Al Azhar University-Gaza **Faculty of Pharmacy**

Manual of Phytochemistry (1)

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Contents

Course Objectives

1- Current updated information of the biosynthetic pathways of the acetate malonate and shikimic acid pathways

2-Origin and isolation / identification methods of bioactive substances belonging to these pathways

3-Therapeutic and toxicological activities of these substances

4- Therapeutic application in pharmacy & home remedies

- **Intended Learning outcomes**

A) Knowledge and understanding

A1) To know the potentially useful medicinal plants of these pathways

A2) To know the importance and value of ethno pharmacology in drug discovery

A3) To study the biosynthesis of secondary metabolites and major biosynthetic pathways A4) To know the Latin and bilingual (English/Arabic) common names of potentially used medicinal plants

A5) To know examples of commonly misused natural drugs and their semisynthetic/synthetic derivatives /analogues

A6) To use different references to collect the necessary information

B) Intellectual skills (cognitive and analytical)

B1) To know and to correlate the mechanisms, concepts and principles of biosynthetic pathways in plants

B2) To expand the horizon of the organic chemistry

B3) To apply the fundamental principles of organic chemistry and biochemistry for construction of natural products

B4) To predict the physico-chemical properties of phenols

B5) To evaluate the plant/plant, plant/drug and plant/nutrient interactions based on the secondary plant constituents

C) Subject specific skills

C1) Ethnobotanical and ethnopharmacological aspects of plant drugs

C2) To acquire updated information on old known medicinal plants

C3) To be familiar with the supposed actions and uses of herbal ingredients whether or not these have been substantiated by animal and human studies

C4) Chemical, biological and therapeutic activities of plant constituents biosynthesized in the mentioned pathways

D) Transferable skills

D1) Provision of advice on the use of medicinal plants as natural remedies

D2) Provision of advice on the limitations and precautions of commonly used herbal medicines especially by pregnant and lactating mothers

D3) Provision of advice on the activities and toxicities of important addictive drugs of plant origin

Chapter 1

Overview

The use of plants as medicines goes back to **early man**. Certainly the great civilizations of the ancient Chinese, Indians, and North Africans provided **written evidence** of man's creativity in utilizing plants for the treatment of a wide variety of diseases.

The science of Pharmacognosy – **the knowledge of drugs** – grew from the early recorded Herbals to provide a **scientific description of natural materials used in medicine.**

It was not until the 19th century that man began to isolate the active principles of medicinal plants and one particular innovative was the discovery of quinine from Cinchona bark by the French scientists Caventou and Pelletier. Much less is known about the isolation of quinine by J.B. Caventou and J.B. Pelletier. Such discoveries led to an interest in plants from the New World and expeditions scoured the almost impenetrable jungles and forests in the quest for new medicines.

Plants **continue to be used** world-wide for the **treatment** of disease and **novel drug** entities continue to be **developed through research** into their constituents. In the developed countries, high-throughput screening tests are used for bioassay-guided fractionation **leading to the isolation of active principles** that may be developed into clinical agents either as the natural product or a synthetic modification or a synthesized analogue with enhanced clinical action or reduced adverse side effects.

Despite the massive arsenal of clinical agents developed by the pharmaceutical industry there has been an aversion by many members of the public and herbal remedies have proved to be popular as alternative or complementary treatments of disease.

The continuous improvement in chemical technology allowed the isolation, structural characterization and further synthesis of the pharmacologically active plant constituents (secondary metabolites).

Definition

Phytochemistry is a branch of Pharmacognosy, with **chemical** and **biological** characters**, in order to obtain the medicament** by natural or semi-synthesis methods.

The subjects of phytochemistry deals with "the chemical structures of **secondary metabolites**, their metabolism, as well as, their distribution and **biological function.**

Phytochemistry is concerned with the enormous variety of **organic substances** that are elaborated by plants and deals with the chemical structures of these substances, their **biosynthesis**, turnover and **metabolism**, their natural distribution and their biological function. Also in all methods are needed for **separation, purification and identification** of the many different constituents present in the plant.

Phytochemistry has in view the following problems:

1. **Estimate the physical characters of raw material.**
    a. Hygroscopic
    b. Amorphous
2. **Determination of substance contents.**
    a. Ingredient (s)
    b. Active principles
3. **Determination of accompanying substance.**
    a. Other chemical groups than the main one.
    b. Vitamins
    c. Minerals
    d. Amino acids
4. **Choosing the most suitable methods for extraction.**
    a. Soxhlet
    b. Reflux
    c. Hot / Cold
    d. Lipophilic
    e. Hydrophilic
5. **Isolation and purification the principal active.**
    a. Chromatography
    b. Gas-chromatography
    c. HPLC
6. **Determination of the structure.**
    a. NMR
    b. IR
    c. GC/Mass

Chapter 2

Phenolic compounds… Phenolic acids

Phenolic form a vast group of substance that is difficult to define in simple terms. The fundamental structural element that characterizes them is the presence of at least one **aromatic ring substituted by at least one hydroxyl group**, **free or engaged** in **another function: ether**, **ester** or **glycoside**. However, phenolic would include secondary metabolites which possess these structural elements, but which evidently belong to quite different phytochemical groups.

