p. 383).

[Jaroenporn, Malaivijitnond, Wattanasirmkit, Watanabe, et al., 2007] S. Jaroenporn, S. Malaivijitnond, K. Wattanasirmkit, G. Watanabe, et al. (2007). "Assessment of fertility and reproductive toxicity in adult female mice after long-term exposure to Pueraria mirifica herb". *Journal of Reproduction and Development* 53.5, pp. 995–1005 (cit. on p. 387).

[Jarred, Keikha, and Dowling, 2002] R. A. Jarred, M. Keikha, and C. Dowling (2002). "Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones". *Cancer Epidemiology, Biomarkers & Prevention* 11, pp. 1689–1696 (cit. on pp. 396, 399).

[Jarry, 1991] H. Jarry (1991). "Agnus castus as a dopaminergic active constituent in Mastodynon". *Z Phytotherapy* 12, pp. 77–82 (cit. on p. 219).

[Jarry and Harnischfeger, 1985] H. Jarry and G. Harnischfeger (1985). "Endocrine effects of constituents of Cimicifuga racemosa. 1. The effect on serum levels of pituitary hormones in ovariectomized rats". German. *Planta Medica* 51.1, pp. 46–49 (cit. on p. 170).

[Jarry, Harnischfeger, and E. Düker, 1985] H. Jarry, G. Harnischfeger, and E. Düker (1985). "The endocrine effects of constituents of Cimicifuga racemosa. 2. In vitro binding of constituents to estrogen receptors". German. *Planta Medica* 51.4, pp. 316–319 (cit. on p. 170).

[Jarry, Metten, et al., 2003] H. Jarry, M. Metten, et al. (2003). "In vitro effects of the Cimicifuga racemosa extract BNO 1055". *Maturitas* 44 (Supplement 1), S31–S38 (cit. on p. 170).

[Jarry, Thelen, et al., 2005] H. Jarry, P. Thelen, et al. (2005). "Cimicifuga racemosa extract BNO 1055 inhibits proliferation of the human prostate cancer cell line LNCaP". *Phytomedicine* 12.3, pp. 178–182 (cit. on p. 174).

[Jarry et al., 1994a] H. Jarry et al. (1994a). "In vitro prolactin but not LH and FSH release is inhibited by compounds in extracts of Agnus castus : direct evidence for a dopaminergic principle by the dopamine receptor assay". *Experimental and Clinical Endocrinology & Diabetes* 102.6, pp. 448–454 (cit. on p. 214).

[Jarry et al., 1994b] — (1994b). "In vitro prolactin but not LH and FSH release is inhibited by compounds in extracts of Agnus castus: direct evidence for a dopaminergic principle by the dopamine receptor assay". *Experimental and Clinical Endocrinology & Diabetes* 102.6, pp. 448–454 (cit. on p. 219).

[Javidnia et al., 2003] K. Javidnia et al. (2003). "Antihirsutism activity of fennel (fruits of Foeniculum vulgare) extract. A double-blind placebo controlled study". *Phytomedicine* 10.6-7, pp. 455–458 (cit. on p. 281).

[M. A. Jenkins, 1996] M. A. Jenkins (1996). *Antioxidants and Free radicals*. URL: http://www.rice.edu/~jenky/sports/antiox.html (cit. on p. 455).

[Jenner, 1964] P. Jenner et al. (1964). "Food flavourings and compounds of related structure. I. Acute oral toxicity". *Food and Cosmetics Toxicology* 2, pp. 327–343 (cit. on p. 132).

[G. C. Jeon et al., 2005a] G. C. Jeon et al. (2005a). "Antitumor activity of spinasterol isolated from Pueraria roots". *Experimental & Molecular Medicine* 37.2, pp. 111–120 (cit. on p. 308).

[G. C. Jeon et al., 2005b] — (2005b). "Antitumor activity of spinasterol isolated from Pueraria roots". *Experimental & Molecular Medicine* 37.2, pp. 111–120 (cit. on p. 382).

[Jepson and J. C. Craig, 2008] R. G. Jepson and J. C. Craig (2008). "Cranberries for preventing urinary tract infections". *Cochrane Database of Systematic Reviews* 1 (CD001321) (cit. on p. 231).

[Jepson, Mihaljevic, and J. Craig, 2004] R. G. Jepson, L. Mihaljevic, and J. Craig (2004). "Cranberries for preventing urinary tract infections". *Cochrane Database of Systematic Reviews* 2 (CD001321) (cit. on pp. 231, 236).

[Ji, Y. F. Chai, and Y. T. Wu, 1999] S. G. Ji, Y. F. Chai, and Y. T. Wu (1999). "Determination of ferulic acid in Angelica sinensis and Chuanxiong by capillary zone electrophoresis". *Biomedical Chromatography* 13.5, pp. 333–334 (cit. on p. 257).

[Jia, Y. Zhao, and X. Liang, 2009] L. Jia, Y. Zhao, and X.J. Liang (2009). "Current evaluation of the millennium phytomedicine-ginseng (II): Collected chemical entities, modern pharmacology, and clinical applications emanated from traditional Chinese medicine." *Current Medicinal Chemistry* 16.22, pp. 2924–2942 (cit. on pp. 78–79, 136–137).

[B. Jiang, Lyles, et al., 2008] B. Jiang, J. T. Lyles, et al. (2008). "Stability evaluation of selected polyphenols and triterpene glycosides in black cohosh". *Journal of Agricultural and Food Chemistry* 56.20, pp. 9510–9519 (cit. on p. 169).

[B. Jiang, H. Yang, et al., 2005] B. Jiang, H. Yang, et al. (2005). "The value of plant collections in ethnopharmacology: a case study of an 85-year-old black cohosh ( Actaea racemosa L.) sample". *Journal of Ethnopharmacology* 96.3, pp. 521–528 (cit. on p. 169).

[B. Jiang, Kronenberg, and Nuntanakorn, 2006] B. Jiang, F. Kronenberg, P. Nuntanakorn, et al. (2006). "Evaluation of the botanical authenticity and phytochemical profile of black cohosh products by high-performance liquid chromatography with selected ion monitoring liquid chromatography-mass spectrometry". *Journal of Agricultural and Food Chemistry* 54, pp. 3242–3253 (cit. on p. 179).

[X. Jiang, K. M. Williams, and Liauw, 2004] X. Jiang, K. M. Williams, and W. S. Liauw (2004). "Effect of St. John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects". *British Journal of Clinical Pharmacology* 57.5, pp. 592–599. [published correction appears in British Journal of Clinical Pharmacology 2004;58(1):102] (cit. on pp. 89, 146).

[Jie, Cammisuli, and Baggiolini, 1984] Y. H. Jie, S. Cammisuli, and M. Baggiolini (1984). "Immunomodulatory effects of Panax ginseng C. A. Meyer in the mouse". *Agents and Actions* 15, pp. 386–391 (cit. on p. 100).

[Johnson, 2007] K. Johnson (2007). *Red Clover, Trifolium pratense L.* URL: https://www.agry.purdue.edu/ext/forages/ForageID/legumes/red_clover.htm (cit. on p. 390).

[B. D. Jones and Runikis, 1987] B. D. Jones and A. M. Runikis (1987). "Interaction of ginseng with phenelzine". *Journal of Clinical Psychopharmacology* 7, pp. 201–202 (cit. on p. 107).

[T. K. Jones and B. M. Lawson, 1998] T. K. Jones and B. M. Lawson (1998). "Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication". *Journal of Pediatrics* 132, pp. 550–552 (cit. on p. 181).

[S. Jordan, Murty, and Perwaiz, 2008] S. Jordan, M. Murty, S. Perwaiz, et al. (2008). "Hepatotoxic reaction associated with a product containing "black cohosh": one case of mistaken identity [abstract 709]". *Journal of the Society of Toxicology* S1 (cit. on p. 179).

[Jovanovski, A. Jenkins, and Dias, 2010] E. Jovanovski, A. Jenkins, and A. G. Dias (2010). "Effects of Korean red ginseng (Panax ginseng C.A. Mayer) and its isolated ginsenosides and polysaccharides on arterial stiffness in healthy individuals". *American Journal of Hypertension* 23.5, pp. 469–472 (cit. on pp. 82, 140).

[D. Joy, J. Joy, and Duane, 2008] D. Joy, J. Joy, and P. Duane (2008). "Black cohosh: a cause of abnormal postmenopausal liver function tests". *Climacteric* 11.1, pp. 84–88 (cit. on p. 190).

[Juhás, Cikos, and Czikková, 2008] S. Juhás, S. Cikos, and S. Czikková (2008). "Effects of borneol and thymoquinone on TNBS-induced colitis in mice". *Folia Biologica* 54.1, pp. 1–7 (cit. on p. 407).

[Juliá Mollá et al., 2009] M. D. Juliá Mollá et al. (2009). "Cimicifuga racemosa treatment and health related quality of life in post-menopausal Spanish women". *Gynecological Endocrinology* 25.1, pp. 21–26 (cit. on p. 172).

[J. I. Jung, Lim, and H. J. Choi, 2006] J. I. Jung, S. S. Lim, and H. J. Choi (2006). "Isoliquiritigenin induces apoptosis by depolarizing mitochondrial membranes in prostate cancer cells". *Journal of Nutritional Biochemistry* 17.10, pp. 689–696 (cit. on p. 319).

[El-Kady, El-Maraghy, and Eman Mostafa, 1995] I. A. El-Kady, S. S. El-Maraghy, and M. Eman Mostafa (1995). "Natural occurrence of mycotoxins in different spices in Egypt". *Folia Microbiologica* 40, pp. 297–300 (cit. on p. 120).

[Kaku, Yunoki, and Ohkura, 2001] S. Kaku, S. Yunoki, and K. Ohkura (2001). "Interactions of dietary fats and proteins on fatty acid composition of immune cells and LTB4 production by peritoneal exudate cells of rats". *Bioscience, Biotechnology, and Biochemistry* 65, pp. 315–321 (cit. on p. 194).

[El-Kamary, Shardell, and Abdel-Hamid, 2009] S. S. El-Kamary, M. D. Shardell, and M. Abdel-Hamid (2009). "A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis". *Phytomedicine* 16.5, pp. 391–400 (cit. on p. 362).

[Kapoor and Klimaszewski, 2000] R. Kapoor and A. Klimaszewski (2000). "Efficacy of borage oil in patients with atopic eczema". *British Journal of Dermatology* 143, pp. 200–201 (cit. on p. 196).

[Karawya et al., 1980] M. S. Karawya et al. (1980). "Mucilagenous contents of certain Egyptian plants". *Planta Medica* 38, pp. 73–78 (cit. on p. 288).

[Karlstad et al., 1993] M. D. Karlstad et al. (1993). "Effect of intravenous lipid emulsions enriched with gamma-linolenic acid on plasma n-6 fatty acids and prostaglandin biosynthesis after burn and endotoxin injury in rats". *Critical Care Medicine* 21, pp. 1740–1749 (cit. on p. 195).

[Karnick, 1994] C. R. Karnick (1994). *Pharmacopoeial Standards of Herbal Plants*. Vol. 1. Delhi, India: Sri Satguru Publications, p. 1112 (cit. on pp. 115, 117).

[Karst and Wippermann, 2009] M. Karst and S. Wippermann (2009). "Cannabinoids against pain. Efficacy and strategies to reduce psychoactivity: a clinical perspective". *Expert Opinion on Investigational Drugs* 18.2, pp. 125–133 (cit. on pp. 343–344).

[Kartmazova et al., 1980] D. S. Kartmazova et al. (1980). "Morphological and anatomical diagnosis of the subterranean vegetative organs of Pueraria lobata . I [in Ukranian]". *Khimiko Farmatsevticheskii Zhurnal* 3, pp. 61–63 (cit. on p. 306).

[Kassir, 1985] Z. A. Kassir (1985). "Endoscopic controlled trial of four drug regimens in the treatment of chronic duodenal ulceration". *Irish Journal of Medical Science* 78, pp. 153–156 (cit. on pp. 319, 332).

[Katdare, Osborne, and Telang, 1998] M. Katdare, M. P. Osborne, and N. T. Telang (1998). "Inhibition of aberrant proliferation and induction of apoptosis in pre-neoplastic human mammary epithelial cells by natural phytochemicals". *Oncology Reports* 5.2, pp. 311–315 (cit. on p. 436).

[Katiyar, 2005] S. K. Katiyar (2005). "Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects (Review)". *International Journal of Oncology* 26.1, pp. 169–176 (cit. on p. 360).

[Katiyar et al., 1997] S. K. Katiyar et al. (1997). "Protective effects of silymarin against photocarcinogenesis in a mouse skin model". *Journal of the National Cancer Institute* 89, pp. 556–566 (cit. on p. 366).

[Kaul, Kreml, and Austria, 2008] N. Kaul, R. Kreml, and J. A. Austria (2008). "A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers". *Journal of the American College of Nutrition* 27.1, pp. 51–58 (cit. on p. 344).

[Kaviarasan, Vijayalakshmi, and Anuradha, 2004] S. Kaviarasan, K. Vijayalakshmi, and C. V. Anuradha (2004). "Polyphenol-rich extract of fenugreek seeds protect erythrocytes from oxidative damage". *Plant Foods for Human Nutrition* 59, pp. 143–147 (cit. on p. 291).

[Kelley and D. G. Carroll, 2010] K. W. Kelley and D. G. Carroll (2010). "Evaluating the evidence for over-the-counter alternatives for relief of hot flashes in menopausal women". *Journal of American Pharmacists Association* 50.5, e106–e115 (cit. on p. 448).

[El-Keltawi, Megalla, and Ross, 1980] N. E. M. El-Keltawi, S. E. Megalla, and S. A. Ross (1980). "Antimicrobial activity of some Egyptian aromatic plants". *Herba polonica* 26, pp. 245–250 (cit. on p. 127).

[D. O. Kennedy, Pace, et al., 2006] D. O. Kennedy, S. Pace, et al. (2006). "Effects of cholinesterase inhibiting sage ( Salvia officinalis ) on mood, anxiety and performance on a psychological stressor battery". *Neuropsychopharmacology* 31.4, pp. 845–852 (cit. on p. 407).

[D. O. Kennedy and A. B. Scholey, 2006] D. O. Kennedy and A. B. Scholey (2006). "The psychopharmacology of European herbs with cognition-enhancing properties". *Current Pharmaceutical Design* 12.35, pp. 4613–4623 (cit. on pp. 406–407, 412).

[Kennelly, Baggett, and Nuntanakorn, 2002] E. J. Kennelly, S. Baggett, P. Nuntanakorn, et al. (2002). "Analysis of thirteen populations of black cohosh for formononetin". *Phytomedicine* 9.5, pp. 461–467 (cit. on p. 169).

[Kerrola, 1994a] K. Kerrola (1994a). "Characterization of volatile composition and odor of Angelica (Angelica archangelica subsp. archangelica L.) root extracts". *Journal of Agricultural and Food Chemistry* 42, pp. 1979–1985 (cit. on p. 112).

[Kerrola, 1994b] — (1994b). "Extraction of volatile compounds of Angelica (Angelica archangelica) root by liquid carbon dioxide". *Journal of Agricultural and Food Chemistry* 42, pp. 2235–2245 (cit. on p. 112).

[Keung, 1993] W. M. Keung (1993). "Biochemical studies of a new class of alcohol dehydrogenase inhibitors from Radix puerariae". *Alcoholism: Clinical and Experimental Research* 17.6, pp. 1254–1260 (cit. on pp. 306–307, 310).

[Keung, 2003] — (2003). "Anti-dipsotropic isoflavones: the potential therapeutic agents for alcohol dependence". *Medicinal Research Reviews* 23.6, pp. 669–696 (cit. on p. 307).

[Keung and Vallee, 1993a] W. M. Keung and B. L. Vallee (1993a). "Daidzin: a potent, selective inhibitor of human mitochondrial aldehyde dehydrogenase". *Proceedings of the National Academy of Sciences* 90.4, pp. 1247–1251 (cit. on p. 306).

[Keung and Vallee, 1993b] — (1993b). "Daidzin and daidzein suppress free-choice ethanol intake by Syrian golden hamsters". *Proceedings of the National Academy of Sciences* 90.21, pp. 10008–10012 (cit. on p. 307).

[Keung and Vallee, 1998] — (1998). "Kudzu root: an ancient Chinese source of modern antidipsotropic agents". *Phytochemistry* 47.4, pp. 499–506 (cit. on p. 307).

[Khafagy, Salam, and Hamid, 1981] S. M. Khafagy, N. A. Salam, and R. A. Hamid (1981). "Constituents of Silybum marianum (L.) Gaertn. (Compositae)". *Scientia Pharmaceutica* 49, pp. 157–161 (cit. on p. 359).

[Al-Khamees, 2011] W. A. A. Al-Khamees (2011). "Status Epilepticus Associated with Borage Oil Ingestion". *Journal of Medical Toxicology*, pp. 154–157 (cit. on p. 204).

[Khosla, D. D. Gupta, and Nagpal, 1995] P. Khosla, D. D. Gupta, and R. K. Nagpal (1995). "Effect of Trigonella foenum graecum (fenugreek) on blood glucose in normal and diabetic rats". *Indian Journal of Physiology and Pharmacology* 39, pp. 173–174 (cit. on p. 289).

[Kidd and Head, 2005] P. Kidd and K. Head (2005). "A review of the bioavailability and clinical efficacy of milk thistle phytosome: a silybin-phosphatidylcholine complex ( Siliphos )". *Alternative Medicine Review* 10.3, pp. 193–203 (cit. on p. 379).

[Kiesewetter, Leodolter, and Thaler, 1977] E. Kiesewetter, I. Leodolter, and H. Thaler (1977). "Results of two double-blind studies on the effect of silymarine in chronic hepatitis (author's transl)". *Leber, Magen, Darm Journal* 7, pp. 318–323 (cit. on p. 366).

[C. Kim, 1976] C. Kim (1976). "Influence of ginseng on mating behavior in male rats". *American journal of Chinese Medicine* 4, pp. 163–168 (cit. on p. 102).

[D. H. Kim et al., 2002] D. H. Kim et al. (2002). "Repellent activity of constituents identified in Foeniculum vulgare fruit against Aedes aegypti (Diptera: Culicidae)." *Journal of Agricultural and Food Chemistry* 50.24, pp. 6993–6996 (cit. on p. 279).

[H. Kim, 1992] H. Kim (1992). "Ginsenosides protect pulmonary vascular endothelium against radicalinduced injury". *Biochemical and Biophysical Research Communications* 189, pp. 670–676 (cit. on p. 101).

[J. H. Kim, C. Y. Park, and S. J. Lee, 2006] J. H. Kim, C. Y. Park, and S. J. Lee (2006). "Effects of sun ginseng on subjective quality of life in cancer patients: a double-blind, placebo-controlled pilot trial". *Journal of Clinical Pharmacy and Therapeutics* 31.4, pp. 331–334 (cit. on pp. 81, 139).

[J. Kim et al., 2011] J. Kim et al. (2011). "Fermented and non-fermented soy food consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational studies". *Cancer Science* 102.1, pp. 231–244 (cit. on p. 436).

[T. H. Kim, S. H. Jeon, and Hahn, 2009] T. H. Kim, S. H. Jeon, and E. J. Hahn (2009). "Effects of tissue-cultured mountain ginseng (Panax ginseng CA Meyer) extract on male patients with erectile dysfunction". *Asian Journal of Andrology* 11.3, pp. 356–361 (cit. on pp. 86, 143).

[Kimura and Okuda, 1997] Y. Kimura and H. l. Okuda (1997). "Histamine-release effectors from Angelica dahurica var. dahurica root". *Journal of Natural Products* 60.3, pp. 249–251 (cit. on p. 260).

[Kiong, 2001] H. N. Kiong (2001). "Gynaecomastia and the herbal tonic Dong Quai". *Singapore Medical Journal* 42.6, pp. 286–287 (cit. on p. 263).

[Kirsch, Beauchamp, and Buettner, 2012] F. Kirsch, J. Beauchamp, and A. Buettner (2012). "Time-dependent aroma changes in breast milk after oral intake of a pharmacological preparation containing 1,8-cineole". *Clinical Nutrition* 31, pp. 682–692 (cit. on p. 158).

[Kirsch and Buettner, 2013] F. Kirsch and A. Buettner (2013). "Characterisation of the metabolites of 1,8-cineole transferred into human milk: Concentrations and ratio of enantiomers". *Metabolites* 3, pp. 47–71. DOI: 10.3390/metabo3010047 (cit. on p. 158).

[Kirsch, Horst, and Rohrig, 2013] F. Kirsch, K. Horst, and W. Rohrig (2013). "Tracing metabolite profiles in human milk: studies on the odorant 1,8-cineole transferred into breast milk after oral intake". *Metabolomics* 9, pp. 483–496. DOI: 10.1007/s11306-012-0466-9 (cit. on p. 158).

[Kitaoka, Uchida, and Okamoto, 2009] K. Kitaoka, K. Uchida, and N. Okamoto (2009). "Fermented ginseng improves the first-night effect in humans". *Sleep* 32.3, pp. 413–421 (cit. on pp. 83, 141).

[Kittur, Wilasrusmee, and Pedersen, 2002] S. Kittur, S. Wilasrusmee, and W. A. Pedersen (2002). "Neurotrophic and neuroprotective effects of milk thistle ( Silybum marianum ) on neurons in culture". *Journal of Molecular Neuroscience* 18.3, pp. 265–269 (cit. on p. 360).

[Knapik, J. E. Wright, and Welch, 1983] J. J. Knapik, J. E. Wright, and M. J. Welch (1983). "The influence of Panax ginseng on indices of substrate utilization during repeated, exhaustive exercise in man". *Federation proceedings* 42, p. 336 (cit. on p. 103).

[Knight, 2015] P. D. Knight (2015). "HOPS IN BEER". *USA Hops*. Hop Growers of America (cit. on p. 299).

[F. N. Ko et al., 1992] F. N. Ko et al. (1992). "Vasorelaxation of rat thoracic aorta caused by osthole isolated from Angelica pubescens". *European Journal of Pharmacology* 219.1, pp. 29–34 (cit. on p. 260).

[W. C. Ko, 1980] W. C. Ko (1980). "A newly isolated antispasmodic - butylidenephthalide". *Japanese Journal of Pharmacology* 30.1, pp. 85–91 (cit. on pp. 258, 260, 264).

[Kojodjojo et al., 2006] P. Kojodjojo et al. (2006). "The effects of carbenoxolone on human myocardial conduction: a tool to investigate the role of gap junctional uncoupling in human arrhythmogenesis". *Journal of the American College of Cardiology* 48.6, pp. 1242–1249 (cit. on p. 320).

[Kolios, Schumann, and Sehmisch, 2010] L. Kolios, J. Schumann, S. Sehmisch, et al. (2010). "Effects of black cohosh ( Cimicifuga racemosa ) and estrogen on metaphyseal fracture healing in the early stage of osteoporosis in ovariectomized rats". *Planta Medica* 76.9, pp. 850–857 (cit. on p. 173).

[Komesaroff et al., 2001] P. A. Komesaroff et al. (2001). "Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women". *Climacteric* 4.2, pp. 144–150 (cit. on pp. 448–451).

[Kong, Y. Z. Zhang, and X. Wu, 2009] X. F. Kong, Y. Z. Zhang, and X. Wu (2009). "Fermentation characterization of Chinese yam polysaccharide and its effects on the gut microbiota of rats". *International Journal of Microbiology* 2009, p. 598152 (cit. on pp. 446, 448).

[Konoike and Yamashita, 2006] S. Konoike and Y. Yamashita (2006). "Antiaging cosmetics containing acylated oligopeptides and Pueraria plants [in Japanese]". *Kokai Tokkyo Koho*. US patent application JP 2006-176431 (cit. on pp. 381, 387).

[Kontiokari et al., 2005] T. Kontiokari et al. (2005). "Cranberry juice and bacterial colonization in children–a placebo-controlled randomized trial". *Clinical Nutrition* 24.6, pp. 1065–1072 (cit. on pp. 233, 240–241).

[Kopec, 1999] K. Kopec (1999). "Herbal medications and breastfeeding". *Journal of Human Lactation* 15, pp. 157–161 (cit. on p. 157).

[Korczyn and Eshel, 1982] A. D. Korczyn and Y. Eshel (1982). "Mydriasis induced by tetrahydrocannabinol (THC) in rats". *Investigative Ophthalmology & Visual Science* 22.3, pp. 408–410 (cit. on p. 341).

[Koriech, 1978] O. M. Koriech (1978). "Ginseng and mastalgia". *British Medical Journal* 297, p. 1556 (cit. on p. 106).

[Korman, E. Cohen, and Preminger, 2001] S. H. Korman, E. Cohen, and A. Preminger (2001). "Pseudo-maple syrup urine disease due to maternal prenatal ingestion of fenugreek". *Journal of Paediatrics and Child Health* 37, pp. 403–404 (cit. on p. 293).

[Kosuge, Yokota, and Sugiyama, 1985] T. Kosuge, M. Yokota, and K. Sugiyama (1985). "Studies on bioactive substances in crude drugs used for arthritic diseases in traditional Chinese medicine. II. Isolation and identification of an anti-inflammatory and analgesic principle from the root of Angelica pubescens Maxim". *Chemical and Pharmaceutical Bulletin* 33.12, pp. 5351–5354 (cit. on p. 260).

[Kozawa et al., 1980] M. Kozawa et al. (1980). "Studies on coumarins from the root of Angelica pubescens Maxim. III. Structures of various coumarins including angelin, a new prenylcoumarin". *Chemical and Pharmaceutical Bulletin* 28.6, pp. 1782–1787 (cit. on p. 257).

[Kraft, Frickey, and Kaufmann, 2008] B. Kraft, N. A. Frickey, and R. M. Kaufmann (2008). "Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers". *Anesthesiology* 109.1, pp. 101–110 (cit. on p. 343).

[Krebs et al., 2004] E. E. Krebs et al. (2004). "Phytoestrogens for treatment of menopausal symptoms: a systematic review". *Obstetrics & Gynecology* 104.4, pp. 824–836 (cit. on p. 439).

[Kren and Walterová, 2005] V. Kren and D. Walterová (2005). "Silybin and silymarinnew effects and applications". *Biomedical papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia* 149.1, pp. 29–41 (cit. on p. 359).

[Kroll, Shaw, and Oberlies, 2007] D. J. Kroll, H. S. Shaw, and N. H. Oberlies (2007). "Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies". *Integrative Cancer Therapies* 6.2, pp. 110–119 (cit. on pp. 359, 374).

[Kronenberg and Fugh-Berman, 2002a] F. Kronenberg and A. Fugh-Berman (2002a). "Complementary and alternative medicine for menopausal symptoms: A review of randomized, controlled trials". *Annals of Internal Medicine* 137.10, pp. 805–813 (cit. on p. 439).

[Kronenberg and Fugh-Berman, 2002b] — (2002b). "Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials". *Annals of Internal Medicine* 137.10, pp. 805–813 (cit. on pp. 259, 263).

[Kruger et al., 1998] M. C. Kruger et al. (1998). "Calcium, gamma-linolenic acid and eicosapentenoic acid supplementation in senile osteoporosis". *Aging (Milano)* 10, pp. 385–394 (cit. on p. 197).

[Kruse et al., 1999] S. O. Kruse et al. (1999). "Fukiic and piscidic acid esters from the rhizome of Cimicifuga racemosa and the in vitro estrogenic activity of fukinolic acid." *Planta Medica* 65, pp. 763–764. eprint: http://www.ncbi.nlm.nih.gov/pubmed/10630125 (cit. on pp. 181, 185–186).

[Kubo et al., 1975] M. Kubo et al. (1975). "Isolation of a new isoflavone from Chinese Pueraria flowers". *Chemical and Pharmaceutical Bulletin* 23.10, pp. 2449–2451 (cit. on pp. 301, 306).

[Kuhnle, H. A. Ward, and Vogiatzoglou, 2011] G. G. Kuhnle, H. A. Ward, A. Vogiatzoglou, et al. (2011). "Association between dietary phyto-oestrogens and bone density in men and postmenopausal women". *British Journal of Nutrition* 106.7, pp. 1063–1069. DOI: 10.1017/S0007114511001309 (cit. on p. 58).

[Kulaputana, Thanakomsirichot, and Anomasiri, 2007] O. Kulaputana, S. Thanakomsirichot, and W. Anomasiri (2007). "Ginseng supplementation does not change lactate threshold and physical performances in physically active Thai men". *Journal of the Medical Association of Thailand* 90.6, pp. 1172–1179 (cit. on pp. 85, 142).

[Kumamoto and Ide, 1998] T. Kumamoto and T. Ide (1998). "Comparative effects of alpha- and gamma-linolenic acids on rat liver fatty acid oxidation". *Lipids* 33, pp. 647–654 (cit. on p. 194).

[Kumazawa, 1990] N. Kumazawa (1990). "Protective effects of various methanol extracts of crude drugs on experimental hepatic injury induced by carbon tetrachloride in rats". *Yakugaku Zasshi* 110, pp. 950–957 (cit. on p. 102).

[Kunzemann and K. Herrmann, 1977] J. Kunzemann and K. Herrmann (1977). "Isolation and identification of flavon(ol)-O-glycosides in caraway (Carum carvi L), fennel (Foeniculum vulgare Mill), anise (Pimpinella anisum L.), and coriander (Coriandrum sativum L.), and of flavon-C-glycosides in anise. I. Phenolics of spices [in German]." *Zeitschrift für Le0bensmittel-Untersuchung und -Forschung* 164.3, pp. 194–200 (cit. on p. 277).

[Kurihara and Kikuchi, 1975] T. Kurihara and M. Kikuchi (1975). "Studies on the constituents of flowers. V. On the components of flower of Pueraria thunbergiana benth. (2). Isolation of a new isoflavone glycoside [in Japanese]". *Yakugaku Zasshi* 95.11, pp. 1283–1285 (cit. on pp. 225, 306).

[Kurihara and Kiruchi, 1973] T. Kurihara and M. Kiruchi (1973). "Studies on the constituents of flowers. I. On the components of flower of Pueraria thunbergiana Benth [in Japanese]". *Yakugaku Zasshi* 93.9, pp. 1201–1205 (cit. on pp. 80, 83, 85, 90, 138, 141–142, 153, 306).

[Kurihara and Kiruchi, 1976] — (1976). "Studies on the constituents of flowers. VI. On the components of the flower of Pueraria thubergiana Benth [in Japanese]". *Yakugaku Zasshi* 96.12, pp. 1486–1488 (cit. on pp. 184, 306).

[Kuruüzüm-Uz et al., 2003] A. Kuruüzüm-Uz et al. (2003). "Glucosides from Vitex agnus-castus". *Phytochemistry* 63.8, pp. 959–964 (cit. on p. 213).

[C. Y. Kwan, 1995] C. Y. Kwan (1995). "Vascular effects of selected antihypertensive drugs derived from traditional medicinal herbs". *Clinical and experimental pharmacology & physiology* 22.1, S297–S299 (cit. on pp. 82, 139).

[H. J. Kwan and Wan, 1994] H. J. Kwan and J. K. Wan (1994). *Clinical study of treatment of diabetes with powder of the steamed insam (ginseng) produced in Kaesong, Korea*. Technical information 6, pp. 33–35 (cit. on pp. 104, 107).

[Kwon et al., 1997] Y. S. Kwon et al. (1997). "Antimicrobial constituents of Angelica dahurica roots". *Phytochemistry* 44.5, pp. 887–889 (cit. on p. 257).

[Laakso and Voutilainen, 1996] P. Laakso and P. Voutilainen (1996). "Analysis of triacylglycerols by silver-ion high-performance liquid chromatography-atmospheric pressure chemical ionization mass spectrometry". *Lipids* 31, pp. 1311–1322 (cit. on p. 193).

[Lahiri-Chatterjee et al., 1999] M. Lahiri-Chatterjee et al. (1999). "A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model". *Cancer Research* 59, pp. 622–632 (cit. on p. 365).

[Lai and B. Tang, 1989] X. L. Lai and B. Tang (1989). "Recent advances in the experimental study and clinical application of Pueraria lobata (Willd) Ohwi [in Chinese]". *Zhongguo Zhong Yao Za Zhi* 14.5, pp. 277, 308–311 (cit. on p. 308).

[A. Lal et al., 2003] A. Lal et al. (2003). "Upregulation of isoflavonoids and soluble proteins in edible legumes by light and fungal elicitor treatments". *Journal of Alternative and Complementary Medicine* 9.3, pp. 371–378 (cit. on p. 306).

[Lam, H. C. Lin, and Lao, 2008] H. W. Lam, H. C. Lin, and S. C. Lao (2008). "The angiogenic effects of Angelica sinensis extract on HUVEC in vitro and zebrafish in vivo". *Journal of Cellular Biochemistry* 103.1, pp. 195–211 (cit. on p. 259).

[Lambert and Cormier, 2001] J. P. Lambert and A. Cormier (2001). "Potential interaction between warfarin and boldo-fenugreek". *Pharmacotherapy* 21, pp. 509–512 (cit. on p. 294).

[Lamlertkittikul and Chandeying, 2004] S. Lamlertkittikul and V. Chandeying (2004). "Efficacy and safety of Pueraria mirifica (Kwao Kruea Khao) for the treatment of vasomotor symptoms in perimenopausal women: Phase II Study". *Journal of the Medical Association of Thailand* 87.1, pp. 33–40 (cit. on p. 384).

[Lange and Schippmann, 1997] D. Lange and U. Schippmann (1997). *Trade Survey of Medicinal Plants in Germany - A Contribution to International Plant Species Conservation*. 32. Bonn, Germany: Bundesamt für Naturschutz (cit. on p. 108).

[Langer and Franz, 1997] T. Langer and C. Franz (1997). "Determination of pyrrolizidine alkaloids in commercial samples of borage seed oil products by GC-MS". *Scientia Pharmaceutica* 65, pp. 321–328 (cit. on p. 205).

[Langes, 1901] H. Langes (1901). "Beobachtungen bei der Verwendung einiger neuer Medikamente. Eumenol, Dionin und Stypticin". *Therapeutische Monatshefte* 7, p. 363 (cit. on pp. 272–273).

[Lapcharoen et al., 2005] P. Lapcharoen et al. (2005). "Three indigenous Thai medicinal plants for control of Aedes aegypti and Culex quinquefasciatus". *Southeast Asian Journal of Tropical Medicine and Public Health* 36.supplement 4, pp. 167–175 (cit. on p. 386).

[Larson, Roby, and Stermitz, 1984] K. M. Larson, M. R. Roby, and F. R. Stermitz (1984). "Unsaturated pyrrolizidines from borage (Borago officinalis), a common garden herb". *Journal of Natural Products* 47, pp. 747–748 (cit. on pp. 193, 205).

[C. B. Lau et al., 2005] C. B. Lau et al. (2005). "Use of dong quai (Angelica sinensis) to treat peri- or postmenopausal symptoms in women with breast cancer: is it appropriate?" *Menopause* 12.6, pp. 734–740 (cit. on pp. 259, 267).

[Lauritzen, 1997] C. Lauritzen (1997). "Treatment of premenstrual tension syndrome with vitex agnus castus. Controlled, double-blind study versus pyridoxine". *Phytomedicine* 4, pp. 183–189 (cit. on p. 220).

[B. M. Lawrence, 1979] B. M. Lawrence (1979). "Progress in essential oils". *Perfumer & Flavorist* 4, pp. 49–55 (cit. on p. 277).

[V. Lawrence, B. Jacobs, and Dennehy, 2000] V. Lawrence, B. Jacobs, and C. Dennehy (2000). *Report on milk thistle: effects on liver disease and cirrhosis and clinical adverse effects*. Evidence Report/Technology Assessment No. 21 (Contract 290-97-0012). Version AHRQ Publication No. 01-E025. San Antonio Evidence-based Practice Center, based at the University of Texas Health Science Center at San Antonio, and The Veterans Evidence-based Research, Dissemination, and Implementation Center, a Veterans Affairs Services Research and Development Center of Excellence. Rockville, MD: Agency for Healthcare Research and Quality (cit. on p. 365).

[L. D. Lawson and B. G. Hughes, 1988] L. D. Lawson and B. G. Hughes (1988). "Triacylglycerol structure of plant and fungal oils containing gamma-linolenic acid". *Lipids* 23, pp. 313–317 (cit. on pp. 192–194).

[B. B. Lee, Haran, and L. M. Hunt, 2007] B. B. Lee, M. J. Haran, and L. M. Hunt (2007). "Spinal-injured neuropathic bladder antisepsis (SINBA) trial". *Spinal Cord* 45.8, pp. 542–550 (cit. on p. 231).

[C. K. Lee, 2007] C. K. Lee (2007). "Effects of the licorice extract against tumor growth and cisplatin-induced toxicity in a mouse xenograft model of colon cancer". *Biological and Pharmaceutical Bulletin* 30.11, pp. 2191–2195 (cit. on pp. 319–320).

[D. G. Lee, H. K. Kim, and Y. Park, 2003] D. G. Lee, H. K. Kim, and Y. Park (2003). "Gram-positive bacteria specific properties of silybin derived from Silybum marianum". *Archives of Pharmacal Research* 26.8, pp. 597–600 (cit. on p. 360).

[H. S. Lee, 2004] H. S. Lee (2004). "Acaricidal activity of constituents identified in Foeniculum vulgare fruit oil against Dermatophagoides spp. (Acari: Pyroglyphidae)". *Journal of Agricultural and Food Chemistry* 52.10, pp. 2887–2889 (cit. on p. 278).

[H. U. Lee, Bae, and D. H. Kim, 2005] H. U. Lee, E. A. Bae, and D. H. Kim (2005). "Hepatoprotective effects of irisolidone on tert-butyl hyperoxide-induced liver injury". *Biological and Pharmaceutical Bulletin* 28.3, pp. 531–533 (cit. on p. 306).

[L. S. Lee et al., 2008] L. S. Lee et al. (2008). "Possible differential induction of phase 2 enzyme and antioxidant pathways by American ginseng, Panax quinquefolius". *Journal of Clinical Pharmacology* 48.5, pp. 599–609 (cit. on pp. 89, 146).

[M. S. Lee et al., 2009] M. S. Lee et al. (2009). "Ginseng for cognitive function in Alzheimer's disease: a systematic review". *Journal of Alzheimer's Disease* 18.2, pp. 339–344 (cit. on pp. 83–84, 141).

[S. C. Lee, C. C. Tsai, and J. C. Chen, 2002] S. C. Lee, C. C. Tsai, and J. C. Chen (2002). "Effects of Chinese yam on hepatonephrotoxicity of acetaminophen in rats". *Acta Pharmacologica Sinica* 23.6, pp. 503–508 (cit. on p. 450).

[S. H. Lee et al., 2008] S. H. Lee et al. (2008). "Interaction between warfarin and Panax ginseng in ischemic stroke patients". *Journal of Alternative and Complementary Medicine* 14.6, pp. 715–721 (cit. on pp. 89, 146).

[W. H. Lee, T. S. Jin, and W. C. Tsai, 2006] W. H. Lee, T. S. Jin, and W. C. Tsai (2006). "Biological inhibitory effects of the Chinese herb danggui on brain astrocytoma". *Pathobiology* 73.3, pp. 141–148 (cit. on p. 260).

[Y. L. Lee et al., 2000] Y. L. Lee et al. (2000). "Does cranberry juice have antibacterial activity?" *Journal of the American Medical Association* 283.13, p. 1691 (cit. on p. 230).

[Y. S. Lee et al., 2002] Y. S. Lee et al. (2002). "Requirement of metabolic activation for estrogenic activity of Pueraria mirifica". *Journal of Veterinary Science* 3.4, pp. 273–277 (cit. on p. 383).

[E. Lehmann-Willenbrock and Riedel, 1988] E. Lehmann-Willenbrock and H. H. Riedel (1988). "Clinical and endocrinologic studies of the treatment of ovarian insufficiency manifestations following hysterectomy with intact adnexa". German. *Zentralblatt für Gynäkologie Gesellschaft für Gynäkologie und Geburtshilfe der DDR* 110.10, pp. 611–618 (cit. on p. 171).

[E Lehmann-Willenbrock and Riedel, 1988] E Lehmann-Willenbrock and H. H. Riedel (1988). "Clinical and endocrinological studies on the therapy of ovarian defunctionalization symptoms after hysterectomy sparing the adnexa". German. *Zentralblatt fur Gynakologie* 110, pp. 611–618. eprint: http://www.ncbi.nlm.nih.gov/pubmed/2841818 (cit. on p. 185).

[Lemos, 2001] M. L. de Lemos (2001). "Effects of soy phytoestrogens genistein and daidzein on breast cancer growth". *Annals of Pharmacotherapy* 35.9, pp. 1118–1121 (cit. on p. 434).

[Leng-Peschlow and Strenge-Hesse, 1991a] E. Leng-Peschlow and A. Strenge-Hesse (1991a). "The milk thistle (Silybum marianum) and silymarin in liver therapy". *Z Phytotherapy* 12, pp. 162–174 (cit. on p. 355).

[Leng-Peschlow and Strenge-Hesse, 1991b] — (1991b). "The milk thistle (Silybum marianum) and silymarin in liver therapy". *Z Phytotherapy* 12, pp. 162–174 (cit. on pp. 364, 367).

[Lentner, 1991] C. Lentner, ed. (1991). *Geigy Scientific Tables*. 8th ed. West Caldwell, NJ: CIBA-Geigy (cit. on p. 228).

[Lerckher et al., 1992] G. Lerckher et al. (1992). "Cannabinoid acids analysis". *Il Farmaco* 47.3, pp. 367–378 (cit. on p. 339).

[A. E. Lethaby et al., 2007] A. E. Lethaby et al. (2007). "Phytoestrogens for vasomotor menopausal symptoms". *Cochrane Database of Systematic Reviews* 4.CD001395 (cit. on pp. 438–439, 443).

[A. Lethaby, Marjoribanks, and Kronenberg, 2013] A. Lethaby, J. Marjoribanks, F. Kronenberg, et al. (2013). "Phytoestrogens for menopausal vasomotor symptoms". *Cochrane Database of Systematic Reviews* 12.CD001395. DOI: 10.1002/14651858.CD001395.pub4 (cit. on p. 58).

[Leung, 1980] A. Y. Leung (1980). *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*. New York: J. Wiley Interscience (cit. on pp. 245, 404–406).

[Leung and S. Foster, 1996] A. Y. Leung and S. Foster (1996). *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*. 2nd ed. New York: John Wiley & Sons, Inc., p. 3234 (cit. on pp. 108, 111–112, 120–122, 125).

[Leventhal, E. G. Boyce, and Zurier, 1993] L. J. Leventhal, E. G. Boyce, and R. B. Zurier (1993). "Treatment of rheumatoid arthritis with gammalinolenic acid". *Annals of Internal Medicine* 119, pp. 867–873 (cit. on p. 195).

[Levis et al., 2010] S. Levis et al. (2010). "Design and baseline characteristics of the soy phytoestrogens as replacement estrogen (SPARE) studya clinical trial of the effects of soy isoflavones in menopausal women". *Contemporary Clinical Trials* 31.4, pp. 293–302 (cit. on p. 439).

[S. Levy, 1999] S. Levy, ed. (1999). *Drug Topics* 19 (22): *New product newswire* (cit. on p. 68).

[W. H. Lewis, Zenger, and R. G. Lynch, 1983] W. H. Lewis, V. E. Zenger, and R. G. Lynch (1983). "No adaptogen response of mice to ginseng and Eleutherococcus infusions". *Journal of Ethnopharmacology* 8, pp. 209–214 (cit. on p. 100).

[W. Li et al., 2003] W. Li et al. (2003). "Identification of caffeic acid derivatives in Actea racemosa ( Cimicifuga racemosa , black cohosh) by liquid chromatography/tandem mass spectrometry". *Rapid Communications in Mass Spectrometry* 17.9, pp. 978–982 (cit. on p. 168).

[Z. Li, Seeram, and Carpenter, 2006] Z. Li, N. P. Seeram, and C. L. Carpenter (2006). "Cranberry does not affect prothrombin time in male subjects on warfarin". *Journal of the American Dietetic Association* 106.12, pp. 2057–2061 (cit. on p. 239).

[G. Liang, 2000] G. Liang (2000). "Preparation of beauty soap from Pueraria mirifica [in Chinese]". *Faming Zhuanli Shenqing Gongkai Shuomingshu*. US patent application CN 2000-109346 (cit. on pp. 381, 387).

[T. Liang and Liao, 1992] T. Liang and S. Liao (1992). "Inhibition of steroid 5-alpha reductase by specific aliphatic unsaturated fatty acids". *Biochemical Journal* 285 (Part 2), pp. 557–562 (cit. on p. 418).

[C. F. Lima, P. B. Andrade, et al., 2005] C. F. Lima, P. B. Andrade, et al. (2005). "The drinking of a Salvia officinalis infusion improves liver antioxidant status in mice and rats". *Journal of Ethnopharmacology* 97.2, pp. 383–389 (cit. on p. 408).

[C. F. Lima, M. F. Azevedo, et al., 2006] C. F. Lima, M. F. Azevedo, et al. (2006). "Metformin-like effect of Salvia officinalis (common sage): is it useful in diabetes prevention?" *British Journal of Nutrition* 96.2, pp. 326–333 (cit. on p. 408).

[C. F. Lima, Carvalho, and Fernandes, 2004] C. F. Lima, F. Carvalho, and E. Fernandes (2004). "Evaluation of toxic/protective effects of the essential oil of Salvia officinalis on freshly isolated rat hepatocytes". *Toxicology in Vitro* 18.4, pp. 457–465 (cit. on pp. 408, 413).

[C. F. Lima, Valentao, et al., 2007] C. F. Lima, P. C. Valentao, et al. (2007). "Water and methanolic extracts of Salvia officinalis protect HepG2 cells from t-BHP induced oxidative damage". *Chemico-Biological Interactions* 167.2, pp. 107–115 (cit. on p. 408).

[J. H. Lin, 1995] J. H. Lin (1995). "Effects of ginseng on the blood chemistry profile of dexamethasonetreated male rats". *American Journal of Chinese Medicine* 23, pp. 167–172 (cit. on p. 102).

[L. Z. Lin, 1998] L. Z. Lin (1998). "Liquid chromatographic-electrospray mass spectrometric study of the phthalides of Angelica sinensis and chemical changes of Z-ligustilide". *Journal of Chromatography A* 810, pp. 71–79 (cit. on p. 269).

[P. L. Lin et al., 2009] P. L. Lin et al. (2009). "Yam storage protein dioscorins from Dioscorea alata and Dioscorea japonica exhibit distinct immunomodulatory activities in mice". *Journal of Agricultural and Food Chemistry* 57.11, pp. 4606–4613 (cit. on p. 450).

[R. C. Lin and T. K. Li, 1998] R. C. Lin and T. K. Li (1998). "Effects of isoflavones on alcohol pharmacokinetics and alcohol-drinking behavior in rats". *American Journal of Clinical Nutrition* 68.suppl 6, 1512S–1515S (cit. on p. 307).

[S. H. Lin et al., 2003] S. H. Lin et al. (2003). "An unusual cause of hypokalemic paralysis: chronic licorice ingestion". *American Journal of the Medical Sciences* 325.3, pp. 153–156 (cit. on p. 334).

[Y. H. Lin, 1994] Y. H. Lin (1994). "Protective effect of sodium ferulate on damage of the rat liver mitochondria induced by oxygen free radicals". *Yao Hsueh Hsueh Pao* 29, pp. 171–175 (cit. on p. 270).

[linav and Chajek-Shaul, 2003] E. linav and T. Chajek-Shaul (2003). "Licorice consumption causing severe hypokalemic paralysis". *Mayo Clinic Proceedings* 78.6, pp. 767–768 (cit. on p. 334).

[Linde, 1967a] H. Linde (1967a). "Contents of Cimicifuga racemosa. 2. On the structure of actein". German. *Archiv Der Pharmazie Und Berichte Der Deutschen Pharmazeutischen* 300.10, pp. 885–892 (cit. on p. 168).

[Linde, 1967b] — (1967b). "Contents of Cimicifuga racemosa. 3. On the constitution of the rings A, B and C of actein". German. *Archiv Der Pharmazie Und Berichte Der Deutschen Pharmazeutischen* 300.12, pp. 982–992 (cit. on p. 168).

[Linde, 1968] — (1968). "Contents of Cimicifuga racemosa. 5. 27-desoxyacetylacteol". German. *Archiv Der Pharmazie Und Berichte Der Deutschen Pharmazeutischen* 301.5, pp. 335–341 (cit. on p. 168).

[Linsenmeyer, Harrison, and Oakley, 2004] T. A. Linsenmeyer, B. Harrison, and A. Oakley (2004). "Evaluation of cranberry supplement for reduction of urinary tract infections in individuals with neurogenic bladders secondary to spinal cord injury. A prospective, double-blinded, placebo-controlled, crossover study". *Journal of Spinal Cord Medicine* 27.1, pp. 29–34 (cit. on p. 231).

[Lirussi, Nassuato, and Orlando, 1995a] F. Lirussi, G. Nassuato, and R. Orlando (1995a). "Treatment of active cirrhosis with ursodeoxycholic acid and a free radical scavenger: A two year prospective study". *Medical Science Research* 23, pp. 31–33 (cit. on p. 355).

[Lirussi, Nassuato, and Orlando, 1995b] — (1995b). "Treatment of active cirrhosis with ursodeoxycholic acid and a free radical scavenger: A two year prospective study". *Medical Science Research* 23, pp. 31–33 (cit. on p. 364).

[Lis-Balchin, 1997] M. Lis-Balchin (1997). "A preliminary study of the effect of essential oils on skeletal and smooth muscle in vitro". *Journal of Ethnopharmacology* 58, pp. 183–187 (cit. on p. 113).

[Liske, Hanggi, and Henneicke-von Zepelin, 2002] E. Liske, M. D. Hanggi, and H. H. Henneicke-von Zepelin (2002). "Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect". *Journal of Women's Health & Gender-Based Medicine* 11, pp. 163–174. eprint: http://www.ncbi.nlm.nih.gov/pubmed/11975864 (cit. on pp. 185–186).

[Liske and Wüstenberg, 1998] E. Liske and P. Wüstenberg (1998). "Therapy of climacteric complaints with Cimicifuga racemosa: herbal medicine with clinically proven evidence." *Menopause* 5.4, p. 250 (cit. on pp. 167, 190).

[Liske and Wüstenberg, 1999] — (1999). "Efficacy and safety of phytomedicines for gynecologic disorders with particular reference to Cimicifuga racemosa and Hypericum perforatum". 1st Asian-European Congress on Menopause. (Bangkok, Thailand). January 26-31 (cit. on pp. 167, 190).

[Little and T. Parsons, 2001] C. Little and T. Parsons (2001). "Herbal therapy for treating rheumatoid arthritis". *Cochrane Database of Systematic Reviews* 1 (CD002948) (cit. on p. 196).

[C. X. Liu and P. G. Xiao, 1992] C. X. Liu and P. G. Xiao (1992). "Recent advances in ginseng research in China". *Journal of ethnopharmacology* 36, pp. 27–38 (cit. on p. 101).

[J. Liu, Burdette, and Sun, 2004] J. Liu, J. E. Burdette, and Y. Sun (2004). "Isolation of linoleic acid as an estrogenic compound from the fruits of Vitex agnus-castus L. (chaste-berry)". *Phytomedicine* 11.1, pp. 18–23 (cit. on p. 213).

[J. Liu, Burdette, and H. Xu, 2001a] J. Liu, J. E. Burdette, and H. Xu (2001a). "Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms". *Journal of Agricultural and Food Chemistry* 49, pp. 2472–2479. eprint: http://www.ncbi.nlm.nih.gov/pubmed/11368622 (cit. on pp. 185–186).

[J. Liu, Burdette, and H. Xu, 2001b] — (2001b). "Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms". *Journal of Agricultural and Food Chemistry* 49, pp. 2472–2479 (cit. on p. 302).

[J. Liu, S. C. Ho, et al., 2009] J. Liu, S. C. Ho, et al. (2009). "Effect of long-term intervention of soy isoflavones on bone mineral density in women: a meta-analysis of randomized controlled trials". *Bone* 44.5, pp. 948–953 (cit. on pp. 440, 443).

[J. Liu, Manheimer, et al., 2003] J. Liu, E. Manheimer, et al. (2003). "Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials". *American Journal of Gastroenterology* 98.3, pp. 538–544 (cit. on pp. 361–362).

[J. Liu, S. X. Xu, et al., 1989] J. Liu, S. X. Xu, et al. (1989). "Angelol-type coumarins from Angelica pubescens f. biserrata and their inhibitory effect on platelet aggregation". *Phytochemistry* 39.5, pp. 1099–1101 (cit. on p. 264).

[J. Liu, Zschocke, et al., 1998] J. Liu, S. Zschocke, et al. (1998). "Inhibitory effects of Angelica pubescens f. biserrata on 5-lipoxygenase and cyclooxygenase". *Planta Medica* 64.6, pp. 525–529 (cit. on p. 260).

[X. Liu and W. A. Lin, 2005] X. Liu and W. A. Lin (2005). "Chinese medicinal cosmetic with wrinkle dispelling and skin caring effects and its preparation [in Chinese]". *Faming Zhuanli Shenqing Gongkai Shuomingshu*. US patent application CN 1579366 (cit. on pp. 381, 387).

[Y. H. Liu, Y. S. Lin, and D. Z. Liu, 2009] Y. H. Liu, Y. S. Lin, and D. Z. Liu (2009). "Effects of different types of yam ( Dioscorea alata ) products on the blood pressure of spontaneously hypertensive rats". *Bioscience, Biotechnology, and Biochemistry* 73.6, pp. 1371–1376 (cit. on p. 450).

[Y. W. Liu et al., 2009] Y. W. Liu et al. (2009). "Effects of oral administration of yam tuber storage protein, dioscorin, to BALB/c mice for 21-days on immune responses". *Journal of Agricultural and Food Chemistry* 57.19, pp. 9274–9279 (cit. on p. 450).

[Z. M. Liu, Y. M. Chen, and S. C. Ho, 2011] Z. M. Liu, Y. M. Chen, and S. C. Ho (2011). "Effects of soy intake on glycemic control: a meta-analysis of randomized controlled trials". *American Journal of Clinical Nutrition* 93.5, pp. 1092–1101 (cit. on p. 437).

[Z. M. Liu, Y. M. Chen, S. C. Ho, et al., 2010] Z. M. Liu, Y. M. Chen, S. C. Ho, et al. (2010). "Effects of soy protein and isoflavones on glycemic control and insulin sensitivity: a 6-mo double-blind, randomized, placebo-controlled trial in postmenopausal Chinese women with prediabetes or untreated early diabetes". *American Journal of Clinical Nutrition* 91.5, pp. 1394–1401 (cit. on p. 438).

[Z. Liu et al., 2001] Z. Liu et al. (2001). "Estrogenicity of black cohosh (Cimicifuga racemosa) and its effect on estrogen receptor level in human breast cancer MCF-7 cells". Chinese. *Wei Sheng Yan Jiu* 30, pp. 77–80. eprint: http://www.ncbi.nlm.nih.gov/pubmed/11321955 (cit. on pp. 185, 187).

[Lo, 1995] A. Lo (1995). "Danggui (Angelica sinensis) affects the pharmacodynamics but not the pharmacokinetics of warfarin in rabbits". *European Journal of Drug Metabolism and Pharmacokinetics* 20, pp. 55–60 (cit. on p. 274).

[Lobo et al., 2010] V. Lobo et al. (2010). "Free radicals, antioxidants and functional foods: Impact on human health". *Pharmacognosy Reviews* 4.8, pp. 118–126. DOI: 10.4103/0973-7847.70902 (cit. on p. 455).

[Loch, Selle, and Boblitz, 2000] E. G. Loch, H. Selle, and N. Boblitz (2000). "Treatment of premenstrual syndrome with a phytopharmaceutical formulation containing Vitex agnus castus". *Journal of women's health & gender-based medicine* 9.3, pp. 315–320 (cit. on p. 224).

[Locher et al., 1998] R. Locher et al. (1998). "Inhibitory action of silibinin on low density lipoprotein oxidation". *Arzneimittelforschung* 48, pp. 236–239 (cit. on p. 365).

[Loewenfeld and Back, 1974] C. Loewenfeld and P. Back (1974). *The Complete Book of Herbs and Spices*. New York, NY: Putnam (cit. on pp. 276, 285).

[Loizzo, Saab, and Tundis, 2008a] M. R. Loizzo, A. M. Saab, and R. Tundis (2008a). "In vitro inhibitory activities of plants used in Lebanon traditional medicine against angiotensin converting enzyme (ACE) and digestive enzymes related to diabetes". *Journal of Ethnopharmacology* 119.1, pp. 109–116 (cit. on p. 408).

[Loizzo, Saab, and Tundis, 2008b] — (2008b). "Phytochemical analysis and in vitro antiviral activities of the essential oils of seven Lebanon species". *Chemistry & Biodiversity* 5.3, pp. 461–470 (cit. on pp. 405, 408).

[Lontos et al., 2003] S. Lontos et al. (2003). "Acute liver failure associated with the use of herbal preparations containing black cohosh". *The Medical Journal of Australia* 179.7, pp. 390–391 (cit. on p. 190).

[Lopatkin, Schläfke, et al., 2007] N. Lopatkin, S. Schläfke, et al. (2007). "Efficacy and safety of a combination of sabal and urtica extract in lower urinary tract symptomslong-term follow-up of a placebo-controlled, double-blind, multicenter trial". *International Urology and Nephrology* 39.4, pp. 1137–1146 (cit. on p. 420).

[Lopatkin, Sivkov, and Walther, 2005] N. Lopatkin, A. Sivkov, and C. Walther (2005). "Long-term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms, a placebo-controlled, double-blind, multicenter trial". *World Journal of Urology* 23.2, pp. 139–146 (cit. on p. 420).

[Lou, 1989] B. Y. Lou (1989). "Eye symptoms due to ginseng poisoning". *Yen ko hsueh pao* 5, pp. 96–97 (cit. on p. 106).

[Low Dog, K. L. Powell, and Weisman, 2003] T. Low Dog, K. L. Powell, and S. M. Weisman (2003). "Critical evaluation of the safety of Cimicifuga racemosa in menopause symptom relief". *Menopause* 10.4, pp. 299–313 (cit. on pp. 162–163, 179, 189).

[G. Lu, X. J. Cheng, and W. X. Yuan, 1988a] G. Lu, X. J. Cheng, and W. X. Yuan (1988a). "Effects of the ginseng root saponins on serum corticosterone and brain neurotransmitters of mice under hypobaric and hypoxic environment". *Yao hsueh hsueh pao* 9, pp. 489–492 (cit. on p. 100).

[G. Lu, X. J. Cheng, and W. X. Yuan, 1988b] G. Lu, X. J. Cheng, and W. X. Yuan (1988b). "Protective action of ginseng root saponins on hypobaric hypoxia in animals". *Yao hsueh hsueh pao* 9, pp. 391–394 (cit. on p. 100).

[Lucassen et al., 1998] P. L. Lucassen et al. (1998). "Effectiveness of treatments in infantile colic: systematic review". *British Medical Journal* 316.7144. published correction appears in British Medical Journal, 1998, volume 317, number 7152, page 171, pp. 1563–1569 (cit. on p. 440).

[Lukaczer, Darland, and Tripp, 2005] D. Lukaczer, G. Darland, and M. Tripp (2005). "Clinical effects of a proprietary combination isoflavone nutritional supplement in menopausal women: a pilot trial". *Alternative Therapies In Health And Medicine* 11.5, pp. 60–65 (cit. on p. 307).

[Lukas, D. Penetar, and Berko, 2005] S. E. Lukas, D. Penetar, and J. Berko (2005). "An extract of the Chinese herbal root kudzu reduces alcohol drinking by heavy drinkers in a naturalistic setting". *Alcoholism: Clinical and Experimental Research* 29.5, pp. 756–762 (cit. on pp. 306–307, 312).

[M. E. Lynch and Clark, 2003] M. E. Lynch and A. J. Clark (2003). "Cannabis reduces opioid dose in the treatment of chronic non-cancer pain". *Journal of Pain and Symptom Management* 25.6, pp. 496–498 (cit. on p. 348).

[D. F. Ma et al., 2008a] D. F. Ma et al. (2008a). "Soy isoflavone intake increases bone mineral density in the spine of menopausal women: meta-analysis of randomized controlled trials". *Clinical Nutrition* 27.1, pp. 57–64 (cit. on pp. 440, 443).

[D. F. Ma et al., 2008b] — (2008b). "Soy isoflavone intake inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials". *European Journal of Clinical Nutrition* 62.2, pp. 155–161 (cit. on pp. 440, 443).

[L. F. Ma, 1988] L. F. Ma (1988). "The effect of Angelica sinensis polysaccharides on mouse bone marrow hematopoiesis". *Zhonghua Xinxueguanbing Zazhi* 9, pp. 148–149 (cit. on pp. 269, 271).

[L. Ma, S. Lin, R. Chen, and X. Wang, 2010] L. Ma, S. Lin, R. Chen, and X. Wang (2010). "Treatment of moderate to severe premenstrual syndrome with Vitex agnus castus (BNO 1095) in Chinese women". *Gynecological Endocrinology* 26.8, pp. 612–616 (cit. on p. 215).

[L. Ma, S. Lin, R. Chen, Y. Zhang, et al., 2010] L. Ma, S. Lin, R. Chen, Y. Zhang, et al. (2010). "Evaluating therapeutic effect in symptoms of moderate-to-severe premenstrual syndrome with Vitex agnus castus (BNO 1095) in Chinese women". *Australian & New Zealand Journal of Obstretics & Gynaecology* 50.2, pp. 189–193 (cit. on p. 215).

[Z. Ma et al., 2005] Z. Ma et al. (2005). "Determination of puerarin in human plasma by high performance liquid chromatography". *Journal of Chromatography B - Analytical Technologies in the Biomedical and Life Sciences* 823.2, pp. 108–114 (cit. on pp. 201, 306).

[Machado Rocha et al., 2008] F. C. Machado Rocha et al. (2008). "Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis". *European Journal of Cancer Care* 17.5, pp. 431–443 (cit. on p. 341).

[MacRae and Pattison, 2002] K. MacRae and J. Pattison (2002). "Home chemotherapy." *Nursing Times* 98.35, pp. 34–35 (cit. on p. 53).

[Madar, Abel, et al., 1988] Z. Madar, R. Abel, et al. (1988). "Glucose-lowering effect of fenugreek in non-insulin dependent diabetics". *European Journal of Clinical Nutrition* 42, pp. 51–54 (cit. on p. 289).

[Madar and A. H. Stark, 2002] Z. Madar and A. H. Stark (2002). "New legume sources as therapeutic agents". *British Journal of Nutrition* 88 (Supplement 3), s287–s292 (cit. on pp. 287–289).

[Maeder, 2015] M. Maeder (2015). *Angelica Archangelica*. URL: http://www.herballegacy.com/Maeder_Angelica_Archangelica.html (visited on 10/16/2015) (cit. on pp. 110–111, 113–115, 117–118).

[Magula, Galisova, and Iliev, 1996a] D. Magula, Z. Galisova, and N. Iliev (1996a). "Effect of silymarin and Fumaria alkaloids in the prophylaxis of drug-induced liver injury during antituberculotic treatment". *Studia Pneumolog Phtiseol Cech* 56, pp. 206–209 (cit. on pp. 354, 356).

[Magula, Galisova, and Iliev, 1996b] — (1996b). "Effect of silymarin and Fumaria alkaloids in the prophylaxis of drug-induced liver injury during antituberculotic treatment". Czech. *Studia Pneumologica et Phtiseologica Cechoslovaca* 56, pp. 206–209 (cit. on pp. 364, 367, 372).

[Mahady, Low Dog, and M. L. Barrett, 2008] G. B. Mahady, T. Low Dog, and M. L. Barrett (2008). "United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity". *Menopause* 15.4, pp. 628–638 (cit. on pp. 176, 190).

[Mahady, Low- Dog, and M. L. Barrett, 2008] G. B. Mahady, T. Low-Dog, and M. L. Barrett (2008). "United States Pharmacopeia review of the black cohosh case reports of hepatoxicity". *Menopause* 15, pp. 628–638. eprint: http://www.ncbi.nlm.nih.gov/pubmed/18340277 (cit. on p. 182).

[Maheu, Mazières, and Valat, 1998] E. Maheu, B. Mazières, and J. P. Valat (1998). "Symptomatic efficacy in avocado/soybean unsaponpifiables in the treatment of osteoarthritis of the knee and hip: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial with a six-month treatment period and a two-month followup demonstrating a persistent effect". *Arthritis & Rheumatism* 41.1, pp. 81–91 (cit. on pp. 440, 443).

[Mahmoud, 1992] M. Mahmoud (1992). *Egyptian Journal of Pharmaceutical Sciences* 33, pp. 21–30 (cit. on p. 120).

[Mahon, Ponka, and W. N. Hall, 1997] B. E. Mahon, A. Ponka, and W. N. Hall (1997). "An international outbreak of Salmonella infections caused by alfalfa sprouts grown from contaminated seeds". *Journal of Infectious Diseases* 175, pp. 876–882 (cit. on pp. 8, 68–69).

[Maki, Butteiger, and Rains, 2010] K. C. Maki, D. N. Butteiger, and T. M. Rains (2010). "Effects of soy protein on lipoprotein lipids and fecal bile acid excretion in men and women with moderate hypercholesterolemia". *Journal of Clinical Lipidology* 4.6, pp. 531–542 (cit. on p. 437).

[Malaivijitnond, Chansri, et al., 2006] S. Malaivijitnond, K. Chansri, et al. (2006). "Using vaginal cytology to assess the estrogenic activity of phytoestrogen-rich herb". *Journal of Ethnopharmacology* 107.3, pp. 354–360 (cit. on pp. 381–382, 387).

[Malaivijitnond, Kiatthaipipat, et al., 2004] S. Malaivijitnond, P. Kiatthaipipat, et al. (2004). "Different effects of Pueraria mirifica , a herb containing phytoestrogens, on LH and FSH secretion in gonadectomized female and male rats". *Journal of Pharmacological Sciences* 96.4, pp. 428–435 (cit. on p. 383).

[Malini et al., 1985] T. Malini et al. (1985). "Effect of Foeniculum vulgare Mill. seed extract on the genital organs of male and female rats". *Indian Journal of Physiology and Pharmacology* 29.1, pp. 21–26 (cit. on p. 278).

[M. Malinow, 1982] M. Malinow (1982). "Systemic lupus erythematosus-like syndrome in monkeys fed alfalfa sprouts: role of a nonprotein amino acid". *Science* 216, pp. 415–417 (cit. on p. 74).

[M. R. Malinow, Bardana, and Goodnight, 1981] M. R. Malinow, E. J. Jr Bardana, and S. H. Jr Goodnight (1981). "Pancytopenia during ingestion of alfalfa seeds". *Lancet* 8220, p. 515 (cit. on p. 74).

[M. R. Malinow, Connor, and P. McLaughlin, 1981] M. R. Malinow, W. E. Connor, and P. McLaughlin (1981). "Cholesterol and bile acid balance in Macaca fascicularis. Effects of alfalfa saponins." *Journal of Clinical Investigation* (67), pp. 156–162 (cit. on p. 67).

[M. R. Malinow, P. McLaughlin, Naito, et al., 1978] M. R. Malinow, P. McLaughlin, H. K. Naito, et al. (1978). "Effect of alfalfa meal on shrinkage (regression) of atherosclerotic plaques during cholesterol feeding in monkeys". *Atherosclerosis* 30, pp. 27–43 (cit. on p. 67).

[M. R. Malinow, P. McLaughlin, and Papworth, 1977] M. R. Malinow, P. McLaughlin, and L. Papworth (1977). "Effect of alfalfa saponins on intestinal cholesterol absorption in rats." *American Journal of Clinical Nutrition* (30), pp. 2061–2067 (cit. on p. 67).

[Mancuso, J. Whelan, and DeMichele, 1997] P. Mancuso, J. Whelan, and S. J. DeMichele (1997). "Effects of eicosapentaenoic and gamma-linolenic acid on lung permeability and alveolar macrophage eicosanoid synthesis in endotoxic rats". *Critical Care Medicine* 25, pp. 523–532 (cit. on p. 195).

[Mancuso, J. Whelan, DeMichele, et al., 1997] P. Mancuso, J. Whelan, S. J. DeMichele, et al. (1997). "Dietary fish oil and fish and borage oil suppress intrapulmonary proinflammatory eicosanoid biosynthesis and attenuate pulmonary neutrophil accumulation in endotoxic rats". *Critical Care Medicine* 25, pp. 1198–1206 (cit. on p. 195).

[Mannering, J. A. Shoeman, and Deloria, 1992] G. J. Mannering, J. A. Shoeman, and L. B. Deloria (1992). "Identification of the antibiotic hops component, colupulone, as an inducer of hepatic cytochrome P-4503A in the mouse". *Drug Metabolism and Disposition* 20, pp. 142–147 (cit. on p. 303).

[Mannering, J. A. Shoeman, and D. W. Shoeman, 1994] G. J. Mannering, J. A. Shoeman, and D. W. Shoeman (1994). "Effects of colupulone, a component of hops and brewers yeast, and chromium on glucose tolerance and hepatic cytochrome P450 in nondiabetic and spontaneously diabetic mice". *Biochemical and Biophysical Research Communications* 200, pp. 1455–1462 (cit. on p. 303).

[Manonai, Chittacharoen, Theppisai, et al., 2007] J. Manonai, A. Chittacharoen, U. Theppisai, et al. (2007). "Effect of Pueraria mirifica on vaginal health". *Menopause* 14.5, pp. 919–924 (cit. on pp. 381, 384).

[Manonai, Chittacharoen, Udomsubpayakul, et al., 2008] J. Manonai, A. Chittacharoen, U. Udomsubpayakul, et al. (2008). "Effects and safety of Pueraria mirifica on lipid profiles and biochemical markers of bone turnover rates in healthy postmenopausal women". *Menopause* 15.3, pp. 530–535 (cit. on pp. 381, 386).

[Marandola, 1997] P. Marandola (1997). "Main phytoderivatives in the management of benign prostatic hyperplasia". *Fitoterapia* 68, p. 195 (cit. on p. 419).

[Marcelli, Bizzoni, and Conte, 1992a] R. Marcelli, P. Bizzoni, and D. Conte (1992a). "Randomized controlled study of the efficacy and tolerability of a short course of IdB 1016 in the treatment of chronic persistent hepatitis". *Eur Bull Drug Res* 1, pp. 131–135 (cit. on p. 355).

[Marcelli, Bizzoni, and Conte, 1992b] — (1992b). "Randomized controlled study of the efficacy and tolerability of a short course of IdB 1016 in the treatment of chronic persistent hepatitis". *European Bulletin of Drug Research* 1, pp. 131–135 (cit. on pp. 365, 367).

[Marcus and Lichtenstein, 1979] C. Marcus and E. P. Lichtenstein (1979). "Biologically active components of anise: toxicity and interactions with insecticides in insects". *Journal of Agricultural and Food Chemistry* 27, pp. 1217–1223 (cit. on p. 282).

[Marena and Lampertico, 1991a] C. Marena and M. Lampertico (1991a). "Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders". *Planta Medica* 57, A124–A125 (cit. on p. 355).

[Marena and Lampertico, 1991b] — (1991b). "Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders". *Planta Medica* 57, A124–A125 (cit. on pp. 365, 367).

[Marks, Partin, and Epstein, 2000] L. S. Marks, A. V. Partin, and J. I. Epstein (2000). "Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia". *Journal of Urology* 163.5, pp. 1451–1456 (cit. on p. 426).

[Marles and Farnsworth, 1995] R. Marles and N. R. Farnsworth (1995). "Antidiabetic plants and their active constituents". *Phytomedicine* 2, pp. 137–189 (cit. on pp. 101–102).

[Marongiu, Piras, and Porcedda, 2010] B. Marongiu, A. Piras, and S. Porcedda (2010). "Extraction, separation and isolation of volatiles from Vitex agnus-castus L. (Verbenaceae) wild species of Sardinia, Italy, by supercritical CO2". *Natural Product Research* 24.6, pp. 569–579 (cit. on p. 213).

[Marshall and Caldwell, 1996] A. D. Marshall and J. Caldwell (1996). "Lack of influence of modulators of epoxide metabolism on the genotoxicity of trans-anethole in freshly isolated rat hepatocytes assessed with the unscheduled DNA synthesis assay". *Food and Chemical Toxicology* 34, pp. 337–345 (cit. on p. 131).

[Martinez and Staba, 1984] B. Martinez and E. J. Staba (1984). "The physiological effects of Aralia, Panax and Eleutherococcus on exercised rats". *Japanese Journal of Pharmacology* 35, pp. 79–85 (cit. on p. 100).

[Martín-Sánchez et al., 2009] E. Martín-Sánchez et al. (2009). "Systematic review and meta-analysis of cannabis treatment for chronic pain". *Pain Medicine* 10.8, pp. 1353–1368 (cit. on p. 343).

[Mason and McBay, 1985] A. P. Mason and A. J. McBay (1985). "Cannabis: pharmacology and interpretation of effects". *Journal of Forensic Sciences* 30.3, pp. 615–631 (cit. on p. 344).

[Massiot, 1988] G. Massiot (1988). "Reinvestigation of the sapogenins and prosapogenins from alfalfa ( Medicago sativa )". *Journal of Agricultural and Food Chemistry* 36, p. 902 (cit. on p. 67).

[Matsuda and Kubo, 1984] H. Matsuda and M. Kubo (1984). "Pharmacological study on Panax ginseng C.A. Meyer. II. Effect of red ginseng on the experimental gastric ulcer". *Yakugaku Zasshi* 104, pp. 449–453 (cit. on p. 102).

[K. Matsumoto, Kohno, and Ojima, 1998] K. Matsumoto, S. Kohno, and K. Ojima (1998). "Effects of methylenechloride-soluble fraction of Japanese angelica root extract, ligustilide and butylidenephthalide, on pentobarbital sleep in group-housed and socially isolated mice". *Life Sciences* 62.23, pp. 2073–2082 (cit. on p. 260).

[T. Matsumoto et al., 1996] T. Matsumoto et al. (1996). "Effect of licorice root on Carrageenan-induced decrease in immune complex clearance in mice". *Journal of Ethnopharmacology* 53.1, pp. 1–4 (cit. on p. 320).

[Matsumura et al., 2005] A. Matsumura et al. (2005). "Comparative study of oestrogenic properties of eight phytoestrogens in MCF7 human breast cancer cells". *The Journal of Steroid Biochemistry and Molecular Biology* 94.5, pp. 431–443 (cit. on p. 382).

[B. Mayer, Baggio, and Freitas, 2009] B. Mayer, C. H. Baggio, and C. S. Freitas (2009). "Gastroprotective constituents of Salvia officinalis L". *Fitoterapia* 80.7, pp. 421–426 (cit. on p. 408).

[K. E. Mayer, Myers, and S. S. Lee, 2005] K. E. Mayer, R. P. Myers, and S. S. Lee (2005). "Silymarin treatment of viral hepatitis: a systematic review". *Journal of Viral Hepatitis* 12.6, pp. 559–567 (cit. on p. 362).

[Mazzanti, Di Sotto, and Franchitto, 2008] G. Mazzanti, A. Di Sotto, and A. Franchitto (2008). "Effects of Cimicifuga racemosa extract on liver morphology and hepatic function indices". *Phytomedicine* 15.11, pp. 1021–1024 (cit. on p. 190).

[McCarty, 2005] M. McCarty (2005). "Potential utility of natural polyphenols for reversing fat-induced insulin resistance". *Medical Hypotheses* 64.3, pp. 628–635 (cit. on p. 361).

[McElhaney, V. Goel, et al., 2006] J. E. McElhaney, V. Goel, et al. (2006). "Efficacy of Cold-fX in the prevention of respiratory symptoms in community-dwelling adults: a randomized, double-blinded, placebo-controlled trial". *Journal of Alternative and Complementary Medicine* 12.2, pp. 153–157 (cit. on pp. 86, 143).

[McElhaney, Gravenstein, and Cole, 2004] J. E. McElhaney, S. Gravenstein, and S. K. Cole (2004). "A placebo-controlled trial of a proprietary extract of North American ginseng (CVT-E002) to prevent acute respiratory illness in institutionalized older adults". *Journal of the American Geriatrics Society* 52.1, pp. 13–19. published correction appears in Journal of the American Geriatrics Society, 2004;52(5) (cit. on pp. 86, 142).

[McGuffin et al., 1997] M. McGuffin et al. (1997). *American Herbal Product Association's Botanical Safety Handbook*. 10. Boca Raton: CRC Press (cit. on p. 116).

[McHarg, Rodgers, and Charlton, 2003] T. McHarg, A. Rodgers, and K. Charlton (2003). "Influence of cranberry juice on the urinary risk factors for calcium oxalate kidney stone formation". *BJU International* 92.7, pp. 765–768 (cit. on p. 237).

[McKay and Blumberg, 2007] D. L. McKay and J. Blumberg (2007). "Cranberries (vaccinium macrocarpon) and cardiovascular disease risk factors". *Nutrition Reviews* 65.11, pp. 490–502 (cit. on pp. 227–228, 232).

[medical-dictionary, 2014] medical-dictionary, ed. (2014). *various*. URL: http://medical-dictionary.thefreedictionary.com/exogenous (cit. on pp. 51, 471).

[MedlinePlus, 2012] MedlinePlus, ed. (2012). *Dong quai*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/936.html (cit. on p. 268).

[MedlinePlus, 2014a] — ed. (2014a). *Alfalfa*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/19.html (cit. on p. 73).

[MedlinePlus, 2014b] — ed. (2014b). *American Ginseng*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/967.html (cit. on p. 91).

[MedlinePlus, 2014c] — ed. (2014c). *Cranberry*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/958.html (cit. on p. 241).

[MedlinePlus, 2014d] — ed. (2014d). *Liquorice*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/881.html (cit. on pp. 326, 332).

[MedlinePlus, 2014e] — ed. (2014e). *Milk Thistle*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/138.html (cit. on pp. 354, 378).

[MedlinePlus, 2014f] — ed. (2014f). *various*. MedlinePlus. URL: http://www.nlm.nih.gov/medlineplus/ (cit. on pp. 63, 379).

[medlineplus, 2015a] medlineplus (2015a). *Dong quai (angelica sinesis [oliv.] Dies), Chinese angelica*. Therapeutic Research Center. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/936.html (cit. on p. 256).

[medlineplus, 2015b] — (2015b). *Saw Palmetto*. URL: http://www.nlm.nih.gov/medlineplus/druginfo/natural/971.html (cit. on pp. 425–426).

[medscape, 2015a] medscape (2015a). *Black Cohosh*. URL: http://reference.medscape.com/drug/actaea-racemosa-baneberry-black-cohosh-344508 (cit. on pp. 168, 175, 189).

[medscape, 2015b] — (2015b). *Chaste Berry*. URL: http://reference.medscape.com/drug/agnolyt-agnus-castus-chasteberry-344510 (cit. on pp. 14, 216, 218, 221, 223–224).

[medscape, 2015c] medscape (2015c). *Cranberry*. URL: http://reference.medscape.com/drug/american-cranberry-black-cranberry-cranberry-344568 (cit. on pp. 15, 228–229, 233–234, 236, 238, 241).

[medscape, 2015d] — (2015d). *Damiana*. URL: http://reference.medscape.com/drug/mexican-damiana-turnera-aphrodisiaca-damiana-344562 (cit. on pp. 246–248).

[medscape, 2015e] — (2015e). *Dong Quai*. URL: http://reference.medscape.com/drug/angelica-atropurpurea-angelica-dahurica-dong-quai-344511 (cit. on pp. 17, 257, 262–263, 266, 268).

[medscape, 2015f] — (2015f). *Fennel*. URL: http://reference.medscape.com/drug/aneth-doux-bitterfenchel-fennel-344583 (cit. on pp. 277, 282–285).

[medscape, 2015g] — (2015g). *Fenugreek*. URL: http://reference.medscape.com/drug/birds-foot-bockshornsam-fenugreek-344582 (cit. on pp. 18, 292, 294–295).

[medscape, 2015h] — (2015h). *Hops*. URL: http://reference.medscape.com/drug/humulus-lupulus-hops-344540 (cit. on pp. 19, 301, 304–305).

[medscape, 2015i] — (2015i). *Marijuana*. URL: http://reference.medscape.com/drug/cannabis-ganja-marijuana-343687 (cit. on pp. 20, 339–340, 345–346, 348, 350–351).

[medscape, 2015j] — (2015j). *Milk Thistle*. URL: http://reference.medscape.com/drug/carduus-marianum-holy-thistle-milk-thistle-344521 (cit. on pp. 21, 359, 368, 371, 379).

[medscape, 2015k] — (2015k). *Red Clover*. URL: http://reference.medscape.com/drug/beebread-cow-clover-red-clover-344581 (cit. on pp. 387, 391, 396, 398–399).

[medscape, 2015l] — (2015l). *Saw Palmetto*. URL: http://reference.medscape.com/drug/american-dwarf-palm-tree-cabbage-palm-saw-palmetto-saw-palmetto-344575 (cit. on pp. 415, 420–422, 427).

[medscape, 2015m] — (2015m). *Soy*. URL: http://reference.medscape.com/drug/isoflavones-daidzein-phytoestrogens-344513 (cit. on pp. 24, 432, 441, 443–444).

[Meeran and Katiyar, 2008] S. M. Meeran and S. K. Katiyar (2008). "Cell cycle control as a basis for cancer chemoprevention through dietary agents". *Frontiers in Bioscience* 13, pp. 2191–2202 (cit. on p. 360).

[Mehra et al., 2006] R. Mehra et al. (2006). "The association between marijuana smoking and lung cancer: a systematic review". *Archives of Internal Medicine* 166.13, pp. 1359–1367 (cit. on p. 352).

[Mei, Tao, and B. Cui, 1991] Q. B. Mei, J. Y. Tao, and B. Cui (1991). "Advances in the pharmacological studies of Radix Angelica sinensis (Oliv.) Diels (Chinese danggui)". *Chinese Medical Journal* 104, pp. 776–781 (cit. on pp. 270–271, 273).

[Melgalve, 1976] I. Melgalve (1976). "Quantity of vitamin C in cranberries. Latv Lauksaimn Akad Raksti". *Chemical Abstracts* 86.1542, p. 12 (cit. on p. 228).

[merck, 2009] merck (2009). *Black Cohosh*. URL: http://www.merckmanuals.com/professional/special-subjects/dietary-supplements/black-cohosh (cit. on pp. 161, 175, 179, 182).

[merck, 2015] — (2015). *Dietary supplement - ginseng*. MSD. URL: http://www.merckmanuals.com/professional/special-subjects/dietary-supplements/ginseng (cit. on pp. 76, 79, 87, 150).

[Mesaik, Azizuddin, and Murad, 2009] M. A. Mesaik, Azizuddin, and S. Murad (2009). "Isolation and immunomodulatory properties of a flavonoid, casticin from Vitex agnus-castus". *Phytotherapy Research* 23.11, pp. 1516–1520 (cit. on pp. 213, 216).

[M. Messina, 2014] M. Messina (2014). "Soy foods, isoflavones, and the health of postmenopausal women". *American Journal of Clinical Nutrition* 100, 423S–430S. Supplement 1 (cit. on p. 430).

[M. J. Messina, 2003] M. J. Messina (2003). "Emerging evidence on the role of soy in reducing prostate cancer risk". *Nutrition Reviews* 61.4, pp. 117–131 (cit. on p. 435).

[M. J. Messina and Loprinzi, 2001] M. J. Messina and C. L. Loprinzi (2001). "Soy for breast cancer survivors: a critical review of the literature". *Journal of Nutrition* 131.11 (supplement), 3095S–3108S (cit. on pp. 431–432).

[M. Messina, McCaskill-Stevens, and Lampe, 2006] M. Messina, W. McCaskill-Stevens, and J. W. Lampe (2006). "Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings". *Journal of the National Cancer Institute* 98.18, pp. 1275–1284 (cit. on p. 434).

[F. G. Meyer, Trueblood, and Heller, 1999] F. G. Meyer, E. E. Trueblood, and J. L. Heller (1999). *The Great Herbal of Leonhart Fuchs: De historia stirpium commentarii insignes, 1542. (Notable commentaries on the history of plants)*. Vol. 1 of 2. Stanford, California: Stanford University Press, p. 348 (cit. on p. 298).

[F. Meyer and E. Meyer, 1959] F. Meyer and E. Meyer (1959). *Arzneimittelforschung* 9, p. 516 (cit. on p. 125).

[J. E. Meyer, 1934] J. E. Meyer (1934). *The Herbalist*. Hammond, IN: Hammond Book Co (cit. on p. 276).

[J. E. Meyer, 1960] — (1960). *The Herbalist*. Chicago, IL: Rand McNally (cit. on p. 160).

[Meyer-Buchtela, 1999] E. Meyer-Buchtela (1999). *Tee-RezepturenEin Handbuch für Apotheker und Ärzte*. Stuttgart, Germany: Deutscher Apotheker Verlag (cit. on pp. 111, 117).

[Miguez et al., 1994] M. P. Miguez et al. (1994). "Hepatoprotective mechanism of silymarin: no evidence for involvement of cytochrome P450 2E1". *Chemico-Biological Interactions* 91, pp. 51–63 (cit. on p. 367).

[Milewicz, 1993] A. Milewicz (1993). "Vitex agnus castus extract in the treatment of luteal phase defects due to latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study". *Arzneimittel Forschung* 43.7, pp. 752–756 (cit. on p. 219).

[C. C. Miller, W. Tang, et al., 1991] C. C. Miller, W. Tang, et al. (1991). "Dietary supplementation with ethyl ester concentrates of fish oil (n-3) and borage oil (n-6) polyunsaturated fatty acids induces epidermal generation of local putative anti-inflammatory metabolites". *Journal of Investigative Dermatology* 96, pp. 98–103 (cit. on p. 194).

[C. C. Miller and Ziboh, 1988] C. C. Miller and V. A. Ziboh (1988). "Gammalinolenic acid-enriched diet alters cutaneous eicosanoids". *Biochemical and Biophysical Research Communications* 154, pp. 967–974 (cit. on p. 194).

[C. C. Miller, Ziboh, et al., 1990] C. C. Miller, V. A. Ziboh, et al. (1990). "Dietary supplementation with oils rich in (n-3) and (n-6) fatty acids influences in vivo levels of epidermal lipoxygenase products in guinea pigs". *Journal of Nutrition* 120, pp. 36–44 (cit. on p. 194).

[L. Miller, 1998] L. Miller (1998). "Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions". *Archives of Internal Medicine* 158, pp. 2200–2211 (cit. on p. 116).

[L. G. Miller, 1998] L. G. Miller (1998). "Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions". *Archives of Internal Medicine* 158, p. 2200 (cit. on p. 72).

[S. R. Milligan, J. C. Kalita, Heyerick, et al., 1999] S. R. Milligan, J. C. Kalita, A. Heyerick, et al. (1999). "Identification of a potent phytoestrogen in hops ( Humulus lupulus L.) and beer". *Journal of Clinical Endocrinology & Metabolism* 84, pp. 2249–2252 (cit. on p. 302).

[S. R. Milligan, J. C. Kalita, and Pocock, 2000] S. R. Milligan, J. C. Kalita, and V. Pocock (2000). "The endocrine activities of 8-prenylnaringenin and related hop ( Humulus lupulus L.) flavonoids". *Journal of Clinical Endocrinology & Metabolism* 85, pp. 4912–4915 (cit. on p. 302).

[S. Milligan, J. Kalita, and Pocock, 2002] S. Milligan, J. Kalita, and V. Pocock (2002). "Oestrogenic activity of the hop phyto-oestrogen, 8-prenylnaringenin". *Reproduction* 123, pp. 235–242 (cit. on p. 302).

[D. E. Mills et al., 1990] D. E. Mills et al. (1990). "Alteration of baroreflex control of forearm vascular resistance by dietary fatty acids". *American Journal of Physiology* 259, R1164–R1171 (cit. on p. 195).

[E. Mills, Wilson, and Clarke, 2005a] E. Mills, K. Wilson, and M. Clarke (2005a). "Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis". *European Journal of Clinical Pharmacology* 61.1, pp. 1–7 (cit. on p. 374).

[E. Mills, Wilson, and Clarke, 2005b] — (2005b). "Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis". *European Journal of Clinical Pharmacology* 61.1, pp. 1–7 (cit. on p. 374).

[S. Mills and Bone, 2000] S. Mills and K. Bone (2000). *Principles and Practice of Phytotherapy*. Edinburgh: Churchill Livingstone, pp. 303–309 (cit. on p. 185).

[Mira, M. S. Azevedo, and Manso, 1987a] M. L. Mira, M. S. Azevedo, and C. Manso (1987a). "The neutralization of hydroxyl radical by silibin, sorbinil and bendazac". *Free Radical Research Communications* 4, p. 129 (cit. on p. 355).

[Mira, M. S. Azevedo, and Manso, 1987b] — (1987b). "The neutralization of hydroxyl radical by silibin, sorbinil and bendazac". *Free Radical Research Communications* 4, p. 129 (cit. on pp. 364, 367).

[Miranda, Stevens, and Helmrich, 1999] C. L. Miranda, J. F. Stevens, and A. Helmrich (1999). "Antiproliferative and cytotoxic effects of prenylated flavonoids from hops ( Humulus lupulus ) in human cancer cell lines". *Food and Chemical Toxicology* 37, pp. 271–285 (cit. on p. 303).

[Miranda, Y. Yang, and Henderson, 2000] C. L. Miranda, Y. Yang, and M. C. Henderson (2000). "Prenylflavonoids from hops inhibit the metabolic activation of the carcinogenic heterocyclic amine 2-amino-3-methylimidazo[4, 5-f]quinoline, mediated by cDNA-expressed human CYP1A2". *Drug Metabolism and Disposition* 28, pp. 1297–1302 (cit. on p. 303).

[Mironets, Krasovskaia, and Polishchuk, 1990a] V. I. Mironets, E. A. Krasovskaia, and I. I. Polishchuk (1990a). "A case of urticaria during Carsil treatment". *Vrach Delo* 7, pp. 86–87 (cit. on p. 355).

[Mironets, Krasovskaia, and Polishchuk, 1990b] — (1990b). "A case of urticaria during Carsil treatment". *Vrach Delo* 7, pp. 86–87 (cit. on p. 365).

[Miura, Kikuzaki, and Nakatani, 2001] K. Miura, H. Kikuzaki, and N. Nakatani (2001). "Apianane terpenoids from Salvia officinalis". *Phytochemistry* 58.8, pp. 1171–1175 (cit. on p. 405).

[Mizukami, 1995] H. Mizukami (1995). "Amplification and sequence of a 5s-rRNA gene spacer region from the crude drug angelica root". *Biological and Pharmaceutical Bulletin* 18.9, pp. 1299–1301 (cit. on p. 256).

[Moerman, 1982] D. E. Moerman (1982). *Geraniums for the Iroquois. A field guide to American Indian medicinal plants*. Algonac, MI: Reference Publications (cit. on p. 300).

[Mohamad, El-Bastawesy, and Abdel-Monem, 2011] R. H. Mohamad, A. M. El-Bastawesy, and M. G. Abdel-Monem (2011). "Antioxidant and anticarcinogenic effects of methanolic extract and volatile oil of fennel seeds (Foeniculum vulgare)". *Journal of Medicinal Food* 14.9, pp. 986–1001 (cit. on pp. 281, 285).

[Mohamed et al., 1976] Y. Mohamed et al. (1976). "Spectrophotometric determination of certain volatile oils. Assay of anethole in volatile oils of anise and fennel". *Indian Journal of Pharmaceutical Sciences* 38, pp. 117–119. Part 3 (cit. on p. 121).

[Moharram, Abdel-Mallek, and Abdel-Hafez, 1989] A. M. Moharram, A. Y. Abdel-Mallek, and A. I. Abdel-Hafez (1989). "Mycoflora of anise and fennel seeds in Egypt". *Journal of Basic Microbiology* 29, pp. 427–435 (cit. on p. 120).

[Molgaard, Schenck, and Olsson, 1987] J. Molgaard, H. von Schenck, and A. G. Olsson (1987). "Alfalfa seeds lower low density lipoprotein cholesterol and apolipoprotein B concentrations in patients with type II hyperlipoproteinemia". *Atherosclerosis* (65), pp. 173–179 (cit. on p. 68).

[Molyneux and Y. Wong, 1975] R. J. Molyneux and Y. Wong (1975). "Nuclear magnetic resonance spectroscopic determination of alpha- and beta-acid homolog composition in hops". *Journal of Agricultural and Food Chemistry* 23, pp. 1201–1204 (cit. on p. 300).

[Moore, Zammit, and Lingford-Hughes, 2007] T. H. Moore, S. Zammit, and A. Lingford-Hughes (2007). "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review". *Lancet* 370.9584, pp. 319–328 (cit. on p. 352).

[A. G. Morgan, McAdam, et al., 1982] A. G. Morgan, W. A. McAdam, et al. (1982). "Comparison between cimetidine and Caved-S in the treatment of gastric ulceration, and subsequent maintenance therapy". *Gut* 23.6, pp. 545–551 (cit. on pp. 319, 332).

[A. G. Morgan, Pacsoo, and McAdam, 1985] A. G. Morgan, C. Pacsoo, and W. A. McAdam (1985). "Maintenance therapy: a two year comparison between Caved-S and cimetidine treatment in the prevention of symptomatic gastric ulcer recurrence". *Gut* 26.6, pp. 599–602 (cit. on pp. 319, 332).

[Morimoto, 1989] I. Morimoto (1989). "A study on immunological effects of L-canavanine". *Kobe Journal of Medical Sciences* 35, pp. 287–298 (cit. on p. 74).

[Morimoto et al., 1990] I. Morimoto et al. (1990). "L-canavanine acts on suppressor-inducer T cells to regulate antibody synthesis: lymphocytes of systemic lupus erythematosus patients are specifically unresponsive to L-canavanine". *Clinical Immunology and Immunopathology* 55, pp. 97–108 (cit. on p. 74).

[Morris, I. Jacobs, and Kligerman, 1994] A. C. Morris, I. Jacobs, and T. M. Kligerman (1994). "No ergogenic effect of ginseng extract after ingestion". *Medical science of sports exercise* 26 (s6) (cit. on p. 103).

[Moscarella, Giusti, and Marra, 1993a] S. Moscarella, A. Giusti, and F. Marra (1993a). "Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease: preliminary results". *Current Therapeutic Research* 53, pp. 98–102 (cit. on pp. 354–355).

[Moscarella, Giusti, and Marra, 1993b] — (1993b). "Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease: preliminary results". *Current Therapeutic Research* 53, pp. 98–102 (cit. on pp. 364, 367, 373).

[Moss, 2013] N. Moss (2013). *A Fancy to Worcesters*. Agricultural research Service, U.S. Department of Agriculture (cit. on p. 299).

[Muangman and Cherdshewasart, 2001] V. Muangman and W. Cherdshewasart (2001). "Clinical trial of the phytoestrogen rich herb, Pueraria mirifica as a crude drug in the treatment of symptoms in menopausal women". *Siriraj Hospital Gazette* 53, pp. 300–309 (cit. on p. 384).

[Mueller, 1899] A. Mueller (1899). "Versuche über die Wirkungsweise des Extrakts des chinesischen Emmenagogon Tang-kui (Man-mu) oder Eumenol-Merek". *Münchener Medizinische Wochenschrift* 46, pp. 796–798 (cit. on pp. 272–273).

[Mühlenstedt et al., 1978] D. Mühlenstedt et al. (1978). "Short luteal phase and prolactin". *International Journal of Fertility & Sterility* 23.3, pp. 213–218 (cit. on p. 219).

[Mullen and Dasarathy, 1998a] K. Mullen and S. Dasarathy (1998a). "Potential new therapies for alcoholic liver disease". *Clinical Liver Disease* 2, pp. 853–874 (cit. on p. 355).

[Mullen and Dasarathy, 1998b] — (1998b). "Potential new therapies for alcoholic liver disease". *Clinical Liver Disease* 2, pp. 853–874 (cit. on pp. 364, 366–367).

[Müller et al., 2002] C. E. Müller et al. (2002). "Interactions of valerian extracts and a fixed valerian-hop extract combination with adenosine receptors". *Life Sciences* 71, pp. 1939–1949 (cit. on p. 302).

[Müller-Riebau, B. Berger, and Yegen, 1995] F. Müller-Riebau, B. Berger, and O. Yegen (1995). "Chemical composition and fungitoxic properties to phytopathogenic fungi of essential oils of selected aromatic plants growing wild in Turkey". *Journal of Agricultural and Food Chemistry* 43, pp. 2262–2266 (cit. on p. 127).

[Müller-Vahl, Prevedel, et al., 2003] K. R. Müller-Vahl, H. Prevedel, et al. (2003). "Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance". *Neuropsychopharmacology* 28.2, pp. 384–388 (cit. on p. 344).

[Müller-Vahl, U. Schneider, and Prevedel, 2003] K. R. Müller-Vahl, U. Schneider, and H. Prevedel (2003). "Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial". *Journal of Clinical Psychiatry* 64.4, pp. 459–465 (cit. on p. 344).

[Muraro, 2001] M. A. Muraro (2001). "Soy and other protein sources". *Pediatric Allergy and Immunology* 12.supplement 14, pp. 85–90 (cit. on p. 438).

[M. Murray, 1997a] M. Murray (1997a). "Remifemin: Answers to some common questions". *American Journal of Natural Medicine* 4.3, p. 35 (cit. on p. 167).

[M. Murray, 1997b] M. Murray (1997b). "Remifenin: answers to common questions". *American Journal of Natural Medicine* 4, pp. 3–5 (cit. on p. 163).

[M. J. Murray et al., 2000] M. J. Murray et al. (2000). "Effects of eicosapentaenoic and gamma-linolenic acids (dietary lipids) on pulmonary surfactant composition and function during porcine endotoxemia". *Chest* 117, pp. 1720–1727 (cit. on p. 195).

[Museum, 2015] Science Museum, ed. (2015). *Doctrine of Signatures*. URL: http://www.sciencemuseum.org.uk/broughttolife/techniques/doctrine.aspx (visited on 10/16/2015) (cit. on pp. 78, 463).

[Muzes, Deak, and Lang, 1990a] G. Muzes, G. Deak, and I. Lang (1990a). "Silymarin (Legalon) kezeles hatasa idult alkoholos majbetegek antioxidans vedorendszerere es a lipid peroxidaciora (kettos vak protokoll)". *Orvosi Hetilap* 131, pp. 863–866 (cit. on p. 355).

[Muzes, Deak, and Lang, 1990b] — (1990b). "Silymarin (Legalon) kezeles hatasa idult alkoholos majbetegek antioxidans vedorendszerere es a lipid peroxidaciora (kettos vak protokoll)". *Orvosi Hetilap* 131, pp. 863–866 (cit. on p. 364).

[Myung et al., 2009] S. K. Myung et al. (2009). "Korean Meta-Analysis (KORMA) Study Group. Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis". *International Journal of Obstetrics & Gynaecology* 116.13, pp. 1697–1705 (cit. on p. 436).

[Naef et al., 2003] M. Naef et al. (2003). "The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions". *Pain* 105.1-2, pp. 79–88 (cit. on p. 343).

[Nakagawa, 1985] S. Nakagawa (1985). "Cytoprotective activity of components of garlic, ginseng and ciwujia on hepatocyte injury induced by carbon tetrachloride in vitro". *Hiroshima Journal of Medical Science* 34, pp. 303–309 (cit. on p. 100).

[Nakai, Cook, and Pyter, 2005] M. Nakai, L. Cook, and L. M. Pyter (2005). "Dietary soy protein and isoflavones have no significant effect on bone and a potentially negative effect on the uterus of sexually mature intact Sprague-Dawley female rats". *Menopause* 12.3, pp. 291–298 (cit. on p. 439).

[Namavar Jahromi, Tartifizadeh, and Khabnadideh, 2003] B. Namavar Jahromi, A. Tartifizadeh, and S. Khabnadideh (2003). "Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea". *International Journal of Gynecology & Obstetrics* 80.2, pp. 153–157 (cit. on p. 279).

[Narasimha and Nigam, 1970] B. G. Narasimha and S. S. Nigam (1970). "In vitro antimicrobial efficiency of some essential oils". *Flavor Ind* 1, pp. 725–729 (cit. on p. 122).

[Naser and Liske, 2009] B. Naser and E. Liske (2009). "Liver failure associated with the use of black cohosh for menopausal symptoms". *The Medical Journal of Australia* 190.2, p. 99 (cit. on p. 189).

[Nasr and Nafeh, 2009] A. Nasr and H. Nafeh (2009). "Influence of black cohosh (Cimicifuga racemosa ) use by postmenopausal women on total hepatic perfusion and liver functions". *Fertility and Sterility* 92.5, pp. 1780–1782 (cit. on p. 190).

[Nasri et al., 2007] S. Nasri et al. (2007). "The effects of Vitex agnus castus extract and its interaction with dopaminergic system on LH and testosterone in male mice". *Pakistan Journal of Biological Sciences* 10.14, pp. 2300–2307 (cit. on p. 216).

[Natelson, 1985] S. Natelson (1985). "Canavanine to arginine ratio in alfalfa (Medicago sativa), clover (Trifolium), and the jack bean (Canavalia ensiformis)". *Journal of Agricultural and Food Chemistry* 33, p. 413 (cit. on p. 74).

[NCCIH, 2012a] NCCIH (2012a). *Asian ginseng*. National Center for Complementary and Integrative Health. URL: https://nccih.nih.gov/health/asianginseng/ataglance.htm (cit. on p. 151).

[NCCIH, 2012b] — (2012b). *Cranberry*. National Center for Complementary and Integrative Health. URL: https://nccih.nih.gov/health/cranberry (cit. on p. 238).

[NCCIH, 2012c] — (2012c). *Fenugreek*. National Center for Complementary and Integrative Health. URL: https://nccih.nih.gov/health/fenugreek (cit. on p. 293).

[NCCIH, 2012d] — ed. (2012d). *herbs at a glance. Black Cohosh*. URL: https://nccih.nih.gov/health/herbsataglance.htm (cit. on p. 180).

[NCCIH, 2012e] — (2012e). *Milk Thistle*. National Center for Complementary and Integrative Health. URL: https://nccih.nih.gov/health/milkthistle/ataglance.htm (cit. on p. 358).

[Nesselhut et al., 1993] T. Nesselhut et al. (1993). "Studies of the proliferative potency of phytodrugs with estrogen-like effect in breast cancer cells". German. *Archives of Gynecology and Obstetrics* 254, pp. 817–818 (cit. on pp. 185–186).

[Nestel, Pomeroy, and Kay, 1999] P. J. Nestel, S. Pomeroy, and S. Kay (1999). "Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women". *Journal of Clinical Endocrinology & Metabolism* 84, pp. 895–898 (cit. on p. 394).

[Neto, 2007a] C. C. Neto (2007a). "Cranberry and blueberry: evidence for protective effects against cancer and vascular diseases". *Molecular Nutrition & Food Research* 51.6, pp. 652–664 (cit. on p. 232).

[Neto, 2007b] — (2007b). "Cranberry and its phytochemicals: a review of in vitro anticancer studies". *Journal of Nutrition* 137, 186s–193s (cit. on pp. 228, 232).

[C. Newall, 1996] C. Newall (1996). *Herbal Medicines*. London, England: Pharmaceutical Press, pp. 30–31 (cit. on pp. 121, 123–124).

[C. A. Newall, L. A. Anderson, and Phillipson, 1996a] C. A. Newall, L. A. Anderson, and J. D. Phillipson, eds. (1996a). *Herbal Medicines: A Guide for Health-Care Professionals. Black Cohosh*. London, England: Pharmaceutical Press. 80-81 (cit. on pp. 168, 175, 181).

[C. A. Newall, L. A. Anderson, and Phillipson, 1996b] — (1996b). *Herbal Medicines: A Guide for Health-Care Professionals*. London, UK: The Pharmaceutical Press, p. 2829 (cit. on pp. 117–118, 189, 202, 247, 326, 390, 395).

[Newberne, 1999] P. Newberne et al. (1999). "The FEMA GRAS assessment of trans-anethole used as a flavouring substance". *Food and Chemical Toxicology* 37, pp. 789–811 (cit. on p. 132).

[Newton et al., 2006] K. M. Newton et al. (2006). "Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial". *Annals of Internal Medicine* 145.12, pp. 869–879 (cit. on p. 172).

[Ng, 2006] T. B. Ng (2006). "Pharmacological activity of sanchi ginseng (Panax notoginseng)". *Journal of Pharmacy and Pharmacology* 58.8, pp. 1007–1019 (cit. on pp. 81, 90, 139, 153).

[Ng, W. W. Li, and Yeung, 1987] T. B. Ng, W. W. Li, and H. W. Yeung (1987). "Effects of ginsenosides, lectins, and Momordica charantia insulin-like peptides on corticosterone production by isolated rat adrenal cells". *Journal of Ethnopharmacology* 21, pp. 21–29 (cit. on p. 100).

[B. Nielsen, 1964] B. Nielsen (1964). "The structure of archangelicin, a coumarin from Angelica archangelica L. subsp. litoralis Thell". *Acta Chemica Scandinavica* 18, pp. 932–936 (cit. on p. 112).

[NIH, n.d.] NIH. *Clinical Trials Database*. U.S. National Institutes of Health. URL: http://clinicaltrials.gov/ct2/home (cit. on pp. 360–362).

[NIH, 2012a] — (2012a). *Herbs at a glance - chasteberry* (cit. on pp. 218–219, 221–222).

[NIH, 2012b] — (2012b). *Herbs at a glance - Saw Palmetto* (cit. on pp. 414–415, 421, 424).

[nih, 2008] nih (2008). *Black Cohosh*. USA.gov. URL: http://ods.od.nih.gov/factsheets/BlackCohosh-HealthProfessional/ (cit. on p. 188).

[Nikolic et al., 2004] D. Nikolic et al. (2004). "Metabolism of 8-prenylnaringenin, a potent phytoestrogen from hops (Humulus lupulus), by human liver microsomes". *Drug metabolism and disposition: the biological fate of chemicals* 32.2, pp. 272–279. DOI: 10.1124 (cit. on p. 301).

[Ninomiya, Matsuda, and Shimoda, 2004] K. Ninomiya, H. Matsuda, and H. Shimoda (2004). "Carnosic acid, a new class of lipid absorption inhibitor from sage". *Bioorganic & Medicinal Chemistry Letters* 14.8, pp. 1943–1946 (cit. on p. 405).

[Niu, W. Chen, and H. T. Wu, 2010] C. S. Niu, W. Chen, and H. T. Wu (2010). "Decrease of plasma glucose by allantoin, an active principle of yam ( Dioscorea spp.), in streptozotocin-induced diabetic rats". *Journal of Agricultural and Food Chemistry* 24.58, pp. 12031–12035 (cit. on p. 450).

[NRCS, 2007] NRCS (2007). *The PLANTS Database - Glycyrrhiza glabra*. Baton Rouge, LA 70874-4490 USA. National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 315).

[NRCS, 2010a] — (2010a). *The PLANTS Database - Cannabis sativa*. Baton Rouge, LA 70874-4490 USA. National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 337).

[NRCS, 2010b] — (2010b). *The PLANTS Database - Silybum marianum*. Baton Rouge, LA 70874-4490 USA. National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 356).

[NRCS, 2011] — (2011). *The PLANTS database - Glycine max*. Baton Rouge, LA 70874-4490 USA. URL: http://plants.usda.gov. National Plant Data Center (cit. on p. 430).

[Nursinglink, 2015] Nursinglink (2015). *Clinically Significant Drug Interaction with the Cytochrome P450 Enzyme System*. URL: http://nursinglink.monster.com/training/articles/320-clinically-significant-drug-interaction-with-the-cytochrome-p450-enzyme-system (cit. on pp. 240, 475).

[OAB, 1991] OAB (1991). *Österreichisches Arzneibuch*. Staatsdruckerei: Wien: Verlag der Österreichischen (cit. on p. 117).

[Oboh and Henle, 2009] G. Oboh and T. Henle (2009). "Antioxidant and inhibitory effects of aqueous extracts of Salvia officinalis leaves on pro-oxidant-induced lipid peroxidation in brain and liver in vitro". *Journal of Medicinal Food* 12.1, pp. 77–84 (cit. on p. 408).

[Odenthal, 1996] K. Odenthal (1996). "Phytotherapy of benign prostatic hyperplasia (BPH) with Cucurbita , Hypoxis , Pygeum , Urtica and Sabal serrulata ( Serenoa repens )". *Phytotherapy Research* 10.S141 (cit. on p. 419).

[ODS, 2008] ODS (2008). *Black Cohosh. Fact Sheet for Health Professionals*. URL: http://ods.od.nih.gov/factsheets/BlackCohosh-HealthProfessional/ (cit. on p. 182).

[ODS, 2011] — (2011). *Botanicals background*. Office of Dietary Supplements. URL: http://www.ods.od.nih.gov/factsheets/BotanicalBackground-HealthProfessional (cit. on p. 60).

[Ody, 1993] P. Ody (1993). *The Complete Medicinal Herbal*. New York, NY: Dorling Kindersley, Inc (cit. on p. 118).

[Oerter Klein et al., 2003] K. Oerter Klein et al. (2003). "Estrogen bioactivity in fo-ti and other herbs used for their estrogen-like effects as determined by a recombinant cell bioassay". *Journal of Clinical Endocrinology & Metabolism* 88.9, pp. 4077–4079 (cit. on p. 320).

[Oerter-Klein et al., 2003] K. Oerter-Klein et al. (2003). "Estrogen bioactivity in fo-ti and other herbs used for their estrogen-like effects as determined by a recombinant cell bioassay". *Journal of Clinical Endocrinology & Metabolism* 88, pp. 4077–4079 (cit. on p. 391).

[Ofek et al., 1991] I. Ofek et al. (1991). "Anti-Escherichia coli adhesin activity of cranberry and blueberry juices". *New England Journal of Medicine* 324.22, p. 1599 (cit. on p. 230).

[Oh et al., 2010] K. J. Oh et al. (2010). "Effects of Korean red ginseng on sexual arousal in menopausal women: placebo-controlled, double-blind crossover clinical study". *Journal of Sexual Medicine* 7.4, pp. 1469–1477. part 1 (cit. on pp. 86, 143).

[Ohnuma, E. Yamaguchi, and Kawakami, 1998] N. Ohnuma, E. Yamaguchi, and Y. Kawakami (1998). "Anaphylaxis to curry powder". *Allergy* 53, pp. 452–454 (cit. on p. 292).

[Ohshima et al., 1988] Y. Ohshima et al. (1988). "Isolation and high performance liquid chromatography (HPLC) of isoflavonoids from the Pueraria root". *Planta Medica* 54.3, pp. 250–254 (cit. on p. 306).

[Ohyama et al., 2005] K. Ohyama et al. (2005). "Human gastric signet ring carcinoma (KATO-III) cell apoptosis induced by Vitex agnus-castus fruit extract through intracellular oxidative stress". *The International Journal of Biochemistry & Cell Biology* 37.7, pp. 1496–1510 (cit. on p. 216).

[Okuyama et al., 1990] T. Okuyama et al. (1990). "Studies on the antitumor-promoting activity of naturally occurring substances. II. Inhibition of tumor-promoter-enhanced phospholipid metabolism by umbelliferous materials". *Chemical and Pharmaceutical Bulletin* 38.4, pp. 1084–1086 (cit. on p. 257).

[Oleszek, 1988] W. Oleszek (1988). "Solid-phase extraction-fractionation of alfalfa saponins". *Journal of the Science of Food and Agriculture* 44.43 (cit. on p. 67).

[Olivia., 2011] Olivia. (2011). *Adverse Effect vs Side Effect*. URL: http://www.differencebetween.com/difference-between-adverse-effect-and-vs-side-effect/ (cit. on p. 454).

[Ono, Eguchi, and Konoshita, 2011] M. Ono, K. Eguchi, and M. Konoshita (2011). "A new diterpenoid glucoside and two new diterpenoids from the fruit of Vitex agnus-castus". *Chemical and Pharmaceutical Bulletin* 59.3, pp. 392–396 (cit. on p. 213).

[Opdyke, 1975] D. L. J. Opdyke (1975). "Angelica root oil". *Food and Cosmetics Toxicology* 13, p. 713 (cit. on pp. 112–113).

[Orhan and Aslan, 2009] I. Orhan and M. Aslan (2009). "Appraisal of scopolamine-induced antiamnesic effect in mice and in vitro antiacetylcholinesterase and antioxidant activities of some traditionally used Lamiaceae plants". *Journal of Ethnopharmacology* 122.2, pp. 327–332 (cit. on pp. 407–408).

[Ormerod et al., 1990] L. D. Ormerod et al. (1990). "Effects of altering the eicosanoid precursor pool on neovascularization and inflammation in the alkali-burned rabbit cornea". *American Journal of Pathology* 137, pp. 1243–1252 (cit. on p. 195).

[Osborn and Sinn, 2006] D. A. Osborn and J. Sinn (2006). "Soy formula for prevention of allergy and food intolerance in infants". *Cochrane Database of Systematic Reviews* 4.CD003741 (cit. on p. 438).

[Ostad, Khakinegad, and Sabzevari, 2004] S. N. Ostad, B. Khakinegad, and O. Sabzevari (2004). "Evaluation of the teratogenicity of fennel essential oil (FEO) on the rat embryo limb buds culture". *Toxicology in Vitro* 18.5, pp. 623–627 (cit. on p. 285).

[Ostad, Soodi, et al., 2001] S. N. Ostad, M. Soodi, et al. (2001). "The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study". *Journal of Ethnopharmacology* 76.3, pp. 299–304 (cit. on pp. 281, 285).

[R. T. Owen, 1981a] R. T. Owen (1981a). "Ginseng: A pharmacological profile". *Drugs of Today* 17, pp. 343–351 (cit. on p. 99).

[R. T. Owen, 1981b] — (1981b). "Ginseng: A pharmacological profile". *Drugs of today* 17, pp. 343–351 (cit. on p. 104).

[Ozbek, Ugras, and Dülger, 2003] H. Ozbek, S. Ugras, and H. Dülger (2003). "Hepatoprotective effect of Foeniculum vulgare essential oil". *Fitoterapia* 74.3, pp. 317–319 (cit. on p. 281).

[Ozcan, Sagdic, and Ozkan, 2006] M. M. Ozcan, O. Sagdic, and G. Ozkan (2006). "Inhibitory effects of spice essential oils on the growth of Bacillus species". *Journal of Medicinal Food* 9.3, pp. 418–421 (cit. on p. 281).

[Page and Lawerence, 1999] R. L. II Page and J. D. Lawerence (1999). "Potentiation of warfarin by dong quai". *Pharmacotherapy* 19.7, pp. 870–876 (cit. on pp. 263–264).

[Pai et al., 2010] M. B. Pai et al. (2010). "Antifungal activity of Punica granatum , Acacia nilotica , Cuminum cyminum , and Foeniculum vulgare on Candida albicans : an in vitro study". *Indian Journal of Dental Research* 21.3, pp. 334–336 (cit. on p. 281).

[Painter, Perwaiz, and Murty, 2010] D. Painter, S. Perwaiz, and M. Murty (2010). *Health Product Infowatch*. Health Canada. URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v20n1-eng.php (cit. on p. 179).

[Palacio, Masri, and Mooradian, 2009] C. Palacio, G. Masri, and A. D. Mooradian (2009). "Black cohosh for the management of menopausal symptoms: a systematic review of clinical trials". *Drugs & Aging* 26.1, pp. 23–36 (cit. on p. 172).

[Palasciano, Portincasa, and Palmieri, 1994a] G. Palasciano, P. Portincasa, and V. Palmieri (1994a). "The effect of silymarin on plasma levels of malon-dialdehyde in patients receiving long-term treatment with psychotropic drugs". *Current Therapeutic Research* 55, pp. 537–545 (cit. on pp. 354, 356).

[Palasciano, Portincasa, and Palmieri, 1994b] — (1994b). "The effect of silymarin on plasma levels of malon-dialdehyde in patients receiving long-term treatment with psychotropic drugs". *Current Therapeutic Research* 55, pp. 537–545 (cit. on pp. 364, 367, 372).

[Palm, 1910] R. Palm (1910). "Erfahrungen mit Eumenol". *Münchener Medizinische Wochenschrift* 1, pp. 23–25 (cit. on pp. 272–273).

[Palmer, Montgomery, and Monteiro, 1978] B. V. Palmer, A. C. Montgomery, and J. C. Monteiro (1978). "Gin Seng and mastalgia". *British Medical Journal* 279, p. 1284 (cit. on p. 106).

[Palombo, DeMichele, and P. J. Boyce, 1999] J. D. Palombo, S. J. DeMichele, and P. J. Boyce (1999). "Effect of short-term enteral feeding with eicosapentaenoic and gamma-linolenic acids on alveolar macrophage eicosanoid synthesis and bactericidal function in rats". *Critical Care Medicine* 27, pp. 1908–1915 (cit. on p. 195).

[Palombo, DeMichele, J. W. Liu, et al., 2000] J. D. Palombo, S. J. DeMichele, J. W. Liu, et al. (2000). "Comparison of growth and fatty acid metabolism in rats fed diets containing equal levels of gamma-linolenic acid from high gamma-linolenic acid canola oil or borage oil". *Lipids* 35, pp. 975–981 (cit. on p. 194).

[Pandian, Anuradha, and Viswanathan, 2002] R. S. Pandian, C. V. Anuradha, and P. Viswanathan (2002). "Gastroprotective effect of fenugreek seeds (Trigonella foenum graecum) on experimental gastric ulcer in rats". *Journal of Ethnopharmacology* 81, pp. 393–397 (cit. on p. 292).

[E. K. Park et al., 2006] E. K. Park et al. (2006). "Intestinal bacteria activate estrogenic effect of main constituents puerarin and daidzin of Pueraria thunbergiana". *Biological and Pharmaceutical Bulletin* 29.12, pp. 2432–2435 (cit. on pp. 306–307).

[M. K. Park et al., 2009] M. K. Park et al. (2009). "Estrogen activities and the cellular effects of natural progesterone from wild yam extract in mcf-7 human breast cancer cells". *American Journal of Chinese Medicine* 37.1, pp. 159–167 (cit. on p. 449).

[M. S. Park et al., 2010] M. S. Park et al. (2010). "Physical and biological properties of yam as a saliva substitute". *Archives of Oral Biology* 55.2, pp. 177–183 (cit. on p. 448).

[Paubert-Braquet, Mencia Huerta, et al., 1997] M. Paubert-Braquet, J. M. Mencia Huerta, et al. (1997). "Effect of the lipidic lipidosterolic extract of Serenoa repens ( Permixon ) on the ionophore A23187-stimulated production of leukotriene B4 (LTB4) from human polymorphonuclear neutrophils". *Prostaglandins, Leukotrienes and Essential Fatty Acids* 57.3, pp. 299–304 (cit. on p. 419).

[Paubert-Braquet, Richardson, and Servent-Saez, 1996] M. Paubert-Braquet, F. O. Richardson, and N. Servent-Saez (1996). "Effect of Serenoa repens extract ( Permixon ) on estradiol/testosterone-induced experimental prostate enlargement in the rat". *Pharmacological Research* 34.3-4, pp. 171–179 (cit. on p. 419).

[Pen, 1981] R. X. Pen (1981). "Pharmacological effects of danggui (Angelica sinensis) on cardiovascular system". *Chinese Traditional Herb Drugs* 12, p. 321 (cit. on pp. 270–271).

[D. M. Penetar et al., 2006] D. M. Penetar et al. (2006). "Pharmacokinetic profile of the isoflavone puerarin after acute and repeated administration of a novel kudzu extract to human volunteers". *Journal of Alternative and Complementary Medicine* 12.6, pp. 543–548 (cit. on pp. 121–122, 124–125, 306, 313).

[Penso, 1980] G. Penso (1980). *Inventory of Medicinal Plants Used in the Different Countries*. World Health Organization (cit. on p. 306).

[Pepeljnjak, 2000] (2000). *Ethnopharmacology 2000: challenges for the new millennium. Antimycotic activities of Pimpinella anisum L. fruit and essential oil*. Zurich, Switzerland, p. 75. P2A (cit. on p. 127).

[Pepping, 1999] J. Pepping (1999). "Black cohosh: Cimicifuga racemosa". *American Journal of Health-System Pharmacy* 56.14, pp. 1400–1402 (cit. on pp. 162, 182, 189).

[Pereira et al., 2005] P. Pereira et al. (2005). "Neurobehavioral and genotoxic aspects of rosmarinic acid". *Pharmacological Research* 52.3, pp. 199–203 (cit. on pp. 407, 413).

[N. S. Perry et al., 2003] N. S. Perry et al. (2003). "Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial". *Pharmacology Biochemistry and Behavior* 75.3, pp. 651–659 (cit. on pp. 407, 410).

[R. Perry, K. Hunt, and Ernst, 2011] R. Perry, K. Hunt, and E. Ernst (2011). "Nutritional supplements and other complementary medicines for infantile colic: a systematic review". *Pediatrics* 127.4, pp. 720–733 (cit. on p. 280).

[V. Petkov, 1978] V. Petkov (1978). "Effect of ginseng on the brain biogenic monoamines and 3', 5'-AMP system. Experiments on rats". *Arzneimittel-Forschung* 28, pp. 338–339 (cit. on p. 100).

[V. D. Petkov, 1993] V. D. Petkov (1993). "Memory effects of standardized extracts of Panax ginseng (G115), Ginkgo biloba (GK501) and their combination Gincosan (PHL00701)". *Planta Medica* 59, pp. 106–114 (cit. on p. 101).

[Petri et al., 1995] G. Petri et al. (1995). "Gas chromatographic analysis of cannabinoids on tandem columns [in Hungarian]". *Acta Pharmaceutica Hungarica* 65.3, pp. 63–67 (cit. on p. 339).

[D. Q. Pham and A. Q. Pham, 2007] D. Q. Pham and A. Q. Pham (2007). "Interaction potential between cranberry juice and warfarin". *American Journal of Health-System Pharmacy* 64.5, pp. 490–494 (cit. on pp. 238–239).

[Phan et al., 2008] K. L. Phan et al. (2008). "Cannabinoid modulation of amygdala reactivity to social signals of threat in humans". *Journal of Neuroscience* 28.10, pp. 2313–2319 (cit. on p. 344).

[Pharmacy, 1994] Pharmacy (1994). "Kudzu extract shows potential for moderating alcohol abuse". *American Journal of Hospital Pharmacy* 51.6, p. 750 (cit. on p. 306).

[Phillipson and L. A. Anderson, 1984] J. D. Phillipson and L. A. Anderson (1984). "Ginseng-quality, safety and efficacy?" *Pharmaceutical Journal* 232, pp. 161–165 (cit. on p. 99).

[Phylactos, Harbige, and Crawford, 1994] A. C. Phylactos, L. S. Harbige, and M. A. Crawford (1994). "Essential fatty acids alter the activity of manganese-superoxide dismutase in rat heart". *Lipids* 29, pp. 111–115 (cit. on p. 194).

[Pi, 1955] X. P. Pi (1955). "Effects of Angelica sinensis on uterus". *National Medical Journal of China* 40, p. 967 (cit. on p. 270).

[P. D. Picon, R. V. Picon, and A. F. Costa, 2010] P. D. Picon, R. V. Picon, and A. F. Costa (2010). "Randomized clinical trial of a phytotherapic compound containing Pimpinella anisum, Foeniculum vulgare, Sambucus nigra, and Cassia augustifolia for chronic constipation". *BMC Complementary and Alternative Medicine* 10, p. 17 (cit. on p. 280).

[Pieralisi, Ripari, and Vecchiet, 1991] G. Pieralisi, P. Ripari, and L. Vecchiet (1991). "Effects of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements on physical performance during exercise". *Clinical therapeutics* 13, pp. 373–382 (cit. on pp. 103, 105).

[Pierard, Coche, and Lanthier, 2009] S. Pierard, J. C. Coche, and P. Lanthier (2009). "Severe hepatitis associated with the use of black cohosh: a report of two cases and an advice for caution". *European Journal of Gastroenterology & Hepatology* 21.8, pp. 941–945 (cit. on p. 190).

[Piscitelli et al., 2002] S. C. Piscitelli et al. (2002). "Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers". *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 22.5, pp. 551–556 (cit. on p. 374).

[Pockaj, Gallagher, and Loprinzi, 2006] B. A. Pockaj, J. G. Gallagher, C. L. Loprinzi, et al. (2006). "Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1". *Journal of Clinical Oncology* 24.18, pp. 2836–2841 (cit. on p. 172).

[Poeckel, Greiner, and Verhoff, 2008] D. Poeckel, C. Greiner, and M. Verhoff (2008). "Carnosic acid and carnosol potently inhibit human 5-lipoxygenase and suppress pro-inflammatory responses of stimulated human polymorphonuclear leukocytes". *Biochemical Pharmacology* 76.1, pp. 91–97 (cit. on pp. 407–408, 413).

[Polk, 1982] L. Polk (1982). "Alfalfa pill treatment of allergy may be hazardous". *Journal of the American Medical Association* 247, p. 1493 (cit. on p. 74).

[Polunin, 1997] M. Polunin (1997). *Healing Foods*. New York, NY: DK Publishing, p. 70 (cit. on p. 431).

[Porcella et al., 2001] A. Porcella et al. (2001). "The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies". *European Journal of Neuroscience* 13.2, pp. 409–412 (cit. on pp. 341, 344).

[Post-White, Ladas, and Kelly, 2007] J. Post-White, E. J. Ladas, and K. M. Kelly (2007). "Advances in the use of milk thistle ( Silybum marianum )". *Integrative Cancer Therapies* 6.2, pp. 104–109 (cit. on pp. 359, 372).

[Pourgholami, 1999] M. H. Pourgholami (1999). "The fruit essential oil of Pimpinella anisum exerts anticonvulsant effects in mice". *Journal of Ethnopharmacology* 66, pp. 211–223 (cit. on p. 128).

[S. L. Powell, Gödecke, and Nikolic, 2008] S. L. Powell, T. Gödecke, D. Nikolic, et al. (2008). "In vitro serotonergic activity of black cohosh and identification of N(omega)-methylserotonin as a potential active constituent". *Journal of Agricultural and Food Chemistry* 56.24, pp. 11718–11726 (cit. on p. 170).

[Pozzatti et al., 2008] P. Pozzatti et al. (2008). "In vitro activity of essential oils extracted from plants used as spices against fluconazole-resistant and fluconazole-susceptible Candida spp". *Canadian Journal of Microbiology* 54.11, pp. 950–956 (cit. on p. 408).

[Pradhan and Girish, 2006] S. C. Pradhan and C. Girish (2006). "Hepatoprotective herbal drug, silymarin from experimental pharmacology to clinical medicine". *Indian Journal of Medical Research* 124.5, pp. 491–504 (cit. on pp. 359–360, 362).

[Predy, V. Goel, R. E. Lovlin, et al., 2006] G. N. Predy, V. Goel, R. E. Lovlin, et al. (2006). "Immune modulating effects of daily supplementation of Cold-fX (a proprietary extract of North American ginseng) in healthy adults". *Journal of Clinical Biochemistry and Nutrition* 39.3, pp. 162–167 (cit. on pp. 86, 143).

[Predy, V. Goel, R. Lovlin, Donner, et al., 2005] G. N. Predy, V. Goel, R. Lovlin, A. Donner, et al. (2005). "Efficacy of an extract of North American ginseng containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: a randomized controlled trial". *Canadian Medical Association Journal* 173.9, pp. 1043–1048 (cit. on pp. 86, 142).

[Predy, V. Goel, R. Lovlin, Shan, et al., 2005] G. N. Predy, V. Goel, R. Lovlin, J. Shan, et al. (2005). "Efficacy of Cold-fX , a natural health product in the prevention of recurrent upper respiratory infections in a susceptible population: a randomized, double-blind, placebo controlled trial". *The Journal of Complementary and Integrative Medicine* 2.1, p. 28 (cit. on pp. 86, 143).

[Press, 2015] Oxford University Press, ed. (2015). *Health*. URL: http://www.oxforddictionaries.com/definition/english/health (cit. on p. 27).

[Prete, 1985] P. Prete (1985). "The mechanism of action of L-canavanine in inducing autoimmune phenomena". *Arthritis & Rheumatism* 20, pp. 1198–1200 (cit. on p. 74).

[Priest and I. Campbell, 2003] F. G. Priest and I. Campbell (2003). *Brewing microbiology*. Springer, p. 5. ISBN: 978-0-306-47288-6 (cit. on p. 298).

[Program, 2010] National Toxicology Program (2010). *NTP brief on soy infant formula*. National Institutes of Health, U.S. Department of Health and Human Services. National Institute of Environmental Health Sciences. URL: http://ntp.niehs.nih.gov/ntp/ohat/genistein-soy/SoyFormulaUpdt/FinalNTPBriefSoyFormula_9_20_2010.pdf (cit. on pp. 442, 444).

[puerariamirificashop.com, 2014] puerariamirificashop.com (2014). *What is Pueraria Mirifica*. puerariamirificashop.com. URL: http://www.puerariamirificashop.com/what-is-pueraria-mirifica/ (cit. on p. 387).

[Punnonen and Lukola, 1980] R. Punnonen and A. Lukola (1980). "Oestrogen-like effect of ginseng". *British Medical Journal* 281, p. 1110 (cit. on p. 106).

[Puupponen-Pimia et al., 2005] R. Puupponen-Pimia et al. (2005). "The action of berry phenolics against human intestinal pathogens". *BioFactors* 23.4, pp. 243–251 (cit. on p. 233).

[Qi, C. Z. Wang, and C. S. Yuan, 2010] L. W. Qi, C. Z. Wang, and C. S. Yuan (2010). "American ginseng: potential structure-function relationship in cancer chemoprevention". *Biochemical Pharmacology* 80.7, pp. 947–954 (cit. on pp. 81, 139).

[Qian, 1987] B. C. Qian (1987). "Effects of ginseng polysaccharides on tumor and immunological function in tumor-bearing mice". *Yao hsueh hsueh pao* 8, pp. 277–280 (cit. on p. 100).

[Qicheng, 1980] F. Qicheng (1980). "Some current study and research approaches relating to the use of plants in the traditional Chinese medicine". *Journal of Ethnopharmacology* 2.1, pp. 57–63 (cit. on pp. 308, 313).

[Quinkler and Stewart, 2003] M. Quinkler and P. M. Stewart (2003). "Hypertension and the cortisol-cortisone shuttle". *Journal of Clinical Endocrinology & Metabolism* 88.6, pp. 2384–2392 (cit. on pp. 325, 334).

[Raal, Orav, and Arak, 2007] A. Raal, A. Orav, and E. Arak (2007). "Composition of the essential oil of Salvia officinalis L. from various European countries". *Natural Product Research* 21.5, pp. 406–411 (cit. on pp. 405–406).

[Rachita., 2014] Rachita. (2014). *Difference Between side effects and adverse effects*. URL: http://www.differencebetween.net/science/health/disease-health/difference-between-side-effects-and-adverse-effects/ (cit. on pp. 453–454).

[Racho et al., 2008] D. Racho et al. (2008). "Effects of black cohosh extract on body weight gain, intra-abdominal fat accumulation, plasma lipids and glucose tolerance in ovariectomized Sprague-Dawley rats". *Maturitas* 60.3-4, pp. 209–215 (cit. on p. 175).

[Radad et al., 2006] K. Radad et al. (2006). "Use of ginseng in medicine with emphasis on neurodegenerative disorders". *Journal of Pharmacological Sciences* 100.3, pp. 175–186 (cit. on pp. 83–84, 140–141).

[Raederstorff and Moser, 1992] D. Raederstorff and U. Moser (1992). "Borage or primrose oil added to standardized diets are equivalent sources for gamma-linolenic acid in rats". *Lipids* 27, pp. 1018–1023 (cit. on p. 194).

[Raggi, Bugamelli, and Nobile, 1994] M. A. Raggi, F. Bugamelli, and L. Nobile (1994). "HPLC determination of glycyrrhizin and glycyrrhetic acid in biological fluids, after licorice extract administration to humans and rats". *Bollettino Chimico Farmaceutico* 133.11, pp. 704–708 (cit. on p. 317).

[Rainone, 2005] F. Rainone (2005). "Milk thistle". *American Family Physician* 72.7, pp. 1281–1288 (cit. on pp. 362, 372, 374).

[Ramasamy and R. Agarwal, 2008] K. Ramasamy and R. Agarwal (2008). "Multitargeted therapy of cancer by silymarin". *Cancer Letters* 269.2, pp. 352–362 (cit. on pp. 360, 378).

[Rambaldi, B. P. Jacobs, and Gluud, 2007] A. Rambaldi, B. P. Jacobs, and C. Gluud (2007). "Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases". *Cochrane Database of Systematic Reviews* 4, p. CD003620 (cit. on pp. 361–362, 372).

[Rambaldi, B. P. Jacobs, Iaquinto, et al., 2005] A. Rambaldi, B. P. Jacobs, G. Iaquinto, et al. (2005). "Milk thistle for alcoholic and/or hepatitis B or C liver diseasesa systematic cochrane hepato-biliary group review with meta-analyses of randomized clinical trials". *American Journal of Gastroenterology* 100.11, pp. 2583–2591 (cit. on p. 361).

[Ramellini and Meldolesi, 1976] G. Ramellini and J. Meldolesi (1976). "Liver protection by silymarin: in vitro effect on dissociated rat hepatocytes". *Arzneimittelforschung* 26, pp. 69–73 (cit. on p. 366).

[Ranganathan, Braley, and Pittman, 2009] M. Ranganathan, G. Braley, and B. Pittman (2009). "The effects of cannabinoids on serum cortisol and prolactin in humans". *Psychopharmacology* 203.4, pp. 737–744 (cit. on pp. 346–347).

[Ravenna, Di Silverio, and M. A. Russo, 1996] L. Ravenna, F. Di Silverio, and M. A. Russo (1996). "Effects of the lipidosterolic extract of Serenoa repens ( Permixon ) on human prostatic cell lines". *Prostate* 29.4, pp. 219–230 (cit. on p. 419).

[Raz, Chazan, and Dan, 2004] R. Raz, B. Chazan, and M. Dan (2004). "Cranberry juice and urinary tract infection". *Clinical Infectious Diseases* 38.10, pp. 1413–1419 (cit. on pp. 230–231).

[Reame et al., 2008] N. E. Reame et al. (2008). "Black cohosh has central opioid activity in postmenopausal women: evidence from naloxone blockade and positron emission tomography neuroimaging". *Menopause* 15.5, pp. 832–840 (cit. on p. 172).

[Reay, D. O. Kennedy, and A. B. Scholey, 2006a] J. L. Reay, D. O. Kennedy, and A. B. Scholey (2006a). "Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained mentally demanding tasks". *Journal of Psychopharmacology* 20.6, pp. 771–781 (cit. on pp. 83, 141).

[Reay, D. O. Kennedy, and A. B. Scholey, 2006b] — (2006b). "The glycaemic effects of single doses of Panax ginseng in young healthy volunteers". *British Journal of Nutrition* 96.4, pp. 639–642 (cit. on pp. 84, 141).

[Reay, A. B. Scholey, and D. O. Kennedy, 2010] J. L. Reay, A. B. Scholey, and D. O. Kennedy (2010). "Panax ginseng (G115) improves aspects of working memory performance and subjective ratings of calmness in healthy young adults". *Human Psychopharmacology* 25.6, pp. 462–471 (cit. on pp. 83–84, 141).

[Reay, A. B. Scholey, Milne, et al., 2009] J. L. Reay, A. B. Scholey, A. Milne, et al. (2009). "Panax ginseng has no effect on indices of glucose regulation following acute or chronic ingestion in healthy volunteers". *British Journal of Nutrition* 101.11, pp. 1673–1678 (cit. on pp. 84, 141).

[Record et al., 1997] I. R. Record et al. (1997). "Genistein inhibits growth of B16 melanoma cells in vivo and in vitro and promotes differentiation in vitro". *International Journal of Cancer* 72.5, pp. 860–864 (cit. on p. 436).

[Reece, 2009] A. S. Reece (2009). "Chronic toxicology of cannabis". *Clinical toxicology* 47.6, pp. 517–524 (cit. on pp. 347, 352).

[Reed et al., 2008] S. D. Reed et al. (2008). "Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study". *Menopause* 15.1, pp. 51–58 (cit. on p. 172).

[Register, Jayo, and Anthony, 2003] T. C. Register, M. J. Jayo, and M. S. Anthony (2003). "Soy phytoestrogens do not prevent bone loss in postmenopausal monkeys". *Journal of Clinical Endocrinology & Metabolism* 88.9, pp. 4362–4370 (cit. on p. 439).

[Reinhold, 1990] E. Reinhold (1990). "Der Einsatz von Ginseng in der Gynäkologie". *Natur- und Ganzheits Medizin* 4, pp. 131–134 (cit. on p. 106).

[Reinwald and Weaver, 2006] S. Reinwald and C. M. Weaver (2006). "Soy isoflavones and bone health: a double-edged sword?" *Journal of Natural Products* 69.3, pp. 450–459 (cit. on p. 58).

[Reiter and Brandt, 1985a] M. Reiter and W. Brandt (1985a). "Relaxant effects on tracheal and ileal smooth muscles of the guinea pig". *Arzneimittelforschung* 35, pp. 408–414 (cit. on p. 128).

[Reiter and Brandt, 1985b] — (1985b). "Relaxant effects on tracheal and ileal smooth muscles of the guinea pig". *Arzneimittelforschung* 35.1A, pp. 408–414 (cit. on p. 281).

[Resource, 2015a] Herbal Resource (2015a). *Anise*. URL: http://www.herbal-supplement-resource.com/anise-herb.html (cit. on p. 124).

[Resource, 2015b] — (2015b). *Basil*. URL: http://www.herbal-supplement-resource.com/sweet-basil-herb.html (cit. on pp. 12, 156–157, 159–160).

[Resource, 2015c] — (2015c). *Black cohosh root*. URL: http://www.herbal-supplement-resource.com/black-cohosh-root.html (cit. on pp. 12, 163, 167–169, 179).

[Resource, 2015d] — (2015d). *Borage*. Ed. by T. Sturlson. URL: http://www.herbal-supplement-resource.com/borage-herb.html (cit. on pp. 192–193, 199, 202, 205).

[Resource, 2015e] — (2015e). *Caraway*. Ed. by T. Sturlson. URL: http://www.herbal-supplement-resource.com/caraway-seeds.html (cit. on pp. 13, 207–211).

[Resource, 2015f] — (2015f). *Chaste Tree*. Ed. by T. Sturlson. URL: http://www.herbal-supplement-resource.com/chaste-tree-berry.html (cit. on pp. 213, 217, 222–224).

[Resource, 2015g] — (2015g). *Cranberry*. Ed. by T. Sturlson. URL: http://www.herbal-supplement-resource.com/cranberry-herb.html (cit. on pp. 228–229).

[Resource, 2015h] — (2015h). *Damiana*. Ed. by T. Sturlson. URL: http://www.herbal-supplement-resource.com/damiana-herb.html (cit. on pp. 16, 244, 246–248).

[Resource, 2015i] — (2015i). *Dill*. URL: http://www.herbal-supplement-resource.com/dill-herb.html (cit. on pp. 249–250, 252–253).

[Resource, 2015j] — (2015j). *Dong Quai*. URL: http://www.herbal-supplement-resource.com/dong-quai.html (cit. on pp. 256, 258, 261–262, 264, 268).

[Resource, 2015k] — (2015k). *Sage*. The Herbal Resource. URL: http://www.herbal-supplement-resource.com/sage-salvia-officinalis.html (cit. on pp. 404, 407, 412).

[Reynolds et al., 2006] K. Reynolds et al. (2006). "A meta-analysis of the effect of soy protein supplementation on serum lipids". *American Journal of Cardiology* 98.5, pp. 633–640 (cit. on p. 437).

[Rezvani et al., 2003] A. H. Rezvani et al. (2003). "Plant derivatives in the treatment of alcohol dependency". *Pharmacology Biochemistry and Behavior* 75.3, pp. 593–606 (cit. on p. 307).

[Rhodes, Primka, and C. Berman, 1993] L. Rhodes, R. L. Primka, and C. Berman (1993). "Comparison of finasteride ( Proscar ), a 5-alpha reductase inhibitor, and various commercial plant extracts in in-vitro and in-vivo 5-alpha-reductase inhibition". *Prostate* 22.1, pp. 43–51 (cit. on p. 418).

[Ribes, Sauvaire, and Baccou, 1984] G. Ribes, Y. Sauvaire, and J. C. Baccou (1984). "Effects of fenugreek seeds on endocrine pancreatic secretions in dogs". *Annals of Nutrition and Metabolism* 28, pp. 37–43 (cit. on p. 290).

[Ribes, Sauvaire, Da Costa, et al., 1986] G. Ribes, Y. Sauvaire, C. Da Costa, et al. (1986). "Antidiabetic effects of subfractions from fenugreek seeds in diabetic dogs". *Proceedings of the Society for Experimental Biology and Medicine* 182, pp. 159–166 (cit. on p. 289).

[Ricci et al., 2010] E. Ricci et al. (2010). "Effects of soy isoflavones and genistein on glucose metabolism in perimenopausal and post-menopausal non-Asian women: a meta-analysis of randomized controlled trials". *Menopause* 17.5, pp. 1080–1086 (cit. on p. 437).

[J. L. Roberts and Hayashi, 1983] J. L. Roberts and J. A. Hayashi (1983). "Exacerbation of SLE associated with alfalfa ingestion". *New England Journal of Medicine* 308, p. 1361 (cit. on p. 74).

[Rodriguez et al., 2001] R. J. Rodriguez et al. (2001). "Influence of prenylated and non-prenylated flavonoids on liver microsomal lipid peroxidation and oxidative injury in rat hepatocytes". *Food and Chemical Toxicology* 39, pp. 437–445 (cit. on p. 303).

[Roemheld-Hamm, 2005] B. Roemheld-Hamm (2005). "Chaste-berry". *American Family Physician* 72.5, pp. 821–824 (cit. on pp. 214–216, 221–222, 224).

[Rogers, 2015] J. Rogers (2015). *How Sage Benefits Us: Its More Than Just for Tea*. WTBF Media. URL: http://www.naturalalternativeremedy.com/how-sage-benefits-us-its-more-than-just-for-tea/ (cit. on pp. 408–411, 413).

[Rompelberg, Verhagen, and Van Bladeren, 1993] C. J. Rompelberg, H. Verhagen, and P. J. Van Bladeren (1993). "Effects of the naturally occurring alkenylbenzenes eugenol and trans-anethole on drug-metabolizing enzymes in the rat liver". *Food and Chemical Toxicology* 31, pp. 637–645 (cit. on p. 132).

[Rong, Boterberg, and Maubach, 2001] H. Rong, T. Boterberg, and J. Maubach (2001). "8-Prenylnaringenin, the phytoestrogen in hops and beer, upregulates the function of the E-cadherin/catenin complex in human mammary carcinoma cells". *European Journal of Cell Biology* 80, pp. 580–585 (cit. on p. 303).

[Rong, De Keukeleire, et al., 1998] H. Rong, D. De Keukeleire, et al. (1998). "Narrow-bore HPLC analysis of isoflavonoid aglycones and their O- and C-glycosides from Pueraria lobata". *Biomedical Chromatography* 12.3, pp. 170–171 (cit. on p. 306).

[Rosado, 2003] M. F. Rosado (2003). "Thrombosis of a prosthetic aortic valve disclosing a hazardous interaction between warfarin and a commercial ginseng product". *Cardiology* 99.2, p. 111 (cit. on pp. 89, 146).

[Roser et al., 2008] P. Roser et al. (2008). "Effects of acute oral Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers". *European Neuropsychopharmacology* 18.8, pp. 569–577 (cit. on p. 346).

[Rotblatt and Ziment, 2002] M. Rotblatt and I. Ziment (2002). *Evidence-Based Herbal Medicine*. Philadelphia, PA: Hanley & Belfus (cit. on p. 202).

[Roufs et al., 2007] J. B. Roufs et al. (2007). "Methods and compositions comprising plant extracts for modulating hair growth or regrowth". US patent application 2007-036742 (cit. on pp. 381, 387).

[Rumyantseva, 1991] Z. N. Rumyantseva (1991). "The pharmacodynamics of hepatoprotectants derived from blessed milk thistle ( Silybum marianum )". *Vrach Delo* 5, pp. 15–19 (cit. on p. 359).

[Russell et al., 2002] L. Russell et al. (2002). "Phytoestrogens: a viable option?" *The American Journal of the Medical Sciences* 324.4, pp. 185–188 (cit. on p. 223).

[E. B. Russo, G. W. Guy, and Robson, 2007] E. B. Russo, G. W. Guy, and P. J. Robson (2007). "Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex , a cannabis-based medicine". *Chemistry & Biodiversity* 4.8, pp. 1729–1743 (cit. on p. 344).

[Ryu and Y. Y. Chien, 1995] S. J. Ryu and Y. Y. Chien (1995). "Ginseng-associated cerebral arteritis". *Neurology* 45, pp. 829–830 (cit. on p. 106).

[Saba, Galeone, and Salvadorini, 1976a] P. Saba, F. Galeone, and F. Salvadorini (1976a). "Therapeutic effects of Silymarin in chronic liver diseases due to psychodrugs". *Gazzetta Medica Italiana Archivio per le Scienze Mediche* 135, pp. 236–251 (cit. on pp. 354, 356).

[Saba, Galeone, and Salvadorini, 1976b] — (1976b). "Therapeutic effects of Silymarin in chronic liver diseases due to psychodrugs". Italian. *Gazzetta Medica Italiana Archivio per le Scienze Mediche* 135, pp. 236–251 (cit. on pp. 364, 367, 372).

[Saba and Mignani, 1979] P. Saba and E. Mignani (1979). "Efficacy of silymarin treatment of acute virus hepatitis". *Medicina generale ed Epatologia* 25, pp. 277–281 (cit. on p. 355).

[Saba, Mignani, and Pagliai, 1979] P. Saba, E. Mignani, and Pagliai (1979). "Efficacy of silymarin treatment of acute virus hepatitis". *Epatologia* 25, pp. 277–281 (cit. on p. 365).

[Sacks et al., 2006] F. M. Sacks et al. (2006). "Soy protein, isoflavones, and cardiovascular health: an American Heart Association science advisory for professionals from the nutrition committee". With a comment. by American Heart Association Nutrition Committee. *Circulation* 113.7, pp. 1034–1044 (cit. on pp. 431, 436–437).

[Saenphet et al., 2005] K. Saenphet et al. (2005). "Mutagenicity of Pueraria mirifica Airy Shaw & Suvatabandhu and antimutagenicity of Thunbergia laurifolia Linn." *Southeast Asian Journal of Tropical Medicine and Public Health* 36.supplement 4, pp. 238–241 (cit. on p. 387).

[Sagar, 2007] S. M. Sagar (2007). "Future directions for research on Silybum marianum for cancer patients". *Integrative Cancer Therapies* 6.2, pp. 166–173 (cit. on p. 360).

[Saiad and Borysov, 1978] S. A. Saiad and M. I. Borysov (1978). "Flavonoids of the flowers of Pueraria lobata [in Ukranian]". *Farm Zh* 6, pp. 83–84 (cit. on pp. 183, 306).

[Saiad and Borysov, 1979] — (1979). "Flavonoids of the rhizomes of Pueraria [in Ukranian]". *Farm Zh* 2, pp. 76–77 (cit. on pp. 181, 306).

[Saiad, Borysov, and Koval'ov, 1979] S. A. Saiad, M. I. Borysov, and V. M. Koval'ov (1979). "Isolation, identification and quantitative determination of robinin in the leaves of Pueraria lobata [in Ukranian]". *Khimiko Farmatsevticheskii Zhurnal* 4, pp. 52–55 (cit. on p. 306).

[Saito, 1974] H. Saito (1974). *Advances in Chinese medicinal materials research. Neuropharmacological studies on Panax ginseng*. Ed. by HM Chang. Singapore: World Scientific Publishing, pp. 509–518 (cit. on p. 100).

[Sakurai, J. H. Wu, and Sashida, 2004] N. Sakurai, J. H. Wu, Y. Sashida, et al. (2004). "Anti-AIDS Agents. Part 57: Actein, an anti-HIV principle from the rhizome of Cimicifuga racemosa (black cohosh), and the anti-HIV activity of related saponins". *Bioorganic & Medicinal Chemistry Letters* 14.5, pp. 1329–1332 (cit. on p. 175).

[Saller, Brignoli, et al., 2008] R. Saller, R. Brignoli, et al. (2008). "An updated systematic review with meta-analysis for the clinical evidence of silymarin". *Forschende Komplementärmedizin* 15.1, pp. 9–20 (cit. on pp. 361–362).

[Saller, Meier, and Brignoli, 2001] R. Saller, R. Meier, and R. Brignoli (2001). "The use of silymarin in the treatment of liver diseases". *Drugs* 61.14, pp. 2035–2063 (cit. on p. 361).

[Sanchanta et al., 2005] P. Sanchanta et al. (2005). *WOCMAP Congress on Medicinal and Aromatic Plants - Quality, Efficacy, Safety, Processing and Trade in Medicinal and Aromatic Plants*. Vol. 5: *Toxicological study of aqueous and ethanolic extracts from*

*Pueraria mirifica Airy Shaw and Suvatabandhu on male rats*. Ed. by E. Brovelli, S. Chansakaow, and D. Farias. Leuven, Belgium: International Society for Horticultural Science (cit. on p. 387).

[Sandeep, Andrew, and Homer, 2005] T. C. Sandeep, R. Andrew, and N. Z. Homer (2005). "Increased in vivo regeneration of cortisol in adipose tissue in human obesity and effects of the 11beta-hydroxysteroid dehydrogenase type 1 inhibitor carbenoxolone". *Diabetes* 54.3, pp. 872–879 (cit. on p. 320).

[Sangster, Caldwell, and R. L. Smith, 1984] S. A. Sangster, J. Caldwell, and R. L. Smith (1984). "Metabolism of anethole. II. Influence of dose size on the route of metabolism of trans-anethole in the rat and mouse". *Food and Chemical Toxicology* 22, pp. 707–713 (cit. on p. 127).

[Sangster, Caldwell, and Hutt, 1987] S. A. Sangster, J. Caldwell, A. J. Hutt, et al. (1987). "The metabolic dispostion of [methoxy 14 C]-labelled trans-anethole, estragole, and p-propylanisole in human volunteers". *Xenobiotica* 17, pp. 1223–1232 (cit. on p. 127).

[Santaella and Fraunfelder, 2007] R. M. Santaella and F. W. Fraunfelder (2007). "Ocular adverse effects associated with systemic medications: recognition and management". *Drugs* 67.1, pp. 75–93 (cit. on p. 325).

[A. S. Santo, A. M. Santo, and Browne, 2010] A. S. Santo, A. M. Santo, and R. W. Browne (2010). "Postprandial lipemia detects the effect of soy protein on cardiovascular disease risk compared with the fasting lipid profile". *Lipids* 45.12, pp. 1127–1138 (cit. on p. 437).

[Saraswat et al., 2008] M. Saraswat et al. (2008). "Dietary sources of aldose reductase inhibitors: prospects for alleviating diabetic complications". *Asia Pacific Journal of Clinical Nutrition* 17.4, pp. 558–565 (cit. on p. 281).

[Sarikurkcu et al., 2009] C. Sarikurkcu et al. (2009). "Studies on the antioxidant activity of essential oil and different solvent extracts of Vitex agnus castus L. fruits from Turkey". *Food and Chemical Toxicology* 47.10, pp. 2479–2483 (cit. on p. 213).

[Sarkar and Y. Li, 2003] F. H. Sarkar and Y. Li (2003). "Soy isoflavones and cancer prevention". *Cancer Investigation* 21.5, pp. 744–757 (cit. on p. 435).

[Sathyapalan, Manuchehri, and Thatcher, 2011] T. Sathyapalan, A. M. Manuchehri, and N. J. Thatcher (2011). "The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study". *Journal of Clinical Endocrinology & Metabolism* 96.5, pp. 1442–1449 (cit. on p. 442).

[Sato et al., 1992] T. Sato et al. (1992). "Mechanism of antioxidant action of pueraria glycoside (PG)-1 (an isoflavonoid) and magiferin (a xanthonoid)". *Chemical and Pharmaceutical Bulletin* 40.3, pp. 721–724 (cit. on p. 308).

[Sauvaire and Baccou, 1978] Y. Sauvaire and J. C. Baccou (1978). "Extraction of diosgenin, (25R)-spirost-5-ene-3beta-ol; problems of the hydrolysis of the saponins". *Lloydia and the Journal of Natural Products* 41, pp. 247–256 (cit. on p. 287).

[Sauvaire, Ribes, et al., 1991] Y. Sauvaire, G. Ribes, et al. (1991). "Implication of steroid saponins and sapogenins in the hypocholesterolemic effect of fenugreek". *Lipids* 26, pp. 191–197 (cit. on p. 288).

[Savelev et al., 2003] S. Savelev et al. (2003). "Synergistic and antagonistic interactions of anticholinesterase terpenoids in Salvia lavandulaefolia essential oil". *Pharmacology Biochemistry and Behavior* 75.3, pp. 661–668 (cit. on p. 406).

[Savio, Harrasser, and Basso, 1998] D. Savio, P. C. Harrasser, and G. Basso (1998). "Softgel capsule technology as an enhancer device for the absorption of natural principles in humans. A bioavailability cross-over randomised study on silybin". *Arzneimittelforschung* 48, pp. 1104–1106 (cit. on p. 365).

[Sawatsri, Yamkunthong, and Sidell, 2004] S. Sawatsri, W. Yamkunthong, and N. Sidell (2004). "P3-206 Pseuraria mirifica initiative promotes the cellular mechanism of neuronal survival in neuron human nueuroblastoma cells". *Neurobiology of Aging* 25.2, S414 (cit. on p. 386).

[Sbrana, 2014] C. Sbrana (2014). "Beneficial mycorrhizal symbionts affecting the production of health-promoting phytochemicals". *Electrophoresis* 35.11, pp. 1535–46 (cit. on p. 54).

[Scaglione, 1990] F. Scaglione (1990). "Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer". *Drugs, experimental and clinical research* 26, pp. 537–542 (cit. on pp. 103–104).

[Scambia et al., 1996] G. Scambia et al. (1996). "Antiproliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin". *European Journal of Cancer* 32A, pp. 877–882 (cit. on p. 366).

[Schandalik, Gatti, and Perucca, 1992] R. Schandalik, G. Gatti, and E. Perucca (1992). "Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients". *Arzneimittelforschung* 42.7, pp. 964–968 (cit. on p. 359).

[Schandalik and Perucca, 1994] R. Schandalik and E. Perucca (1994). "Pharmacokinetics of silybin following oral administration of silipide in patients with extrahepatic biliary obstruction". *Drugs under experimental and clinical research* 20.1, pp. 37–42 (cit. on p. 359).

[Schapera, 2003] C. H. Schapera (2003). "Potential causes of secondary hypertension". *American Family Physician* 68.1, p. 42 (cit. on p. 334).

[Schauenberg and Paris, 1990] P. Schauenberg and F. Paris (1990). *Guide to Medicinal Plants*. New Canaan, CT: Keats Publishing (cit. on p. 357).

[Schellenberg, 2001] R. Schellenberg (2001). "Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study". *British Medical Journal* 322.7279, pp. 134–137 (cit. on p. 215).

[Schelz, Molnar, and Hohmann, 2006] Z. Schelz, J. Molnar, and J. Hohmann (2006). "Antimicrobial and antiplasmid activities of essential oils". *Fitoterapia* 77.4, pp. 279–285 (cit. on p. 281).

[Schmid, Woehs, et al., 2009] D. Schmid, F. Woehs, et al. (2009). "Aqueous extracts of Cimicifuga racemosa and phenolcarboxylic constituents inhibit production of proinflammatory cytokines in LPS-stimulated human whole blood". *Canadian Journal of Physiology and Pharmacology* 87.11, pp. 963–972 (cit. on p. 175).

[Schmid, Gruber, and Woehs, 2009] D. Schmid, M. Gruber, F. Woehs, et al. (2009). "Inhibition of inducible nitric oxide synthesis by Cimicifuga racemosa ( Actaea racemosa , black cohosh) extracts in LPS-stimulated RAW 264.7 macrophages". *Journal of Pharmacy and Pharmacology* 61.8, pp. 1089–1096 (cit. on p. 175).

[C. F. Schmidt, 1924] C. F. Schmidt (1924). "Experiments with Chinese drugs. 1. Tang-kuei". *Chinese Medical Journal* 38, p. 362 (cit. on p. 270).

[Schmidtlein and K. Herrmann, 1975] H. Schmidtlein and K. Herrmann (1975). "On the phenolic acids of vegetables. IV. Hydroxycinnamic acids and hydroxybenzoic acids of vegetables and potatoes [in German]". *Zeitschrift für Le0bensmittel-Untersuchung und -Forschung* 159.5, pp. 255–263 (cit. on p. 277).

[H. P. Schneider and Bohnet, 1981] H. P. Schneider and H. G. Bohnet (1981). "Hyperprolactinemic ovarian insufficiency [In German]". *Der Gynäkologe* 14.2, pp. 104–118 (cit. on p. 219).

[Schnitzler et al., 2008] P. Schnitzler et al. (2008). "Comparative in vitro study on the anti-herpetic effect of phytochemically characterized aqueous and ethanolic extracts of Salvia officinalis grown at two different locations". *Phytomedicine* 15.1-2, pp. 62–70 (cit. on p. 408).

[A. B. Scholey, Tildesley, and Ballard, 2008] A. B. Scholey, N. T. Tildesley, and C. G. Ballard (2008). "An extract of Salvia (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers". *Psychopharmacology* 198.1, pp. 127–139 (cit. on pp. 407, 412).

[A. Scholey, Ossoukhova, and L. Owen, 2010] A. Scholey, A. Ossoukhova, and L. Owen (2010). "Effects of American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study". *Psychopharmacology* 212.3, pp. 345–356 (cit. on pp. 83, 141).

[Schonfeld, Weisbrod, and Muller, 1997] J. von Schonfeld, B. Weisbrod, and M. K. Muller (1997). "Silibinin, a plant extract with antioxidant and membrane stabilizing properties, protects exocrine pancreas from cyclosporin A toxicity". *Cellular and Molecular Life Sciences* 53.11-12, pp. 917–920 (cit. on p. 366).

[Schröder, Roobol, and Boevé, 2005] F. H. Schröder, M. J. Roobol, and E. R. Boevé (2005). "Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement". *European Urology* 48.6, pp. 922–930 (cit. on p. 360).

[Schult et al., 2004] T. M. Schult et al. (2004). "Effect of isoflavones on lipids and bone turnover markers in menopausal women". *Maturitas* 48, pp. 209–218 (cit. on pp. 394–395).

[Schulz, Hänsel, and V. E. Tyler, 1998] V. Schulz, R. Hänsel, and V. E. Tyler (1998). *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine*. New York: Springer (cit. on p. 219).

[Schuppan, Strosser, and Burkard, 1998a] D. Schuppan, W. Strosser, and G. Burkard (1998a). "Influence of Legalon(TM) 140 on the metabolism of collagen in patients with chronic liver disease–Review by measurement of PIIINP-values". *Zeitschrift fur Allgemeinmedizin* 74, pp. 577–584 (cit. on p. 355).

[Schuppan, Strosser, and Burkard, 1998b] — (1998b). "Influence of Legalon(TM) 140 on the metabolism of collagen in patients with chronic liver disease–Review by measurement of PIIINP-values". *Zeitschrift fur Allgemeinmedizin* 74, pp. 577–584 (cit. on pp. 364, 367).

[Schwab et al., 2006] U. S. Schwab et al. (2006). "Effects of hempseed and flaxseed oils on the profile of serum lipids, serum total and lipoprotein lipid concentrations and haemostatic factors". *European Journal of Nutrition* 45.8, pp. 470–477 (cit. on p. 344).

[Scientific and Commission, 1985] Technical Scientific and Research Commission, eds. (1985). *African pharmacopoeia*. Vol. 1. Lagos: Organization of African Unity (cit. on p. 126).

[Scott and Elmer, 2002] G. N. Scott and G. W. Elmer (2002). "Update on natural productdrug interactions". *American Journal of Health-System Pharmacy* 59.4, pp. 339–347 (cit. on p. 265).

[Scully, 2007] C. Scully (2007). "Cannabis; adverse effects from an oromucosal spray". *British Dental Journal* 203.6 (E12), pp. 336–337 (cit. on p. 346).

[Seamon, 2006] M. J. Seamon (2006). "The legal status of medical marijuana". *Annals of Pharmacotherapy* 40.12, pp. 2211–2215 (cit. on pp. 338–340).

[Seely et al., 2008] D. Seely et al. (2008). "Safety and efficacy of panax ginseng during pregnancy and lactation". *Canadian Journal of Clinical Pharmacology* 15.1, e87–e94 (cit. on pp. 88–89, 98, 145, 150, 153).

[Sehmisch, Boeckhoff, and Wille, 2009] S. Sehmisch, J. Boeckhoff, and J. Wille (2009). "Vitex agnus castus as prophylaxis for osteopenia after orchidectomy in rats compared with estradiol and testosterone supplementation". *Phytotherapy Research* 23.6, pp. 851–858 (cit. on p. 216).

[Seidlova-Wuttke, Jarry, and Wuttke, 2009] D. Seidlova-Wuttke, H. Jarry, and W. Wuttke (2009). "Effects of estradiol benzoate, raloxifen and an ethanolic extract of Cimicifuga racemosa in nonclassical estrogen regulated organs of ovariectomized rats". *Planta Medica* 75.12, pp. 1279–1285 (cit. on p. 170).

[Sekizawa and Shibamoto, 1982a] J. Sekizawa and T. Shibamoto (1982a). "Genotoxicity of safrole-related chemicals in microbial test systems". *Mutation Research* 101, pp. 127–140 (cit. on p. 131).

[Sekizawa and Shibamoto, 1982b] — (1982b). "Genotoxicity of safrole-related chemicals in microbial test systems". *Mutation Research* 101.2, pp. 127–140 (cit. on p. 285).

[Selvarajah et al., 2010] D. Selvarajah et al. (2010). "Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product ( Sativex ) in painful diabetic neuropathy: depression is a major confounding factor". *Diabetes Care* 33.1, pp. 128–130 (cit. on p. 343).

[Sewell, Mosandl, and Bohles, 1999] A. Sewell, A. Mosandl, and H. Bohles (1999). "False diagnosis of maple syrup urine disease owing to ingestion of herbal tea". *New England Journal of Medicine* 341, p. 769 (cit. on p. 293).

[Sewón and Tyystjärvi, 1993] P. Sewón and E. Tyystjärvi (1993). "Stearidonic and -linolenic acid contents of common borage leaves". *Phytochemistry* 33, pp. 1029–1032 (cit. on p. 193).

[Shader and Greenblatt, 1985] R. I. Shader and D. J. Greenblatt (1985). "Phenelzine and the dream machine-ramblings and reflections". *Journal of Clinical Psychopharmacology* 5, p. 67 (cit. on p. 107).

[Shah et al., 1985] N. Shah et al. (1985). "Essential oil of Feronia limonia : substitute for anise and fennel oils". *Parfum Kosmetic* 66, pp. 182–183 (cit. on p. 121).

[Shahin, Ismail, and Shaaban, 2009] A. Y. Shahin, A. M. Ismail, and O. M. Shaaban (2009). "Supplementation of clomiphene citrate cycles with Cimicifuga racemosa or ethinyl oestradiola randomized trial". *Reproductive BioMedicine Online* 19.4, pp. 501–507 (cit. on p. 173).

[Shams et al., 2010] T. Shams et al. (2010). "Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis". *Alternative Therapies In Health And Medicine* 16.1, pp. 36–44 (cit. on p. 172).

[Sharaf and Goma, 1965] G. Sharaf and N. Goma (1965). "Phytoestrogens and their antagonism to progesterone and testosterone". *ournal of Endocrinology* 31, pp. 289–290 (cit. on p. 129).

[P. Sharma, Wisniewski, and Braga-Basaria, 2009] P. Sharma, A. Wisniewski, and M. Braga-Basaria (2009). "Lack of an effect of high dose isoflavones in men with prostate cancer undergoing androgen deprivation therapy". *Journal of Urology* 182.5, pp. 2265–2272 (cit. on p. 435).

[R. D. Sharma, Raghuram, and Rao, 1990] R. D. Sharma, T. C. Raghuram, and N. S. Rao (1990). "Effect of fenugreek seeds on blood glucose and serum lipids in type diabetes". *European Journal of Clinical Nutrition* 44, pp. 301–306 (cit. on p. 289).

[Shear et al., 1995] N. H. Shear et al. (1995). "Acetaminophen-induced toxicity to human epidermoid cell line A431 and hepatoblastoma cell line Hep G2, in vitro, is diminished by silymarin". *Skin Pharmacology and Physiology* 8, pp. 279–291 (cit. on p. 367).

[Shebek and Rindone, 2000] J. Shebek and J. P. Rindone (2000). "A pilot study exploring the effect of kudzu root on the drinking habits of patients with chronic alcoholism". *Journal of Alternative and Complementary Medicine* 6.1, pp. 45–48 (cit. on pp. 307, 312).

[Shedd-Wise, Alekel, and Hofmann, 2011] K. M. Shedd-Wise, D. L. Alekel, and H. Hofmann (2011). "The soy isoflavones for reducing bone loss study: 3-yr effects on pQCT bone mineral density and strength measures in postmenopausal women". *Journal of Clinical Densitometry* 14.1, pp. 47–57 (cit. on p. 440).

[Sheehy, Murty, and Pilon, 2005] C. Sheehy, M. Murty, and K. Pilon (2005). "Black cohosh: international reports of liver toxicity". *Canadian Adverse Reaction Newsletter* 15.3, p. 2 (cit. on p. 176).

[el-Sheikh, Dakkak, and Saddique, 1988] M. el-Sheikh, M. R. Dakkak, and A. Saddique (1988). "The effect of Permixon on androgen receptors". *Acta Obstetricia et Gynecologica Scandinavica* 67.5, pp. 397–399 (cit. on p. 418).

[Shen et al., 2006] P. Shen et al. (2006). "Differential effects of isoflavones, from Astragalus membranaceus and Pueraria thomsonii , on the activation of PPARalpha, PPARgamma, and adipocyte differentiation in vitro". *Journal of Nutrition* 136.4, pp. 899–905 (cit. on p. 308).

[Sheu et al., 1987] S. j. Sheu et al. (1987). "Analysis and processing of Chinese herbal drugs; VI. The study of Angelicae radix". *Planta Medica* 53.4, pp. 377–378 (cit. on p. 257).

[Shi, L. Chang, and G. He, 1995] M. Shi, L. Chang, and G. He (1995). "Stimulating action of Carthamus tinctorius L., Angelica sinensis (Oliv.) Diels and Leonurus sibiricus L. on the uterus". *Chung Kuo Chung Yao Tsa Chih* 20, pp. 173–175 (cit. on p. 270).

[Shibata, 1985] S. Shibata (1985). *Economic and medicinal plants research*. Vol. 1: *Chemistry and pharmacology of Panax*. Ed. by H. Wagner, N. R. Farnsworth, and H. Hikino. London: Academic Press (cit. on p. 99).

[Shibata, 1994] — (1994). *International Journal of Pharmacognosy* 32.1, pp. 75–89 (cit. on pp. 316, 319).

[Shimada, V. E. Tyler, and J. L. McLaughlin, 1997] H. Shimada, V. E. Tyler, and J. L. McLaughlin (1997). "Biologically active acylglycerides from the berries of saw-palmetto ( Serenoa repens )". *Journal of Natural Products* 60.4, pp. 417–418 (cit. on p. 416).

[Shipp, Mehigh, and Helferich, 1994] E. B. Shipp, C. S. Mehigh, and W. G. Helferich (1994). "The effect of colupulone (a HOPS beta-acid) on hepatic cytochrome P-450 enzymatic activity in the rat". *Food and Chemical Toxicology* 32, pp. 1007–1014 (cit. on p. 303).

[Shmuely, Yahav, and Samra, 2007] H. Shmuely, J. Yahav, and Z. Samra (2007). "Effect of cranberry juice on eradication of Helicobacter pylori in patients treated with antibiotics and a proton pump inhibitor". *Molecular Nutrition & Food Research* 51.6, pp. 746–751 (cit. on p. 233).

[el-Shobaki, Z. A. Saleh, and N. Saleh, 1990] F. A. el-Shobaki, Z. A. Saleh, and N. Saleh (1990). "The effect of some beverage extracts on intestinal iron absorption". *Zeitschrift für Ernährungswissenschaft* 29, pp. 264–269 (cit. on p. 123).

[Shukla and Tripathi, 1987] H. S. Shukla and S. C. Tripathi (1987). "Antifungal substance in the essential oil of anise (Pimpinella anisum L.)" *Agricultural and Biological Chemistry* 51, pp. 1991–1993 (cit. on p. 127).

[Shuster, 1996] J. Shuster (1996). "Black cohosh root? Chasteberry tree? Seizures!" *Hospital Pharmacy Journal* 31, pp. 1553–1554 (cit. on p. 190).

[Sicherer, Sampson, and Burks, 2000] S. H. Sicherer, H. A. Sampson, and A. W. Burks (2000). "Peanut and soy allergy: a clinical and therapeutic dilemma". *Allergy* 55.6, pp. 515–521 (cit. on p. 442).

[Siegel, 1979] R. K. Siegel (1979). "Ginseng abuse syndrome: problems with the panacea". *Journal of the American Medical Association* 241, pp. 1614–1615 (cit. on pp. 105–106).

[Sievenpiper, M. K. Sung, and Di Buono, 2006] J. L. Sievenpiper, M. K. Sung, and M. Di Buono (2006). "Korean red ginseng rootlets decrease acute postprandial glycemia: results from sequential preparation- and dose-finding studies". *Journal of the American College of Nutrition* 25.2, pp. 100–107 (cit. on pp. 84, 141).

[Sigurjonsdottir et al., 1995] H. A. Sigurjonsdottir et al. (1995). "Is blood pressure commonly raised by moderate consumption of liquorice?" *Journal of Human Hypertension* 9.5, pp. 345–348 (cit. on p. 334).

[Silva Brum, 2001] L. F. Silva Brum et al. (2001). "Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes". *Neurochemical Research* 26, pp. 191–194 (cit. on p. 128).

[Silva Brum, Elisabetsky, and Souza, 2001] L. F. Silva Brum, E. Elisabetsky, and D. O. Souza (2001). "Effects of linalool on [ 3 H] MK801 and [ 3 H] muscimol binding in mouse cortical membranes". *Phytotherapy Research* 15, pp. 422–425 (cit. on p. 128).

[Simoncikova, Wein, and Gasperikova, 2002] P. Simoncikova, S. Wein, and D. Gasperikova (2002). "Comparison of the extrapancreatic action of gamma-linolenic acid and n-3 PUFAs in the high fat diet-induced insulin resistance". *Endocrine Regulations* 36, pp. 143–149 (cit. on p. 197).

[Simpson and A. R. Smith, 1992] W. J. Simpson and A. R. Smith (1992). "Factors affecting antibacterial activity of hop compounds and their derivatives". *Journal of Applied Bacteriology* 72, pp. 327–334 (cit. on p. 303).

[B. Singh and Kale, 2008] B. Singh and R. K. Kale (2008). "Chemomodulatory action of Foeniculum vulgare (Fennel) on skin and forestomach papillomagenesis, enzymes with xenobiotic metabolism and antioxidant status in murine model system". *Food and Chemical Toxicology* 46.12, pp. 3842–3850 (cit. on p. 280).

[R. P. Singh and R. Agarwal, 2005] R. P. Singh and R. Agarwal (2005). "Mechanisms and preclinical efficacy of silibinin in preventing skin cancer". *European Journal of Cancer* 41.13, pp. 1969–1979 (cit. on p. 359).

[R. P. Singh and R. Agarwal, 2009] — (2009). "Cosmeceuticals and silibinin". *Clinics in Dermatology* 27.5, pp. 479–484 (cit. on p. 359).

[V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984a] V. K. Singh, S. S. Agarwal, and B. M. Gupta (1984a). "Immunomodulatory activity of Panax ginseng extract". *Planta Medica* 50, pp. 462–465 (cit. on p. 100).

[V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984b] — (1984b). "Immunomodulatory activity of Panax ginseng extract". *Planta Medica* 50.6, pp. 462–465 (cit. on pp. 85, 142).

[V. K. Singh, S. S. Agarwal, and B. M. Gupta, 1984c] — (1984c). "Immunomodulatory effects of Panax ginseng extract". *Planta Medica* 50, p. 459 (cit. on p. 100).

[Singhal, R. K. Gupta, and Joshi, 1982] P. C. Singhal, R. K. Gupta, and L. D. Joshi (1982). "Hypocholesterolemic effect of Trigonella foenum-graecum (METHI)". *Current Science* 51, p. 136 (cit. on pp. 288–289).

[Sirtori, 2001] C. R. Sirtori (2001). "Risks and benefits of soy phytoestrogens in cardiovascular diseases, cancer, climacteric symptoms and osteoporosis". *Drug Safety* 24.9, pp. 665–682 (cit. on pp. 435–436).

[Skakun and Moseichuk, 1988a] N. Skakun and I. Moseichuk (1988a). "Clinical pharmacology of Legalon". *Vrach Delo* 5, pp. 5–10 (cit. on p. 355).

[Skakun and Moseichuk, 1988b] — (1988b). "Clinical pharmacology of Legalon". *Vrach Delo* 5, pp. 5–10 (cit. on pp. 364–365).

[Skalli and Soulaymani Bencheikh, 2011] S. Skalli and R. Soulaymani Bencheikh (2011). "Epileptic seizure induced by fennel essential oil". *Epileptic Disorders* 13.3, pp. 345–347 (cit. on p. 282).

[Skottova and Krecman, 1998] N. Skottova and V. Krecman (1998). "Silymarin as a potential hypocholesterolaemic drug". *Physiological Research* 47, pp. 1–7 (cit. on p. 365).

[Sliutz et al., 1993] G. Sliutz et al. (1993). "Obstetric management of patients with HELLP syndrome [in German]". *Z Geburtshilfe Perinatol* 197.3, pp. 112–118 (cit. on p. 223).

[Small, 1990] E. Small (1990). "The evolution of hemolytic saponin content in wild and cultivated alfalfa ( Medicago sativa , Fabaceae)". *Economic Botany* 44, p. 226 (cit. on p. 67).

[M. Smith, K. M. Lin, and Y. P. Zheng, 2001] M. Smith, K. M. Lin, and Y. P. Zheng (2001). "An open trial of nifedipine-herb interactions: nifedipine with St. John's wort, ginseng or ginko biloba". *Clinical Pharmacology & Toxicology* 69.2, p. 86. URL: http://www.nature.com/clpt/journal/v69/n2/pdf/clpt200111a.pdf (cit. on pp. 89, 146).

[Snow, 1996] J. M. Snow (1996). "Cimicifuga racemosa (L.) Nutt. (Ranunculaceae)". *Journal of Alternative and Complementary Medicine* 1.4, pp. 17–19 (cit. on p. 166).

[Society., 2004] North American Menopause Society. (2004). "Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society". *Menopause* 11, pp. 11–33 (cit. on p. 392).

[Society, 2004] "Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society" (2004). *Menopause* 11.1. Ed. by North American Menopause Society, pp. 11–33 (cit. on p. 259).

[Soldati, 1984] F. Soldati, ed. (1984). *Toxicological studies on ginseng*. Proceedings of the fourth International Ginseng Symposium. (Daejeon, Republic of Korea). Korean Ginseng and Tobacco Research Institute (cit. on p. 105).

[Son et al., 2007] I. S. Son et al. (2007). "Antioxidative and hypolipidemic effects of diosgenin, a steroidal saponin of yam ( Dioscorea spp.), on high-cholesterol fed rats". *Bioscience, Biotechnology, and Biochemistry* 71.12, pp. 3063–3071 (cit. on p. 450).

[Sonnenbichler and Zetl, 1987a] J. Sonnenbichler and I. Zetl (1987a). *Assessment and Management of Hepatobiliary Disease. Stimulating influence of a flavonolignane derivative on proliferation, RNA synthesis and protein synthesis in liver cells*. Ed. by L. Okoliczanyi, G. Csomos, and G. Crepaldi. Berlin: Springer-Verlag (cit. on p. 355).

[Sonnenbichler and Zetl, 1987b] — (1987b). *Assessment and Management of Hepatobiliary Disease. Stimulating influence of a flavonolignane derivative on proliferation, RNA synthesis and protein synthesis in liver cells*. Ed. by L. Okoliczanyi, G. Csomos, and G. Crepaldi. Berlin: Springer-Verlag (cit. on pp. 364, 367).

[Sonnenborn, 1987] U. Sonnenborn (1987). "Ginseng-neuere Untersuchungen immunologischer, und endokrinologischer Aktivitäten einer alten Arzneipflanze". *Deutsche Apotheker Zeitung* 125, pp. 2052–2055 (cit. on p. 100).

[Sonnenborn, 1989a] — (1989a). "Ginseng-Nebenwirkungen: Fakten oder Vermutungen?" *Medizinische Monatsschrift für Pharmazeuten* 12, pp. 46–53 (cit. on p. 100).

[Sonnenborn, 1989b] — (1989b). "Ginseng-Nebenwirkungen: Fakten oder Vermutungen?" *Medizinische Monatsschrift für Pharmazeuten* 12, pp. 46–53 (cit. on pp. 105–106).

[Sonnenborn and Hänsel, 1992] U. Sonnenborn and R. Hänsel (1992). *Adverse reactions of herbal drugs. Panax ginseng*. Ed. by P. A. G. M. De Smet. Berlin: Springer-Verlag, pp. 179–192 (cit. on pp. 105–107).

[Sonnenborn and Proppert, 1990] U. Sonnenborn and Y. Proppert (1990). "Ginseng (Panax ginseng C.A. Meyer)". *Zeitschrift fur phytotherapy* 11, pp. 35–49 (cit. on p. 106).

[Sonnenborn and Proppert, 1991] — (1991). "Ginseng (Panax ginseng C.A. Meyer)". *British Journal of Phytotherapy* 2, pp. 3–14 (cit. on pp. 99, 101).

[Sookvanichsilp, Soonthornchareonnon, and Boonleang, 2008] N. Sookvanichsilp, N. Soonthornchareonnon, and C. Boonleang (2008). "Estrogenic activity of the dichloromethane extract from Pueraria mirifica". *Fitoterapia* 79.7-8, pp. 509–514 (cit. on pp. 381–382, 387).

[Sotaniemi, Haapakoski, and Rautio, 1995] E. A. Sotaniemi, E. Haapakoski, and A. Rautio (1995). "Ginseng therapy in non-insulin-dependent diabetic patients". *Diabetes care* 18, pp. 1373–1375 (cit. on pp. 104, 107).

[Soto et al., 1998] C. P. Soto et al. (1998). "Prevention of alloxan-induced diabetes mellitus in the rat by silymarin". *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology* 119, pp. 125–129 (cit. on p. 365).

[Sowmya and Rajyalkshmi, 1999] P. Sowmya and P. Rajyalkshmi (1999). "Hypocholeserolemic effects of germinated fenugreek seeds in human subjects". *Plant Foods for Human Nutrition* 53, pp. 359–365 (cit. on p. 289).

[Spinella, 2001] M. Spinella (2001). "Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects". *Epilepsy & Behavior* 2.6, pp. 524–532 (cit. on p. 205).

[Spoerke, 1980] D. G. Spoerke (1980). *Herbal Medications*. Santa Barbara, CA: Woodbridge Press (cit. on p. 125).

[Sprecher, 1987] E. Sprecher (1987). "Ginseng: miracle drug or phytopharmacon?" *Deutsche Apotheker Zeitung* 9, pp. 52–61 (cit. on p. 99).

[Sprinz, 1971] H. Sprinz (1971). "Factors influencing intestinal cell renewal". *Cancer* 28, pp. 71–74 (cit. on p. 74).

[Stanchev, 1993] S. Stanchev (1993). "A short synthesis of 15-pentadecanolide". *Tetrahedron Letters* 34, pp. 6107–6108 (cit. on p. 112).

[A. Stark and Madar, 1993] A. Stark and Z. Madar (1993). "The effect of an ethanol extract derived from fenugreek ( Trigonella foenum traecum ) on bile acid absorption and cholesterol levels in rats". *British Journal of Nutrition* 69, pp. 277–287 (cit. on p. 288).

[P. M. Stavro et al., 2006] P. M. Stavro et al. (2006). "Long-term intake of North American ginseng has no effect on 24-hour blood pressure and renal function". *Hypertension* 47.4, pp. 791–796 (cit. on pp. 82, 140).

[Steinberg, M. J. Murray, and R. D. Lewis, 2011] F. M. Steinberg, M. J. Murray, and R. D. Lewis (2011). "Clinical outcomes of a 2-y soy isoflavone supplementation in menopausal women". *American Journal of Clinical Nutrition* 93.2, pp. 356–367 (cit. on p. 441).

[Steinhaus and Scheiberle, 2000] M. Steinhaus and P. Scheiberle (2000). "Comparison of the most odor-active compounds in fresh and dried hop cones (Humulus lupulus L. variety spalter select) based on GC-olfactometry and odor dilution techniques." *Journal of Agricultural and Food Chemistry* 48, pp. 1776–1783 (cit. on p. 300).

[Stevens, Ivancic, et al., 1997] J. F. Stevens, M. Ivancic, et al. (1997). "Prenylflavonoids from Humulus lupulus". *Phytochemistry* 44, pp. 1575–1585 (cit. on p. 300).

[Stevens, Miranda, et al., 2002] J. F. Stevens, C. L. Miranda, et al. (2002). "Identification and in vitro biological activities of hop proanthocyanidins: inhibition of nNOS activity and scavenging of reactive nitrogen species". *Journal of Agricultural and Food Chemistry* 50, pp. 3435–3443 (cit. on p. 304).

[Stevens, A. W. Taylor, Clawson, et al., 1999] J. F. Stevens, A. W. Taylor, J. E. Clawson, et al. (1999). "Fate of xanthohumol and related prenylflavonoids from hops to beer". *Journal of Agricultural and Food Chemistry* 47, pp. 2421–2428 (cit. on p. 301).

[Stevens, A. W. Taylor, and Deinzer, 1999] J. F. Stevens, A. W. Taylor, and M. L. Deinzer (1999). "Quantitative analysis of xanthohumol and related prenylflavonoids in hops and beer by liquid chromatography-tandem mass spectrometry". *Journal of Chromatography* 832, pp. 97–107 (cit. on p. 301).

[Stevens, A. W. Taylor, and Nickerson, 2000] J. F. Stevens, A. W. Taylor, and G. B. Nickerson (2000). "Prenylflavonoid variation in (Humulus lupulus): distribution and taxonomic significance of xanthogalenol and 4-O-methylxanthohumol". *Phytochemistry* 53, pp. 759–775 (cit. on p. 301).

[Stoll, 1987] W. Stoll (1987). "Phytotherapy influences atrophic vaginal epithelium: Double-blind study of Cimicifuga vs. estrogenic substance". German. *Therapeutikon* 1, pp. 23–31 (cit. on pp. 184–185).

[J. Story, 1982] J. Story (1982). "Adsorption of bile acids by components of alfalfa and wheat bran in vitro." *Journal of Food Science* (47), p. 1276 (cit. on p. 67).

[J. A. Story, LePage, and Petro, 1984] J. A. Story, S. L. LePage, and M. S. Petro (1984). "Interactions of alfalfa plant and sprout saponins with cholesterol in vitro and in cholesterol-fed rats". *American Journal of Clinical Nutrition* (39), pp. 917–929 (cit. on pp. 68, 74).

[Strandberg, Andersson, and Järvenpää, 2003] T. E. Strandberg, S. Andersson, and A. L. Järvenpää (2003). "Risk factors for preterm delivery". *Lancet* 361.9355, p. 436 (cit. on p. 326).

[Strasser et al., 2006] F. Strasser et al. (2006). "Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial". *Journal of Clinical Oncology* 24.21. Cannabis -In-Cachexia-Study-Group, pp. 3394–3400 (cit. on pp. 340–341).

[Strauch, Perles, and Vergult, 1994] G. Strauch, P. Perles, and G. Vergult (1994). "Comparison of finasteride ( Proscar ) and Serenoa repens ( Permixon ) in the inhibition of 5-alpha reductase in healthy male volunteers". *European Urology* 26.3, pp. 247–252 (cit. on p. 418).

[Studlar, 1985] M. Studlar (1985). "Die Behandlung chronischer Leberkrankungen mit Silymarin und B-Vitaminen". *Die Therapiewoche* 35, pp. 3375–3378 (cit. on p. 355).

[Stuunknown., 1985] Stuunknown. (1985). "Die Behandlung chronischer Leberkrankungen mit Silymarin und B-Vitaminen". *Die Therapiewoche* 35, pp. 3375–3378 (cit. on p. 364).

[Sucontphunt et al., 2007] A. Sucontphunt et al., eds. (2007). *Antioxidant and neuroprotective activity of Pueraria mirifica extracts against glutamate toxicity in neuronal cells*. (234th National Meeting). August 19-23, 2007. American Chemical Society. Boston, MA. (cit. on p. 386).

[Sultan, Terraza, and Devillier, 1984] C. Sultan, A. Terraza, and C. Devillier (1984). "Inhibition of androgen metabolism and binding by a liposterolic extract of Serenoa repens B in human foreskin fibroblasts". *Journal of Steroid Biochemistry* 20.1, pp. 515–519 (cit. on p. 418).

[C. Sung et al., 1982] C. Sung et al. (1982). "Effect of extracts of Angelica polymorpha on reaginic antibody production". *Journal of Natural Products* 45.4, pp. 398–406 (cit. on p. 259).

[Sur, M. Das, and Gomes, 2001] P. Sur, M. Das, and A. Gomes (2001). "Trigonella foenum graecum (fenugreek) seed extract as an antineoplastic agent". *Phytotherapy Research* 15, pp. 257–259 (cit. on pp. 290–291, 296).

[K. M. Sutton, 2014] K. M. Sutton (2014). "Thymoquinone, a bioactive component of black caraway seeds, causes G1 phase cell cycle arrest and apoptosis in triple-negative breast cancer cells with mutant p53". *Nutrition and cancer* 66.3, pp. 408–18 (cit. on p. 208).

[Y. Suzuki, 1991a] Y. Suzuki (1991a). "Effects of tissue cultured ginseng on gastric secretion and pepsin activity". *Yakugaku Zasshi* 111, pp. 770–774 (cit. on p. 102).

[Y. Suzuki, 1991b] — (1991b). "Effects of tissue cultured ginseng on the function of the stomach and small intestine". *Yakugaku Zasshi* 111, pp. 765–769 (cit. on p. 102).

[Swanson, 1979] A. B. Swanson et al. (1979). "The mutagenicities of safrole, estragole, eugenol, trans-anethole, and some of their known or possible metabolites for Salmonella typhimurium mutants". *Mutation Research* 60, pp. 143–153 (cit. on p. 131).

[Syed, Au, and Cahill, 2008] R. Syed, K. Au, and C. Cahill (2008). "Pharmacological interventions for clozapine-induced hypersalivation". *Cochrane Database of Systematic Reviews* 16.3, p. CD005579 (cit. on p. 448).

[Tabacchi, 1974] R. Tabacchi (1974). *Helvetica Chimica Acta* 57, p. 849 (cit. on pp. 119, 121).

[Tabata et al., 1997] N. Tabata et al. (1997). "Xanthohumols, diacylglycerol acyltransferase inhibitors, from Humulus lupulus". *Phytochemistry* 46, pp. 683–687 (cit. on p. 303).

[Tahara, Ingham, and Dziedzic, 1987] S. Tahara, J. L. Ingham, and S. Z. Dziedzic (1987). "Structure elucidation of kwakhurin, a new prenylated isoflavone from Pueraria mirifica roots". *Journal of Biosciences* 42.5, pp. 510–518 (cit. on p. 382).

[Takeda, Yonezawa, and Katoh, 1981] A. Takeda, M. Yonezawa, and N. Katoh (1981). "Restoration of radiation injury by ginseng. I. Responses of X-irradiated mice to ginseng extracts". *Journal of Radiation Research* 22, pp. 323–335 (cit. on p. 99).

[Taku, N. Lin, and Cai, 2010] K. Taku, N. Lin, and D. Cai (2010). "Effects of soy isoflavone extract supplements on blood pressure in adult humans: systematic review and meta-analysis of randomized placebo-controlled trials". *Journal of Hypertension* 28.10, pp. 1971–1982 (cit. on pp. 437, 443).

[Taku, Melby, et al., 2010] K. Taku, M. K. Melby, et al. (2010). "Effects of soy isoflavone supplements on bone turnover markers in menopausal women: systematic review and meta-analysis of randomized controlled trials". *Bone* 47.2, pp. 413–423 (cit. on pp. 440, 443).

[Taku, Umegaki, et al., 2007] K. Taku, K. Umegaki, et al. (2007). "Soy isoflavones lower serum total and LDL cholesterol in humans: a meta-analysis of 11 randomized controlled trials". *American Journal of Clinical Nutrition* 85.4. published correction appears in American Journal of Clinical Nutrition; 2007; vol 86, number 3; page 809., pp. 1148–1156 (cit. on pp. 437, 443).

[Takwale, Tan, and S. Agarwal, 2003] A. Takwale, E. Tan, and S. Agarwal (2003). "Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial". *British Medical Journal* 327, p. 1385 (cit. on p. 196).

[Tamagno, 2009] G. Tamagno (2009). "Are changes of prolactin levels the effectors of Vitex agnus castus beneficial effects on the pre-menstrual syndrome?" *Maturitas* 63.4, p. 369 (cit. on p. 214).

[Tamayo and Diamond, 2007] C. Tamayo and S. Diamond (2007). "Review of clinical trials evaluating safety and efficacy of milk thistle ( Silybum marianum [L.] Gaertn.)" *Integrative Cancer Therapies* 6.2, pp. 146–157 (cit. on pp. 372, 378).

[Tanamly, Tadros, and Labeeb, 2004] M. D. Tanamly, F. Tadros, and S. Labeeb (2004). "Randomised double-blinded trial evaluating silymarin for chronic hepatitis C in an Egyptian village: study description and 12-month results". *Digestive and Liver Disease* 36.11, pp. 752–759 (cit. on p. 362).

[W. Tang and Eisenbrand, 1992] W. Tang and G. Eisenbrand (1992). *Chinese Drugs of Plant Origin: Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*. Berlin: Springer-Verlag, pp. 113–125 (cit. on pp. 256, 259).

[Tani, Fujiwara, and Kato, 1984] S. Tani, H. Fujiwara, and A. Kato (1984). "Studies on constituents of Angelica dahurica . II. Identification of gamma-nonalactone and gamma-decalactone by GC and GC/MS as a part of the odor components". *Journal of Natural Products* 47.4, p. 734 (cit. on p. 257).

[Tao, 1984] J. Y. Tao (1984). "Studies on the antiasthmatic action of ligustilide of dang-gui, Angelica sinensis (Oliv.) Diels". *Yao Hsueh Hsueh Pao* 198, pp. 561–565 (cit. on p. 270).

[Tao, Ruan, and Mei, 1984] J. Y. Tao, Y. P. Ruan, and Q. B. Mei (1984). "[Studies on the antiasthmatic action of ligustilide of dang-gui, Angelica sinensis (Oliv.) Diels. [in Chinese]". 19.8, pp. 561–565 (cit. on p. 259).

[M. Taylor, 2001] M. Taylor (2001). "Botanicals: medicines and menopause". *Clinical Obstetrics and Gynecology* 44.4, pp. 853–863 (cit. on pp. 222–223).

[Team, 2011] National Plant Data Team (2011). *Panax ginseng - The PLANTS Database*. National Plant Data Team. URL: http://plants.usda.gov (cit. on pp. 77, 137).

[Teare and J. Zajicek, 2005] L. Teare and J. Zajicek (2005). "The use of cannabinoids in multiple sclerosis". *Expert Opinion on Investigational Drugs* 14.7, pp. 859–869 (cit. on p. 342).

[Teede et al., 2003] H. J. Teede et al. (2003). "Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women". *Arteriosclerosis, Thrombosis, and Vascular Biology* 23, pp. 1066–1071 (cit. on p. 394).

[Tehara, 2006] T. Tehara (2006). "Antiaging cosmetics containing natural products [in Japanese]". *Kokai Tokkyo Koho*. US patent application JP 2006-241033 (cit. on pp. 381, 387).

[Tekel' et al., 1999] J. Tekel' et al. (1999). "Determination of the hop-derived phytoestrogen, 8-prenylnaringenin, in beer by gas chromatography/mass spectrometry". *Journal of Agricultural and Food Chemistry* 47, pp. 5059–5063 (cit. on p. 300).

[Terasawa, 1985] K. Terasawa (1985). "Chemical and clinical evaluation of crude drugs derived from Angelica acutiloba and A. sinensis". *Fitoterapia* 56, pp. 201–208 (cit. on pp. 269, 272).

[Terris, Issa, and Tacker, 2001] M. K. Terris, M. M. Issa, and J. R. Tacker (2001). "Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis". *Urology* 57.1, pp. 26–29 (cit. on p. 237).

[Teschke, 2010] R. Teschke (2010). "Black cohosh and suspected hepatotoxicity: inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review". *Menopause* 17.2, pp. 426–440 (cit. on p. 190).

[Teschke, Bahre, et al., 2009] R. Teschke, R. Bahre, et al. (2009). "Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases". *Menopause* 16.5, pp. 956–965 (cit. on p. 190).

[Teschke and Schwarzenboeck, 2009] R. Teschke and A. Schwarzenboeck (2009). "Suspected hepatotoxicity by Cimicifugae racemosae rhizoma (black cohosh, root): critical analysis and structured causality assessment". *Phytomedicine* 16.1, pp. 72–84 (cit. on p. 190).

[TGC, 2015] TGC, ed. (2015). *Electrolysis Pain*. TransGenderCare. URL: http://www.transgendercare.com/electrolysis/pain/pain.htm (cit. on p. 54).

[Thies et al., 2001a] F. Thies et al. (2001a). "Dietary supplementation with eicosapentenoic acid, but not with other long-chain n-3 or n-6 polyunsaturated fatty acids, decreases natural killer cell activity in healthy subjects aged $>$ 55 y". *American Journal of Clinical Nutrition* 73, pp. 539–548 (cit. on p. 195).

[Thies et al., 2001b] — (2001b). "Dietary supplementation with gamma-linolenic acid or fish oil decreases T lymphocyte proliferation in healthy older humans". *Journal of Nutrition* 131, pp. 1918–1927 (cit. on p. 195).

[Thirunavukkarasu, Anuradha, and Viswanathan, 2003] V. Thirunavukkarasu, C. V. Anuradha, and P. Viswanathan (2003). "Protective effect of fenugreek (Trigonella foenum graecum) seeds in experimental ethanol toxicity". *Phytotherapy Research* 17, pp. 737–743 (cit. on p. 291).

[Thompson Coon and Ernst, 2003] J. S. Thompson Coon and E. Ernst (2003). "Herbs for serum cholesterol reduction: a systematic view". *The Journal of Family Practice* 52, pp. 468–478 (cit. on p. 289).

[Tice et al., 2003] J. A. Tice et al. (2003). "Phytoestrogen supplements for the treatment of hot flashes: The Isoflavone Clover Extract (ICE) Study: a randomized controlled trial". *Journal of the American Medical Association* 290, pp. 207–214 (cit. on pp. 392–393).

[Tidy, 2015] C. Tidy (2015). *Phyto-oestrogens*. URL: http://patient.info/doctor/phyto-oestrogens (cit. on pp. 57–59).

[Tildesley, D. O. Kennedy, et al., 2005] N. T. Tildesley, D. O. Kennedy, et al. (2005). "Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers". *Physiology & Behavior* 83.5, pp. 699–709 (cit. on p. 407).

[Tildesley, O., and E. K. Perry, 2003] N. T. Tildesley, Kennedy. D. O., and E. K. Perry (2003). "Salvia lavandulaefolia (Spanish sage) enhances memory in healthy young volunteers". *Pharmacology Biochemistry and Behavior* 75.3, pp. 669–674 (cit. on pp. 406–407, 410).

[Tocher et al., 1997] D. R. Tocher et al. (1997). "Fatty acyl desaturation in isolated hepatocytes from Atlantic salmon ( Salmo salar ): stimulation by dietary borage oil containing gamma-linolenic acid". *Lipids* 32, pp. 1237–1247 (cit. on p. 194).

[Tognolini et al., 2007] M. Tognolini et al. (2007). "Protective effect of Foeniculum vulgare essential oil and anethole in an experimental model of thrombosis". *Pharmacological Research* 56.3, pp. 254–260 (cit. on p. 281).

[Tomida et al., 2006] I. Tomida et al. (2006). "Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study". *Journal of Glaucoma* 15.5, pp. 349–353 (cit. on pp. 341, 344).

[Tomlinson, Sherlock, and B. Hughes, 2007] J. W. Tomlinson, M. Sherlock, and B. Hughes (2007). "Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 activity in vivo limits glucocorticoid exposure to human adipose tissue and decreases lipolysis". *Journal of Clinical Endocrinology & Metabolism* 92.3, pp. 857–864 (cit. on p. 320).

[Tong, Heong, and S. Chang, 2006] H. Tong, S. Heong, and S. Chang (2006). "Effect of ingesting cranberry juice on bacterial growth in urine". *American Journal of Health-System Pharmacy* 63.15, pp. 1417–1419 (cit. on p. 231).

[Trinchet, Coste, and V. Levy, 1989a] J. Trinchet, T. Coste, and V. Levy (1989a). "A randomized double blind trial of silymarin in 116 patients with alcoholic hepatitis". *Gastroentérologie Clinique et Biologique* 13, pp. 120–124 (cit. on p. 355).

[Trinchet, Coste, and V. Levy, 1989b] — (1989b). "A randomized double blind trial of silymarin in 116 patients with alcoholic hepatitis". *Gastroentérologie Clinique et Biologique* 13, pp. 120–124 (cit. on p. 364).

[Trisomboon, Malaivijitnond, J. Suzuki, et al., 2004] H. Trisomboon, S. Malaivijitnond, J. Suzuki, et al. (2004). "Long-term treatment effects of Pueraria mirifica phytoestrogens on parathyroid hormone and calcium levels in aged menopausal cynomolgus monkeys". *Journal of Reproduction and Development* 50.6, pp. 639–645 (cit. on p. 384).

[Trisomboon, Malaivijitnond, Watanabe, Cherdshewasart, et al., 2006] H. Trisomboon, S. Malaivijitnond, G. Watanabe, W. Cherdshewasart, et al. (2006). "The estrogenic effect of Pueraria mirifica on gonadotrophin levels in aged monkeys". *Endocrine* 29.1, pp. 129–134 (cit. on p. 384).

[Trisomboon, Malaivijitnond, Watanabe, and Taya, 2004] H. Trisomboon, S. Malaivijitnond, G. Watanabe, and K. Taya (2004). "Estrogenic effects of Pueraria mirifica on the menstrual cycle and hormone-related ovarian functions in cyclic female cynomolgus monkeys". *Journal of Pharmacological Sciences* 94.1, pp. 51–59 (cit. on p. 384).

[Trisomboon, Malaivijitnond, Watanabe, and Taya, 2005] — (2005). "Ovulation block by Pueraria mirifica : a study of its endocrinological effect in female monkeys". *Endocrine* 26.1, pp. 33–39 (cit. on p. 383).

[Trisomboon et al., 2006] H. Trisomboon et al. (2006). "Effect of Pueraria mirifica on the sexual skin coloration of aged menopausal cynomolgus monkeys". *Journal of Reproduction and Development* 52.4, pp. 537–542 (cit. on p. 384).

[Trisomboon et al., 2007a] — (2007a). "Assessment of urinary gonadotropin and steroid hormone profiles of female cynomolgus monkeys after treatment with Pueraria mirifica". *Journal of Reproduction and Development* 53.2, pp. 395–403 (cit. on p. 384).

[Trisomboon et al., 2007b] — (2007b). "The influence of Pueraria mirifica herb containing phytoestrogens on the urinary gonadotropin and estradiol levels in aged menopausal monkeys". *Animal Science Journal* 78.4, pp. 378–386 (cit. on p. 384).

[Trittibach, Frueh, and Goldblum, 2005] P. Trittibach, B. E. Frueh, and D. Goldblum (2005). "Bilateral angle-closure glaucoma after combined consumption of "ecstasy" and marijuana". *American Journal of Emergency Medicine* 23.6, pp. 813–814 (cit. on p. 341).

[Truhaut, 1989] R. Truhaut et al. (1989). "Chronic toxicity/carcinogenicity study of trans-anethole in rats". *Food and Chemical Toxicology* 27, pp. 11–20 (cit. on p. 132).

[N. M. Tsai, S. Z. Lin, and C. C. Lee, 2005] N. M. Tsai, S. Z. Lin, and C. C. Lee (2005). "The antitumor effects of Angelica sinensis on malignant brain tumors in vitro and in vivo". *Clinical Cancer Research* 11.9, pp. 3475–3484 (cit. on p. 260).

[Tsvetkov, 1970] R. Tsvetkov (1970). *Planta Medica* 18, pp. 350–353 (cit. on p. 120).

[Tubcharoen, Chiwatansin, et al., 2003] S. Tubcharoen, W. Chiwatansin, et al., eds. (2003). *The optimum level of Pueraria mirifica in stewer rabbit rations*. (Kasetsart University Annual Conference). 41st. February 3-7, 2003. Kasetsart University Annual Conference. Kanchanaburi, Thailand, pp. 331–337 (cit. on p. 388).

[Tubcharoen, Tungtakulsub, et al., 2003] S. Tubcharoen, P. Tungtakulsub, et al., eds. (2003). *Effect of Pueraria mirifica as layer diet on peak-egg production of laying hens*. (Kasetsart University Annual Conference). 41st. February 3-7, 2003. Kasetsart University Annual Conference. Kanchanaburi, Thailand, pp. 315–322 (cit. on p. 388).

[Türkyilmaz et al., 2008] Z. Türkyilmaz et al. (2008). "A striking and frequent cause of premature thelarche in children: Foeniculum vulgare". *Journal of Pediatric Surgery* 43.11, pp. 2109–2111 (cit. on p. 283).

[V. Tyler, 1994] V. Tyler (1994). *Herbs of choice. Performance and immune deficiencies*. New York: Pharmaceutical Products Press, pp. 155–157 (cit. on p. 106).

[V. E. Tyler, 1983] V. E. Tyler (1983). "Damiana: History of an Herbal Hoax". *Pharmacy in History* 25.2, p. 55 (cit. on pp. 244, 246).

[V. E. Tyler, 1995] — (1995). "Was Lydia E. Pinkham's Vegetable Compound an effective remedy?" *Pharmacy in History* 37.1, pp. 24–28 (cit. on p. 163).

[Uebelhack et al., 2006] R. Uebelhack et al. (2006). "Black cohosh and St. John's wort for climacteric complaints: a randomized trial". *Obstetrics & Gynecology* 107.2 (Part 1), pp. 247–255 (cit. on p. 172).

[Ulbricht, Basch, and Ulbricht, 2003] C. Ulbricht, E. Basch, and C. Ulbricht (2003). "Wild yam (Dioscoreaceae)". *Journal of Herbal Pharmacotherapy* 3.4, pp. 77–91 (cit. on p. 448).

[Unger, 2004] R. W. Unger (2004). *Beer in the Middle Ages and Renaissance*. University of Pennsylvania Press, p. 100 (cit. on p. 298).

[unknown, n.d.(a)] unknown. *Australian Therapeutic Goods Administration alert*. URL: http://www.tga.gov.au/cm/blkcohosh.htm (cit. on p. 182).

[unknown, n.d.(b)] — . *Workshop on the Safety of Black Cohosh in Clinical Studies*. URL: http://ods.od.nih.gov/click.aspx?target=http%3a%2f%2fnccam.nih.gov%2fnews%2fevents%2fblackcohosh%2fblackcohosh_mtngsumm.htm%3fnav%3dgsa&key=1B96A4E852945CDACC79E2827C42B403F1C3E893 (cit. on p. 182).

[unknown, 1752] — (1752). *The London magazine*, p. 332 (cit. on p. 299).

[unknown, 1875] — (1875). "New York Alumni Association of the Philadelphia College of Pharmacy: Meeting Minutes August 3, 1875". *American Journal of Pharmacy* 47, p. 426 (cit. on p. 244).

[unknown, 1972] unknown (1972). *Egyptian pharmacopoeia*. 3rd. Cairo: General Organization for Government Printing (cit. on p. 126).
[unknown, 1973] — (1973). *Food and Cosmetics Toxicology* 11, p. 865 (cit. on pp. 121, 124).
[unknown, 1984] — ed. (1984). *AHA Quarterly Newsletter* 3.4 (cit. on p. 67).
[unknown, 1986] — ed. (1986). *Hungarian pharmacopoeia*. 7th ed. Budapest: Medicina Könyvhiadó (cit. on p. 126).
[unknown, 1987] — ed. (1987). *Thai pharmacopoeia*. Vol. 1. Bangkok: Department of Medical Sciences, Ministry of Public Health (cit. on p. 126).
[unknown, 1992] — (1992). *Pharmacopoeia of the People's Republic of China*. English. Guangzhou: Guangdong Science and Technology Press (cit. on p. 105).
[unknown, 1995] — ed. (1995). *Farmakope Indonesia*. 4th ed. Jakarta: Departmen Kesehatan (cit. on p. 126).
[unknown, 1996a] — (1996a). *Compendium of Materia Medica - State Administration of Traditional Chinese Medicine*. Shanghai: Shanghai Science and Technical Press, pp. 1341–1355 (cit. on p. 272).
[unknown, 1996b] — ed. (1996b). *European pharmacopoeia*. 3rd ed. Strasbourg: Council of Europe (cit. on pp. 126, 132).
[unknown, 1999] — (1999). "Adverse reaction: milk thistle-associated toxicity". *Nurse Drug Alert* 23.51 (cit. on pp. 364, 367).
[unknown, 2003a] — (2003a). "Cannabis -based medicines–GW pharmaceuticals: high CBD, high THC, medicinal cannabis–GW pharmaceuticals, THC:CBD". *Drugs in R&D* 4.5, pp. 306–309 (cit. on p. 338).
[unknown, 2003b] — (2003b). "Recurrent cystitis in non-pregnant women". *Clinical Evidence* 9, pp. 2152–2160 (cit. on p. 231).
[unknown, 2004a] — (2004a). *Alternative Medicine. Red Clover. Health and Age*. This site appears to be dead as of 2015/07/21 and unreachable. URL: http://www.healthandage.com/html/res/com/ConsHerbs/RedCloverch.html (cit. on p. 390).
[unknown, 2004b] — (2004b). "Final report of the amended safety assessment of Dioscorea Villosa (Wild Yam) root extract". *International Journal of Toxicology* Supplement 2, pp. 49–54 (cit. on pp. 447–450, 452).
[unknown, 2005] — (2005). "Herbal treatment helps curb urge to drink". *Harvard Women's Health Watch* 13.1, pp. 6–7 (cit. on p. 307).
[unknown, 2009a] — (2009a). "A short history of hops". *Zythophile* (cit. on p. 298).
[unknown, 2009b] — (2009b). "Panax ginseng". *Alternative Medicine Review* 14.2, pp. 172–176 (cit. on pp. 85, 142).

[unknown, 2013a] unknown (2013a). *Basil use while Breastfeeding*. Drugs.com. URL: http://www.drugs.com/breastfeeding/basil.html (cit. on p. 158).
[unknown, 2013b] — (2013b). *Hormones*. URL: http://taimapedia.org/index.php?title=Hormones (cit. on p. 427).
[unknown, 2014a] — ed. (2014a). *Alfalfa-Phytoestrogens in alfalfa*. wikipedia.org. URL: http://en.wikipedia.org/wiki/Alfalfa-Phytoestrogens_in_alfalfa (cit. on p. 63).
[unknown, 2014b] — (2014b). *American Ginseng*. URL: https://umm.edu/health/medical/altmed/herb/american-ginseng (cit. on pp. 76, 79, 86–87, 89–91, 98).
[unknown, 2014c] — (2014c). *Asian Ginseng*. URL: https://umm.edu/health/medical/altmed/herb/asian-ginseng (cit. on pp. 136, 138, 143–145, 147, 151, 153).
[unknown, 2014d] — (2014d). *Black Cohosh*. URL: https://umm.edu/health/medical/altmed/herb/black-cohosh (cit. on pp. 164, 169, 173–174, 176, 182, 188–189).
[unknown, 2014e] — (2014e). *Cranberry*. URL: https://umm.edu/health/medical/altmed/herb/cranberry (cit. on pp. 227, 231, 233–234, 239–241).
[unknown, 2014f] — ed. (2014f). *Herbal Hormones*. URL: www.hemingways.org/GIDinfo/herbal.html (cit. on p. 63).
[unknown, 2014g] — ed. (2014g). *Herbal Hormones*. URL: www.hemingways.org/GIDinfo/herbal.html (cit. on p. 223).
[unknown, 2014h] — (2014h). *Is there any benefit to the student-athlete of taking Ginseng? FAQ's in Sports Nutrition*. URL: http://www.umass.edu/cnshp/faq.html (cit. on pp. 11, 149).
[unknown, 2014i] — (2014i). *Licorice*. URL: https://umm.edu/health/medical/altmed/herb/licorice (cit. on pp. 54, 314, 320–322, 329, 332–333).
[unknown, 2014j] — (2014j). *Milk Thistle*. URL: https://umm.edu/health/medical/altmed/herb/milk-thistle (cit. on pp. 353, 360, 362–363, 371, 375, 377–378).
[unknown, 2014k] — (2014k). *Our Herb Garden*. URL: http://www.ourherbgarden.com/ (cit. on p. 208).
[unknown, 2014l] — (2014l). *Saw Palmetto*. URL: https://umm.edu/health/medical/altmed/herb/saw-palmetto (cit. on pp. 414, 417–418, 420, 423, 425–427).
[unknown, 2014m] — (2014m). *Wild Yam*. URL: https://umm.edu/health/medical/altmed/herb/wild-yam (cit. on pp. 446, 448–452).
[unknown, 2015a] — (2015a). *Alfalfa*. URL: http://www.herbal-supplement-resource.com/alfalfa-herb.html (cit. on pp. 66, 69, 73).
[unknown, 2015b] — (2015b). *Angelica*. URL: http://www.herbal-supplement-resource.com/angelica-benefits.html (visited on 10/16/2015) (cit. on pp. 109, 114, 117–118).
[unknown, 2015c] — (2015c). *Aniseed*. URL: http://www.herbwisdom.com/herb-aniseed.html (cit. on pp. 10, 120, 123–125).

[unknown, 2015d] unknown (2015d). *Dong Quai*. URL: https://umm.edu/health/medical/altmed/herb/dong-quai (cit. on pp. 17, 255, 261–266, 268).

[unknown, 2015e] — (2015e). *Red Clover*. URL: https://umm.edu/health/medical/altmed/herb/red-clover (cit. on pp. 390, 392–393, 395–399).

[unknown, 2015f] — (2015f). *Tetrahydrocannabinol - THC*. URL: https://www.ch.ic.ac.uk/vchemlib/mim/bristol/thc/thc_text.htm (cit. on p. 351).

[Upton, 2002] R. Upton, ed. (2002). *American Herbal Pharmacopoeia and Therapeutic Compendium. Black Cohosh Rhizome Actaea racemosa L. syn. Cimicifuga racemosa (L.) Nutt. Standards of analysis, quality control, and therapeutics*. Santa Cruz, CA, pp. 1–38 (cit. on p. 166).

[Urasopon, Hamada, Asaoka, et al., 2007] N. Urasopon, Y. Hamada, K. Asaoka, et al. (2007). "Pueraria mirifica , a phytoestrogen-rich herb, prevents bone loss in orchidectomized rats". *Maturitas* 56.3, pp. 322–331 (cit. on pp. 385–386).

[Urasopon, Hamada, Cherdshewasart, et al., 2008] N. Urasopon, Y. Hamada, W. Cherdshewasart, et al. (2008). "Preventive effects of Pueraria mirifica on bone loss in ovariectomized rats". *Maturitas* 59.2, pp. 137–148 (cit. on pp. 385–386).

[USA, 2004] Food Additives. USA (2004). *GRAS Substances. Multi-purpose GRAS Food Substances. Degussa Food Ingredients*. URL: http://www.degussa-health-nutrition.com/degussa/html/e/health/eng/kh/f4.7.htm (cit. on p. 124).

[USDA, 2008a] USDA (2008a). *Pueraria*. The PLANTS Database. National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 306).

[USDA, 2008b] — (2008b). *The PLANTS Database - Dioscorea villosa*. Baton Rouge, LA 70874-4490 USA. National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 446).

[USDA, 2011] — (2011). *Vitex agnus-castus*. The PLANTS Database. USDA, NRCS. Greensboro, NC 27401-4901 USA.: National Plant Data Team. URL: http://plants.usda.gov (visited on 03/14/2011) (cit. on p. 212).

[A. USDA, 2009] ARS USDA (2009). *National Genetic Resources Program. Germplasm Resources Information Network - (GRIN) [Online Database]*. National Germplasm Resources Laboratory, URL: http://www.ars-grin.gov/cgi-bin/npgs/html/taxon.pl?406655. Beltsville, Maryland (cit. on p. 256).

[N. USDA, 2008] NRCS USDA, ed. (2008). *The PLANTS Database. Vaccinium macrocarpon Aiton*. Baton Rouge, LA, 70874-4490 USA.: National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 227).

[N. USDA, 2009] — (2009). *The PLANTS Database - Salvia officinalis L.* Baton Rouge, LA 70874-4490 USA. National Plant Data Center. URL: http://plants.usda.gov (cit. on p. 404).

[Vailati, Aristia, and Sozze, 1993a] A. Vailati, L. Aristia, and E. Sozze (1993a). "Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis". *Fitoterapia* 64, pp. 219–228 (cit. on p. 355).

[Vailati, Aristia, and Sozze, 1993b] — (1993b). "Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis". *Fitoterapia* 64, pp. 219–228 (cit. on pp. 365, 367).

[Valette et al., 1984] G. Valette et al. (1984). "Hypocholesterolaemic effect of fenugreek seeds in dogs". *Atherosclerosis* 50, pp. 105–111 (cit. on pp. 288–289).

[Van Beneden, Keene, and Strang, 1999] C. A. Van Beneden, W. E. Keene, and R. A. Strang (1999). "Multinational outbreak of Salmonella enterica serotype Newport infections due to contaminated alfalfa sprouts". *Journal of the American Medical Association* 282, pp. 158–162 (cit. on pp. 8, 68–69).

[Van Berkel et al., 1998] G. Van Berkel et al. (1998). "Derivatization for electrospray ionization mass spectrometry. Electrochemically ionizable derivatives". *Analytical Chemistry* 70.8, pp. 1544–1554 (cit. on p. 416).

[Van Coppenolle, Le Bourhis, and Carpentier, 2000] F. Van Coppenolle, X. Le Bourhis, and F. Carpentier (2000). "Pharmacological effects of the liposterolic extract of Serenoa repens ( Permixon ) on rat prostate hyperplasia induced by hyperprolactinemia: Comparison with finasteride". *Prostate* 43.1, pp. 49–58 (cit. on p. 418).

[Van Dongen and Leusink, 1953] K. Van Dongen and H. Leusink (1953). "The action of opium-alkaloids and expectorants on the ciliary movements in the air passages". *Archives of International Pharmacodynamics* 93, pp. 261–276 (cit. on p. 129).

[Van Schepdael, 1993] P. Van Schepdael (1993). "Les effets du ginseng G115 sur la capacité physique de sportifs d'endurance". *Acta therapeutica* 19, pp. 337–347 (cit. on pp. 103, 105).

[Van Wyk, 2005] Ben-Erik. Van Wyk (2005). *Food plants of the world: An illustrated guide*. Portland, Oregon: Timber Press, p. 211 (cit. on p. 298).

[Vanderhoof et al., 1997] J. A. Vanderhoof et al. (1997). "Use of soy fiber in acute diarrhea in infants and toddlers". *Clinical pediatrics* 36.3, pp. 135–139 (cit. on p. 440).

[Vaney, Heinzel-Gutenbrunner, and Jobin, 2004] C. Vaney, M. Heinzel-Gutenbrunner, and P. Jobin (2004). "Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study". *Multiple Sclerosis Journal* 10.4, pp. 417–424 (cit. on p. 342).

[Varchney and Jani, 1979] J. P. Varchney and D. C. Jani (1979). *National Academy Science Letters* 2, p. 331 (cit. on p. 287).

[Varma, Talwar, and Garg, 1980] P. N. Varma, S. K. Talwar, and G. P. Garg (1980). "Chemical investigation of Silybum marianum". *Planta Medica* 38.4, pp. 377–378 (cit. on p. 359).

[Vats et al., 2004] V. Vats et al. (2004). "Anti-cataract activity of Pterocarpus marsupium bark and Trigonella Foenum-graecum seeds extract in alloxan diabetic rats". *Journal of Ethnopharmacology* 93, pp. 289–294 (cit. on p. 292).

[Vela-navarrete et al., 2005] R. Vela-navarrete et al. (2005). "Serenoa repens treatment modifies BAX/BCL-2 index expression and caspase-3 activity in prostatic tissue from patients with benign prostatic hyperplasia". *Journal of Urology* 173.2, pp. 507–510 (cit. on p. 419).

[Velussi, Cernigoi, and Viezzoli, 1993a] M. Velussi, A. M. Cernigoi, and L. Viezzoli (1993a). "Silymarin reduces hyperinsulinemia, malondialdehyde levels, and daily insulin need in cirrhotic diabetic patients". *Current Therapeutic Research* 53, pp. 533–545 (cit. on p. 355).

[Velussi, Cernigoi, and Viezzoli, 1993b] — (1993b). "Silymarin reduces hyperinsulinemia, malondialdehyde levels, and daily insulin need in cirrhotic diabetic patients". *Current Therapeutic Research* 53, pp. 533–545 (cit. on p. 365).

[Verhoeven et al., 2005] M. O. Verhoeven et al. (2005). "Effect of a combination of isoflavones and Actaea racemosa Linnaeus on climacteric symptoms in healthy symptomatic perimenopausal women: a 12-week randomized, placebo-controlled, double-blind study". *Menopause* 12.4, pp. 412–420 (cit. on p. 172).

[Verma and Thuluvath, 2007] S. Verma and P. J. Thuluvath (2007). "Complementary and alternative medicine in hepatology: review of the evidence of efficacy". *Clinical Gastroenterology and Hepatology* 5.4, pp. 408–416 (cit. on pp. 361–362).

[J. H. Vogel, Bolling, and Costello, 2005] J. H. Vogel, S. F. Bolling, and R. B. Costello (2005). "Integrating complementary medicine into cardiovascular medicine. (A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents [Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine])". *Journal of the American College of Cardiology* 46.1, pp. 184–221 (cit. on p. 437).

[Vogler, Pittler, and Ernst, 1999] B. K. Vogler, M. H. Pittler, and E. Ernst (1999). "The efficacy of ginseng. A systematic review of randomised clinical trials". *European Journal of Clinical Pharmacology* 55.8, pp. 567–575 (cit. on p. 149).

[Vohra, Johnston, and Laycock, 2008] S. Vohra, B. C. Johnston, and K. L. Laycock (2008). "Safety and tolerability of North American ginseng extract in the treatment of pediatric upper respiratory tract infection: a phase II randomized, controlled trial of 2 dosing schedules". *Journal of Pediatrics* 122.2, e402–e410 (cit. on pp. 86, 143).

[Vonderheid-Guth et al., 2000] B. Vonderheid-Guth et al. (2000). "Pharmacodynamic effects of valerian and hops extract combination (Ze 91019) on the quantitative-topographical EEG in healthy volunteers". *European Journal of Medical Research* 5, pp. 139–144 (cit. on p. 302).

[Vukovic-Gacic et al., 2006] B. Vukovic-Gacic et al. (2006). "Antimutagenic effect of essential oil of sage ( Salvia officinalis L.) and its monoterpenes against UV-induced mutations in Escherichia coli and Saccharomyces cerevisiae". *Food and Chemical Toxicology* 44.10, pp. 1730–1738 (cit. on p. 408).

[Vuksan, Sievenpiper, and Koo, 2000] V. Vuksan, J. L. Sievenpiper, and V. Y. Koo (2000). "American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus". *European Journal of Neurology* 160.7, pp. 1009–1013 (cit. on pp. 84, 141).

[Vuksan, M. P. Stavro, and Sievenpiper, 2000] V. Vuksan, M. P. Stavro, and J. L. Sievenpiper (2000). "Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes". *Diabetes Care* 23.9, pp. 1221–1226 (cit. on pp. 84, 141).

[Vuksan, M. K. Sung, and Sievenpiper, 2008] V. Vuksan, M. K. Sung, and J. L. Sievenpiper (2008). "Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety." *Nutrition, Metabolism & Cardiovascular Diseases* 18.1, pp. 46–56 (cit. on pp. 84, 90, 141, 153).

[Wade et al., 2004] D. T. Wade et al. (2004). "Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients". *Multiple Sclerosis Journal* 10.4, pp. 434–441 (cit. on p. 342).

[Wadsworth et al., 2007] T. L. Wadsworth et al. (2007). "Effects of dietary saw palmetto on the prostate of transgenic adenocarcinoma of the mourse prostate model (TRAMP)". *Prostate* 67.6, pp. 661–673 (cit. on p. 419).

[Wagner and Flachsbarth, 1981] H. Wagner and H. Flachsbarth (1981). "A new antiphlogistic principle from Sabal serrulata I [in German]". *Planta Medica* 41.3, pp. 244–251 (cit. on p. 416).

[Wagner, Flachsbarth, and G. Vogel, 1981] H. Wagner, H. Flachsbarth, and G. Vogel (1981). "A new antiphlogistic principle from Sabal serrulata , II [in German]". *Planta Medica* 41.3, pp. 252–258 (cit. on p. 416).

[Wagner, Norr, and Winterhoff, 1994] H. Wagner, H. Norr, and H. Winterhoff (1994). "Plant adaptogens". *Phytomedicine* 1, pp. 63–76 (cit. on pp. 99, 101).

[Waites et al., 2004] K. B. Waites et al. (2004). "Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury". *Journal of Spinal Cord Medicine* 27.1, pp. 35–40 (cit. on p. 231).

[Wallace, Schulteis, and J. H. Atkinson, 2007] M. Wallace, G. Schulteis, and J. H. Atkinson (2007). "Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers". *Anesthesiology* 107.5, pp. 785–796 (cit. on p. 343).

[B. X. Wang, 1989] B. X. Wang (1989). "Studies on the mechanism of ginseng polypeptide induced hypoglycemia". *Yao hsueh hsueh pao* 25, pp. 727–731 (cit. on pp. 101–102).

[H. Wang, J. Li, et al., 2004] H. Wang, J. Li, et al. (2004). "Antifibrotic effect of the Chinese herbs, Astragalus mongholicus and Angelica sinensis , in a rat model of chronic puromycin aminonucleoside nephrosis". *Life Sciences* 74.13, pp. 1645–1658 (cit. on p. 261).

[H. Wang and Peng, 1994] H. Wang and R. X. Peng (1994). "Sodium ferulate alleviated paracetamol-induced liver toxicity in mice". *Yao Hsueh Hsueh Pao* 15, pp. 81–83 (cit. on p. 270).

[L. Y. Wang, A. P. Zhao, and X. S. Chai, 1994] L. Y. Wang, A. P. Zhao, and X. S. Chai (1994). "Effects of puerarin on cat vascular smooth muscle in vitro [in Chinese]". *Zhongguo Yao Li Xue Bao* 15.2, pp. 180–182 (cit. on p. 308).

[M. J. Wang, W. W. Lin, and H. L. Chen, 2002] M. J. Wang, W. W. Lin, and H. L. Chen (2002). "Silymarin protects dopaminergic neurons against lipopolysaccharide-induced neurotoxicity by inhibiting microglia activation". *European Journal of Neuroscience* 16.11, pp. 2103–2112 (cit. on p. 360).

[M. Wang, Guilbert, and L. Ling, 2001] M. Wang, L. J. Guilbert, and L. Ling (2001). "Immunomodulating activity of CVT-E002, a proprietary extract from North American ginseng (Panax quinquefolium)". *Journal of Pharmacy and Pharmacology* 53.11, pp. 1515–1523 (cit. on pp. 85, 142).

[T. Wang et al., 2008] T. Wang et al. (2008). "Adverse effects of medical cannabinoids: a systematic review". *Canadian Medical Association Journal* 178.13, pp. 1669–1678 (cit. on p. 346).

[Y. Wang and B. Zhu, 1996] Y. Wang and B. Zhu (1996). "The effect of Angelica polysaccharide on proliferation and differentiation of hematopoietic progenitor cells". *Chung Hua I Hsueh Tsa Chih* 76, pp. 363–366 (cit. on pp. 269, 272).

[Z. Y. Wang and Nixon, 2001] Z. Y. Wang and D. W. Nixon (2001). "Licorice and cancer". *Nutrition and Cancer* 39.1, pp. 1–11 (cit. on pp. 317, 319).

[M. A. Ware, Doyle, et al., 2003] M. A. Ware, C. R. Doyle, et al. (2003). "Cannabis use for chronic non-cancer pain: results of a prospective survey". *Pain* 102.1-2, pp. 211–216 (cit. on p. 343).

[M. A. Ware, Fitzcharles, et al., 2010] M. A. Ware, M. A. Fitzcharles, et al. (2010). "The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial". *Anesthesia & Analgesia* 110.2, pp. 604–610 (cit. on p. 344).

[Warnecke, 1985] G. Warnecke (1985). "Influencing of menopausal complaints with a phytodrug: successful therapy with Cimicifuga monoextract". German. *Medizinische Welt* 36, pp. 871–874 (cit. on p. 186).

[Watt and Breyer-Brandwijk, 1962] J. M. Watt and M. G. Breyer-Brandwijk (1962). *The medicinal and poisonous plants of southern and eastern Africa*. 2nd. Edinburgh and London: E&S Livingstone, Ltd (cit. on pp. 338–339).

[Wattanapitayakul, Chularojmontri, and Srichirat, 2005] S. K. Wattanapitayakul, L. Chularojmontri, and S. Srichirat (2005). "Effects of Pueraria mirifica on vascular function of ovariectomized rabbits". *Journal of the Medical Association of Thailand* 88 (Supplement 1), S21–S29 (cit. on p. 383).

[webmd, 2009] webmd (2009). *Kudzu*. URL: http://www.m.webmd.com/vitamins/ai/ingredientmono-750/kudzu/source-3 (cit. on pp. 19, 310–313).

[D. E. Webster et al., 2011] D. E. Webster et al. (2011). "Opioidergicmechanisms underlying the actions of Vitex agnus-castus L". *Biochemical Pharmacology* 81.1, pp. 170–177 (cit. on p. 214).

[Weckesser et al., 2007] S. Weckesser et al. (2007). "Screening of plant extracts for antimicrobial activity against bacteria and yeasts with dermatological relevance". *Phytomedicine* 14.7-8, pp. 508–516 (cit. on p. 408).

[P. Wei, M. Liu, and Y. Chen, 2012] P. Wei, M. Liu, Y. Chen, et al. (2012). "Systematic review of soy isoflavone supplements on osteoporosis in women". *Asian Pacific Journal of Tropical Medicine* 5.3, pp. 243–248. DOI: 10.1016/S1995-7645(12)60033-9 (cit. on p. 58).

[Z. M. Wei, 1985] Z. M. Wei (1985). "A study on the electrophysiology in antiarrhythmia effect of Angelica sinensis". *Journal of Beijing College of Traditional Chinese Medicine* 8, p. 40 (cit. on p. 271).

[Weiss, 1988] R. F. Weiss (1988). *Herbal Medicine*. Beaconsfield, England: Beaconsfield Publishers, p. 4647 (cit. on p. 111).

[Weisser et al., 1996] H. Weisser et al. (1996). "Effects of the Sabal serrulata extract IDS 89 and its subfractions on 5alpha-reductase activity in human benign prostatic hyperplasia". *Prostate* 28.5, pp. 300–306 (cit. on p. 418).

[Wenzel, Stolte, and Soose, 1996] S. Wenzel, H. Stolte, and M. Soose (1996). "Effects of silibinin and antioxidants on high glucose-induced alterations of fibronectin turnover in human mesangial cell cultures". *Journal of Pharmacology and Experimental Therapeutics* 279, pp. 1520–1526 (cit. on p. 366).

[A. M. Whelan, Jurgens, and Bowles, 2006] A. M. Whelan, T. M. Jurgens, and S. K. Bowles (2006). "Natural health products in the prevention and treatment of osteoporosis: systematic review of randomized controlled trials". *Annals of Pharmacotherapy* 40.5, pp. 836–849 (cit. on p. 58).

[White et al., 2010] R. W. deVere White et al. (2010). "Effects of a high dose, aglycone-rich soy extract on prostate-specific antigen and serum isoflavone concentrations in men with localized prostate cancer". *Nutrition and Cancer* 62.8, pp. 1036–1043 (cit. on p. 435).

[Whiting, Clouston, and Kerlin, 2002] P. W. Whiting, A. Clouston, and P. Kerlin (2002). "Black cohosh and other herbal remedies associated with acute hepatitis". *The Medical Journal of Australia* 177.8, pp. 440–443 (cit. on p. 189).

[WHO, 1948] WHO (1948). *WHO definition of Health*. URL: http://www.who.int/about/definition/en/print.html (cit. on p. 27).

[WHO, 1989] — (1989). "Medicinal plants in China. Manila". *WHO Regional Publications*. Western Pacific Series 2 (cit. on p. 99).

[WHO, 1999a] — (1999a). *WHO Monographs on Selected Medicinal Plants. Fructus Silybi Mariae*. Vol. 1. Geneva, Switzerland: World Health Organization, pp. 300–316 (cit. on pp. 356–357, 359, 372, 379).

[WHO, 1999b] — (1999b). *Radix Ginseng*. URL: http://apps.who.int/medicinedocs/en/d/Js2200e/19.html (cit. on p. 108).

[WHO, 1999c] — (1999c). *WHO Monographs on Selected Medicinal Plants. Radix ginseng*. Version 1. World Health Organization. URL: http://apps.who.int/medicinedocs/en/d/Js2200e. Geneva, Switzerland (cit. on pp. 77, 79–80, 88–90, 98, 137–138, 145, 150, 153).

[WHO, 2004] — (2004). *Radix Angelicae Sinensis*. URL: http://apps.who.int/medicinedocs/en/d/Js4927e/5.html (cit. on p. 274).

[Wichtl and N. Bisset, 1994] M Wichtl and NG Bisset, eds. (1994). *Herbal Drugs and Phytopharmaceuticals*. Stuttgart, Germany: Medpharm Scientific Publishers, p. 7072 (cit. on pp. 108–109, 111, 117, 120–121, 123).

[Wikström, 1956] A. Wikström (1956). "La structure d'un isomère du raffinose isolé des racines de l' Angélica archangélica L. subsp. norvégica (Rupr.) Nordh". *Acta Chemica Scandinavica* 10, pp. 1199–1207 (cit. on p. 112).

[Wilcox and Galloway, 1961] E. B. Wilcox and L. S. Galloway (1961). "Serum and liver cholesterol, total lipids and lipid phosphorus levels of rats under various dietary regimes". *American Journal of Clinical Nutrition* (9), pp. 236–243 (cit. on p. 67).

[Wilkins, 2006] M. R. Wilkins (2006). "Working Party on Cannabis and Cannabis -based Medicines. Cannabis and Cannabis -based medicines: potential benefits and risks to health". *Clinical Medicine* 6.1, pp. 16–18 (cit. on pp. 338, 346).

[A. Williams and Barry, 1989] A. Williams and B. W. Barry (1989). "Essential oils as novel human skin penetration enhancers". *International Journal of Pharmaceutics* 57, R7–R9 (cit. on p. 123).

[E. A. Williams and Menary, 1988] E. A. Williams and R. C. Menary (1988). "Polyphenolic inhibitors of alpha-acid oxidase activity". *Phytochemistry* 27, pp. 35–39 (cit. on p. 304).

[Wilsey, Marcotte, and Tsodikov, 2008] B. Wilsey, T. Marcotte, and A. Tsodikov (2008). "A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain". *The Journal of Pain* 9.6, pp. 506–521 (cit. on p. 343).

[Wilt et al., 1998] T. Wilt et al. (1998). "Saw palmetto extracts for treatment of benign prostatic hyperplasia". *Journal of the American Medical Association* 280.18, pp. 1604–1609 (cit. on p. 419).

[Winston, 1999] D. Winston (1999). *Saw Palmetto for Men & Women*. Pownal,VT: Storey Books (cit. on p. 415).

[Winterfeld et al., 2012] U. Winterfeld et al. (2012). "Management of deficient lactation in Switzerland and Canada: A survey of midwives' current practices". *Breastfeeding Medicine* 7, pp. 317–8 (cit. on p. 157).

[Winterhoff et al., 2003] H. Winterhoff et al. (2003). "Cimicifuga extract BNO 1055: reduction of hot flushes and hints on antidepressant activity". *Maturitas* 44 (Supplement 1), S51–S58 (cit. on pp. 162, 170).

[WMD, 2009a] WMD (2009a). *Borage*. WebMD. URL: http://www.webmd.com/vitamins-supplements/ingredientmono-596-borage.aspx?activeingredientid=596&activeingredientname=borage (cit. on pp. 13, 191, 201–204).

[WMD, 2009b] — (2009b). *Caraway*. Webmd.com. URL: http://www.webmd.com/vitamins-supplements/ingredientmono-204-CARAWAY.aspx?activeIngredientId=204&activeIngredientName=CARAWAY&source=3 (cit. on p. 211).

[WMD, 2009c] — (2009c). *Marijuana*. Webmd.com. URL: http://www.webmd.com/vitamins-supplements/ingredientmono-947-MARIJUANA.aspx?activeIngredientId=947&activeIngredientName=MARIJUANA&source=3 (cit. on pp. 336, 345, 347–350).

[Wohlfart, Hänsel, and H. Schmidt, 1983] R. Wohlfart, R. Hänsel, and H. Schmidt (1983). "The sedative-hypnotic action of hops. 4. Pharmacology of the hop substance 2-methyl-3-buten-2-ol (in German)". *Planta Medica* 48, pp. 120–123 (cit. on p. 302).

[Wojcikowski et al., 2008] K. Wojcikowski et al. (2008). "Dioscorea villosa (wild yam) induces chronic kidney injury via pro-fibrotic pathways". *Food and Chemical Toxicology* 46.9, pp. 3122–3131 (cit. on pp. 450–451).

[C. Wong, 2015] C. Wong (2015). *The benefits of alfalfa*. URL: http://altmedicine.about.com/od/herbsupplementguide/a/Alfalfa.htm (cit. on pp. 63, 269, 273–274).

[W. W. Wong, R. D. Lewis, and Steinberg, 2009] W. W. Wong, R. D. Lewis, and F. M. Steinberg (2009). "Soy isoflavone supplementation and bone mineral density in menopausal women: a 2-y multicenter clinical trial". *American Journal of Clinical Nutrition* 90.5, pp. 1433–1439 (cit. on p. 440).

[Woo, E. Lau, and S. C. Ho, 2003] J. Woo, E. Lau, and S. C. Ho (2003). "Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause". *Menopause* 10.4, pp. 352–361 (cit. on p. 307).

[Woolridge et al., 2005] E. Woolridge et al. (2005). "Cannabis use in HIV for pain and other medical symptoms". *Journal of Pain and Symptom Management* 29.4, pp. 358–367 (cit. on p. 343).

[Worthington-Roberts and Breskin, 1983] B. Worthington-Roberts and M. Breskin (1983). "Fads or facts? A pharmacist's guide to controversial nutrition products"." *Journal of the American Pharmacists Association* 23.8, pp. 30–42 (cit. on p. 67).

[Wretensjö and Svensson, 1990] I. Wretensjö and L. Svensson (1990). "Gas chromatographic-mass spectrometric identification of the fatty acids in borage oil using the picolinyl ester derivatives". *Journal of Chromatography* 521, pp. 89–97 (cit. on p. 193).

[C. I. Wright et al., 2007] C. I. Wright et al. (2007). "Herbal medicines as diuretics: a review of the scientific evidence". *Journal of Ethnopharmacology* 114.1, pp. 1–31 (cit. on p. 281).

[S. Wright, M. Ware, and G. Guy, 2006] S. Wright, M. Ware, and G. Guy (2006). "The use of a cannabis-based medicine ( Sativex ) in the treatment of pain caused by rheumatoid arthritis." *Rheumatology: Oxford Journals | Medicine & Health* 45.6, p. 781 (cit. on p. 343).

[D. F. Wu, 1988] D. F. Wu (1988). "Sodium ferulate alleviates prednisolone-induced liver toxicity in mice". *Acta Pharmaceutica Sinica* 30, pp. 801–805 (cit. on p. 270).

[D. F. Wu and Peng, 1995] D. F. Wu and R. X. Peng (1995). "The effect of sodium ferulate on bromobenzene-induced liver injury in mice". *Zhongguo Yaoxue Zazhi* 30, pp. 597–599 (cit. on p. 270).

[J. W. Wu, L. C. Lin, and T. H. Tsai, 2009] J. W. Wu, L. C. Lin, and T. H. Tsai (2009). "Drug-drug interactions of silymarin on the perspective of pharmacokinetics". *Journal of Ethnopharmacology* 121.2, pp. 185–193 (cit. on p. 374).

[W. H. Wu et al., 2005] W. H. Wu et al. (2005). "Estrogenic effect of yam ingestion in healthy postmenopausal women". *Journal of the American College of Nutrition* 24.4, pp. 235–243 (cit. on pp. 449–450).

[Wüthrich and Hofer, 1984] B. Wüthrich and T. Hofer (1984). "Food allergy: the celery-mugwort-spice syndrome. Association with mango allergy [in German]?" *Deutsche Medizinische Wochenschrift* 109.25, pp. 981–986 (cit. on p. 283).

[Wuttke, J. Gorkow, and Jarry, 1995] W. Wuttke, J. Gorkow, and H. Jarry (1995). *Phytopharmaka in Forschung and klinischer Anwendung. Dopaminergic compounds in Vitex agnus castus*. Ed. by D Loew and N Rietbrock. Darmstadt: Steinkopff Verlag, pp. 81–91 (cit. on p. 220).

[Wuttke, Jarry, et al., 2003] W. Wuttke, H. Jarry, et al. (2003). "Chaste tree (Vitex agnus-castus)pharmacology and clinical indications". *Phytomedicine* 10.4, pp. 348–357 (cit. on p. 214).

[Wuttke, Seidlová-Wuttke, and C. Gorkow, 2003] W. Wuttke, D. Seidlová-Wuttke, and C. Gorkow (2003). "The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers". *Maturitas* 44 (Supplement 1), S67–S77 (cit. on p. 172).

[Xie, R. C. Lin, and Antony, 1994] C. I. Xie, R. C. Lin, and V. Antony (1994). "Daidzin, an antioxidant isoflavonoid, decreases blood alcohol levels and shortens sleep time induced by ethanol intoxication". *Alcoholism: Clinical and Experimental Research* 18.6, pp. 1443–1447 (cit. on p. 307).

[Xiong, 1982] X. Xiong (1982). "The protective effect of Radix Angelicae Sinensis against acute liver damage by D-galactosamine in rats: a histochemical study". *Wu-han I Hsueh Yuan Hsueh Pao* 11, pp. 68–72 (cit. on p. 270).

[B. J. Xu, Y. N. Zheng, and C. K. Sung, 2005] B. J. Xu, Y. N. Zheng, and C. K. Sung (2005). "Natural medicines for alcoholism treatment: a review". *Drug and Alcohol Review* 24.6, pp. 525–536 (cit. on pp. 306–307).

[L. N. Xu, 1990] L. N. Xu (1990). "Effect of sodium ferulate on arachidonic acid metabolism". *Acta Pharmaceutica Sinica* 25, p. 412 (cit. on p. 271).

[L. X. Xu, A. R. Liu, and X. Q. Zhang, 1987] L. X. Xu, A. R. Liu, and X. Q. Zhang (1987). "Differential pulse polarographic determination of flavonoids in Pueraria lobata [in Chinese]". *Yao Xue Xue Bao* 22.3, pp. 208–211 (cit. on pp. 281, 284, 306).

[Xue, D. Z. Li, and Q. Z. Wang, 2009] C. Y. Xue, D. Z. Li, and Q. Z. Wang (2009). "Application of LightCycler polymerase chain reaction and melting curve analysis to the authentication of the traditional Chinese medicinal plant Cimicifuga foetida". *Planta Medica* 75.8, pp. 873–875 (cit. on p. 161).

[Yadav, Moorthy, and Baquer, 2004] U. C. Yadav, K. Moorthy, and N. Z. Baquer (2004). "Effects of sodium-orthovanadate and Trigonella foenum-graecum seeds on hepatic and renal lipogenic enzymes and lipid profile during alloxan diabetes". *Journal of Biosciences* 29, pp. 81–91 (cit. on p. 289).

[Yagi, Shindo, and Masahiro, 2007] N. Yagi, M. Shindo, and A. Masahiro (2007). "Skin-lightening and antiaging cosmetics containing Pueraria mirifica rhizome extracts [in Japanese]". *Jpn Kokai Tokkyo Koho*. US patent application JP 2007-126395 (cit. on pp. 381, 387).

[K. Yamamoto et al., 2000] K. Yamamoto et al. (2000). "Suppression of cyclooxygenase-2 gene transcription by humulon of beer hop extract studied with reference to glucocorticoid". *FEBS Lett* 465, pp. 103–106 (cit. on p. 303).

[M. Yamamoto, 1977] M. Yamamoto (1977). "Stimulatory effect of Panax ginseng principals on DNA and protein synthesis in rat testes". *Arzneimittel-Forschung* 27, pp. 1404–1405 (cit. on p. 102).

[Yan and Spitznagel, 2009] L. Yan and E. L. Spitznagel (2009). "Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis". *American Journal of Clinical Nutrition* 89.4, pp. 1155–1163 (cit. on p. 435).

[Yan, Spitznagel, and Bosland, 2010] L. Yan, E. L. Spitznagel, and M. C. Bosland (2010). "Soy consumption and colorectal cancer risk in humans: a meta-analysis". *Cancer Epidemiology, Biomarkers & Prevention* 19.1, pp. 148–158 (cit. on p. 436).

[C. L. Yang et al., 2009] C. L. Yang et al. (2009). "Identification of the bioactive constituent and its mechanisms of action in mediating the anti-inflammatory effects of black cohosh and related Cimicifuga species on human primary blood macrophages". *Journal of Medicinal Chemistry* 52.21, pp. 6707–6715 (cit. on p. 175).

[Q. Yang et al., 2002] Q. Yang et al. (2002). "Effect of Angelica sinensis on the proliferation of human bone cells". *Clinica Chimica Acta* 324.1-2, pp. 89–97 (cit. on pp. 259, 269).

[Z. W. Yang, 1986] Z. W. Yang (1986). *Pharmacology and applications of Chinese materia medica*. Vol. 1: *Renshen*. Ed. by HM Chang and PPH But. Singapore: World Scientific Publishing, pp. 17–31 (cit. on p. 101).

[Yasue et al., 2007] H. Yasue et al. (2007). "Severe hypokalemia, rhabdomyolysis, muscle paralysis, and respiratory impairment in a hypertensive patient taking herbal medicines containing licorice". *Internal Medicine* 46.9, pp. 575–578 (cit. on pp. 325, 334).

[Yasukawa, Takeuchi, and Takido, 1995] K. Yasukawa, M. Takeuchi, and M. Takido (1995). "Humulon, a bitter in the hop, inhibits tumor promotion by 12-O- tetradecanoylphorbol-13-acetate in two-stage carcinogenesis in mouse skin". *Oncology* 52, pp. 156–158 (cit. on p. 303).

[Yasukawa, A. Yamaguchi, et al., 1993] K. Yasukawa, A. Yamaguchi, et al. (1993). "Inhibitory effect of edible plant extracts on 12-O-tetradecanoylphorbol-13-acetate-induced ear edema in mice". *Phytotherapy Research* 7, pp. 185–189 (cit. on p. 303).

[Yazulla, 2008] S. Yazulla (2008). "Endocannabinoids in the retina: from marijuana to neuroprotection". *Progress in Retinal and Eye Research* 27.5, pp. 501–526 (cit. on p. 341).

[Yeu and Grostern, 2007] E. Yeu and R. Grostern (2007). "Saw palmetto and intraoperative floppy-iris syndrome". *Journal of Cataract & Refractive Surgery* 33.5, pp. 927–928 (cit. on p. 423).

[Yilmazer, Stevens, and Buhler, 2001] M. Yilmazer, J. F. Stevens, and D. R. Buhler (2001). "In vitro glucuronidation of xanthohumol, a flavonoid in hop and beer, by rat and human liver microsomes". *FEBS Lett* 491, pp. 252–256 (cit. on p. 301).

[Yilmazer, Stevens, Deinzer, et al., 2001] M. Yilmazer, J. F. Stevens, M. L. Deinzer, et al. (2001). "In vitro biotransformation of xanthohumol, a flavonoid from hops ( Humulus lupulus ), by rat liver microsomes". *Drug Metabolism and Disposition* 29, pp. 223–231 (cit. on p. 301).

[Yin, 1980] Z. Z. Yin (1980). "The effect of danggui (Angelica sinensis) and its ingredient ferulic acid on rat platelet aggregation and release of 5-HT". *Acta Pharmaceutica Sinica* 15, p. 321 (cit. on p. 271).

[Yinglu et al., 2009] F. Yinglu et al. (2009). "A new way: alleviating postembolization syndrome following transcatheter arterial chemoembolization". *Journal of Alternative and Complementary Medicine* 15.2, pp. 175–181 (cit. on pp. 81, 139).

[Yonezawa, Katoh, and Takeda, 1985] M. Yonezawa, N. Katoh, and A. Takeda (1985). "Restoration of radiation injury by ginseng. IV. Stimulation of recoveries in CFUs and megakaryocyte counts related to the prevention of occult blood appearance in X-irradiated mice". *Journal of Radiation Research* 26, pp. 436–442 (cit. on p. 99).

[Youngken, 1950] H. W. Youngken (1950). *Textbook of pharmacognosy*. 6th ed. Philadelphia, PA: Blakiston (cit. on p. 126).

[Yue and Jansson, 2001] Q. Y. Yue and K. Jansson (2001). "Herbal drug curbicin and anticoagulant effect with and without warfarin: possibly related to the vitamin E component". *Journal of the American Geriatrics Society* 49.6, p. 838 (cit. on p. 424).

[T. K. Yun, Y. S. Yun, and I. W. Han, 1980] T. K. Yun, Y. S. Yun, and I. W. Han, eds. (1980). *An experimental study on tumor inhibitory effect of red ginseng in mice and rats exposed to various chemical carcinogens*. Proceedings of the third International Ginseng Symposium. Seoul: Korean Ginseng Research Institute, pp. 87–113 (cit. on p. 100).

[T. K. Yun, S. Zheng, and S. Y. Choi, 2010] T. K. Yun, S. Zheng, and S. Y. Choi (2010). "Non-organ-specific preventive effect of long-term administration of Korean red ginseng extract on incidence of human cancers". *Journal of Medicinal Food* 13.3, pp. 489–494 (cit. on pp. 81, 139).

[Zaidi, Kadota, and Tezuka, 2007] S. F. Zaidi, S. Kadota, and Y. Tezuka (2007). "Inhibition on human liver cytochrome P450 3A4 by constituents of fennel (Foeniculum vulgare): identification and characterization of a mechanism-based inactivator". *Journal of Agricultural and Food Chemistry* 55.25, pp. 10162–10167 (cit. on p. 284).

[J. P. Zajicek, Sanders, and D. E. Wright, 2005] J. P. Zajicek, H. P. Sanders, and D. E. Wright (2005). "Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up". *Journal of Neurology, Neurosurgery & Psychiatry* 76.12, pp. 1664–1669 (cit. on pp. 342, 344, 346).

[J. Zajicek et al., 2003] J. Zajicek et al. (2003). "Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial". *Lancet* 362.9395, pp. 1517–1526 (cit. on p. 342).

[Zava, Dollbaum, and Blen, 1998] D. T. Zava, C. M. Dollbaum, and M. Blen (1998). "Estrogen and progestin bioactivity of foods, herbs, and spices." *Proceedings of the Society for Experimental Biology and Medicine* 217, pp. 369–378. eprint: http://www.ncbi.nlm.nih.gov/pubmed/9492350 (cit. on pp. 185–186).

[Zerega et al., 2002] N. J. Zerega et al. (2002). "Using amplified fragment length polymorphisms (AFLP) to identify black cohosh ( Actaea racemosa )". *Economic Botany* 56.2, pp. 154–164 (cit. on p. 161).

[Zhan et al., 2005] G. L. Zhan et al. (2005). "Effects of marijuana on aqueous humor dynamics in a glaucoma patient". *Journal of Glaucoma* 14.2, pp. 175–177 (cit. on p. 341).

[J. Q. Zhang, Mao, and Y. P. Zhou, 1993] J. Q. Zhang, X. M. Mao, and Y. P. Zhou (1993). "Effects of silybin on red blood cell sorbitol and nerve conduction velocity in diabetic patients [in Chinese]". *Zhongguo Zhong Xi Yi Jie He Za Zhi* 13.12, pp. 725–726, 708 (cit. on p. 361).

[J. S. Zhang, 1987] J. S. Zhang (1987). "Modification of radiation response in mice by fractionated extracts of Panax ginseng". *Radiation Research* 112, pp. 156–163 (cit. on p. 99).

[L. Zhang et al., 2005] L. Zhang et al. (2005). "Efficacy of cranberry juice on Helicobacter pylori infection: a double-blind, randomized placebo-controlled trial". *Helicobacter* 10.2, pp. 139–145 (cit. on p. 233).

[H. Zhao et al., 2008] H. Zhao et al. (2008). "Effect of SBD.4A a defined multicomponent preparation of Angelica sinensis in periodontal regeneration models". *Phytotherapy Research* 22.7, pp. 923–928 (cit. on p. 259).

[S. P. Zhao and Y. Z. Zhang, 1985] S. P. Zhao and Y. Z. Zhang (1985). "Quantitative TLC-densitometry of isoflavones in Pueraria lobata (Willd) Ohwi [in Chinese]". *Yao Xue Xue Bao* 20.3, pp. 203–208 (cit. on pp. 112–113, 306).

[C. D. Zheng and Min, 2008] C. D. Zheng and S. Min (2008). "Cardioprotection of Shenfu Injection against myocardial ischemia/reperfusion injury in open heart surgery". *Chinese Journal of Integrative Medicine* 14.1, pp. 10–16 (cit. on pp. 82, 140).

[Y. Zhou and A. S. Lee, 1998] Y. Zhou and A. S. Lee (1998). "Mechanism for the suppression of the mammalian stress response by genistein, and anticancer phytoestrogen from soy". *Journal of the National Cancer Institute* 90.5, pp. 381–388 (cit. on p. 436).

[Y. Zhou, X. Su, et al., 1995] Y. Zhou, X. Su, et al. (1995). "Comparative study on pharmacological effects of various species of Pueraria [in Chinese]". *Zhongguo Zhong Yao Za Zhi* 20.10, pp. 619–621, 640 (cit. on pp. 308, 313).

[D. P. Q. Zhu, 1987] D. P. Q. Zhu (1987). "Dong quai". *American Journal of Chinese Medicine* 15, pp. 117–125 (cit. on pp. 269–270, 273–274).

[Zi, Feyes, and R. Agarwal, 1998] X. Zi, D. K. Feyes, and R. Agarwal (1998). "Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins". *Clinical Cancer Research* 4, pp. 1055–1064 (cit. on p. 365).

[Zi, Grasso, et al., 1998] X. Zi, A. W. Grasso, et al. (1998). "A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells". *Cancer Research* 58, pp. 1920–1929 (cit. on p. 365).

[Zi, Mukhtar, and R. Agarwal, 1997] X. Zi, H. Mukhtar, and R. Agarwal (1997). "Novel cancer chemopreventive effects of a flavonoid antioxidant silymarin: inhibition of mRNA expression of an endogenous tumor promoter TNF alpha". *Biochemical and Biophysical Research Communications* 239, pp. 334–339 (cit. on p. 366).

[Ziboh and Fletcher, 1992] V. A. Ziboh and M. P. Fletcher (1992). "Dose-response effects of dietary gamma-linolenic acid-enriched oils on human polymorphonuclear-neutrophil biosynthesis of leukotriene B4". *American Journal of Clinical Nutrition* 55, pp. 39–45 (cit. on p. 195).

[Ziboh, Naguwa, and Vang, 2004] V. A. Ziboh, S. Naguwa, and K. Vang (2004). "Suppression of leukotriene B4 generation by ex-vivo neutrophils isolated from asthma patients on dietary supplementation with gammalinolenic acid-containing borage oil: possible implication in asthma." *Clinical and Developmental Immunology* 11, pp. 13–21 (cit. on pp. 192, 197).

[Zierau et al., 2002] O. Zierau et al. (2002). "Antiestrogenic activities of Cimicifuga racemosa extracts." *Journal of Steroid Biochemistry and Molecular Biology* 80, pp. 125–130. eprint: http://www.ncbi.nlm.nih.gov/pubmed/11867271 (cit. on p. 186).

[Zima et al., 1998] T. Zima et al. (1998). "The effect of silibinin on experimental cyclosporine nephrotoxicity". *Renal Failure* 20, pp. 471–479 (cit. on p. 365).

[Zimmermann et al., 2010] R. Zimmermann et al. (2010). "Coagulation activation and fluid retention associated with the use of black cohosh: A case study". *Climacteric* 13.2, pp. 187–191 (cit. on p. 190).

[Zschocke et al., 1998] S. Zschocke et al. (1998). "Comparative study of roots of Angelica sinensis and related Umbelliferous drugs by thin layer chromatography, high-performance liquid chromatography, and liquid chromatography-mass spectrometry". *Phytochemical Analysis* 9.6, pp. 283–290 (cit. on p. 257).

[Zurier, Rossetti, and E. W. Jacobson, 1996] R. B. Zurier, R. G. Rossetti, and E. W. Jacobson (1996). "Gamma-linolenic acid treatment of rheumatoid arthritis. A randomized, placebo-controlled trial". *Arthritis & Rheumatism* 39, pp. 1808–1817 (cit. on p. 196).

# Index of Names

## B

## C

## D



## E



## F

## G

## H

# I



# J

## K



## L

## M



## N

## O



## P



## Q

## R



## S

## T



## V



## W

## X



## Y

# Index of Side-Effects

## M



## R



## S

# Index of Interactions

## L

Liquorice



## M

Milk Thistle

## S

# General Index

## P



## W