The term "phenolic" is used also to **refer to** a few different **substances made with phenol**, an organic compound. It can describe a type of **resin** used to create various consumer items and is the name given to a class of plant-based chemical compounds. It can also refer to **carbolic acid**, an organic material that has been used in various medical and cleaning products.

Any member within the class of organic phenols may be termed a phenolic compound. Compounds in this class are **simple hydrocarbon** groups, similar to alcohols. Phenolics are varied and found in a range of natural things — from **capsaicin**, the heat agent in chili peppers, to neurotransmitters in the brain, like dopamine.

Phenols are found in many plants, including **fruits** and **vegetables**. While the study of these substances is ongoing, it is known that their **antioxidant properties** — found in **berries** and many types of **tea** — may protect cells from damage and death. These substances are also found in other foods, such as **olive oil**, and in certain dietary nutrients, like **vitamin E**.

Phenolics are able to act as antioxidants in a number of ways. Phenolic hydroxyl groups are good hydrogen donors: hydrogen-donating antioxidants can react with reactive oxygen and reactive nitrogen species in a termination reaction, which breaks the cycle of generation of new radicals.

Phenolic structures often have the potential to strongly interact with proteins, due to their hydrophobic benzenoid rings and hydrogen-bonding potential of the phenolic hydroxyl groups. This gives phenolics the ability to act as antioxidants also by virtue of their capacity to inhibit some enzymes involved in radical generation, such as various cytochrome P450 isoforms, lipoxygenases, cyclooxygenase and xanthine oxidase.

The antioxidant capacity of phenolic compounds is also attributed to their ability to chelate metal ions involved in the production of free radicals. However, **phenolics can act as pro-oxidants** by chelating metals in a manner that maintains or increases their catalytic activity or by reducing metals, thus increasing their ability to form free radicals.

Carbolic acid is another name for phenol or phenic acid, and is a natural substance that is solid, white, and crystalline. It was originally derived from **coal tar**, and has been used in ***soaps***, ***cosmetics***, and ***cleaning agents***.

Main classes of phenolics

Phenolic acids

a. Benzoic acid derivatives
b. Cinnamic acid derivatives

This term is reserve to benzoic and cinnamic acid derivatives only; **also we can call phenolic acids only compounds having C_6-C_1 units,** and include cinnamic derivatives in the larger group of phenylpropanoids.

Phenolic acids derived from benzoic acid C_6-C_1 phenolic acids that are hydroxylated derivatives of benzoic acid are quite common in the Free State, as well as combined into esters or glycosides. Gallic acid and its dimmer (hexa-hydroxy-diphenic acid) are constituents of hydrolysable tannins.

The **4** most common ones are **p-hydroxybenzoic**, **vanillic**, **syringic** and **protocatechuic acids**. They may be found either associated with lignin (i.e. in cell wall formation) or present in alcohol-insoluble fractions of leaves or alternatively in alcohol soluble portions conjugated as glycosides.

Gallic acid is worth mentioning as it is found in many woody plants. This tri-hydroxyl derivative is known to participate in the formation of hydrolysable gallotannins. Its dimeric condensation product (hexahydroxydiphenic acid) and related dilactone, ellagic acid, are common metabolites.

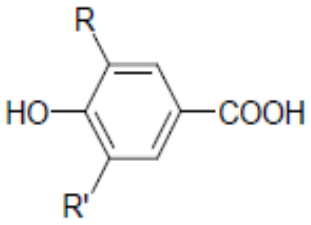
Lignin is the second most abundant biopolymer after cellulose and contributes largely to the impermeability, strength and resistance to enzymatic degradation of lignified cell walls.

Phenolic acids derived from cinnamic acid (**p-coumaric**, **caffeic**, **ferulic**, **sinapic acids**) are very widely distributed; others (o-coumaric, o-ferulic acids) are uncommon. They occur rarely in the Free State except as extraction artifacts, and are very often found esterified.

They can also be amides (tyramine) or combination with sugars: glucose esters, most commonly, or glucose ethers.

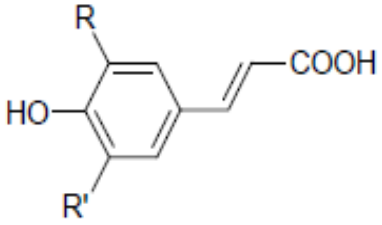
Note also that these acids frequently esterify the hydroxyl groups of many secondary metabolites: flavonoids, anthocyanins, saponins and rarely alkaloids.

Benzoic acid derivatives



R = R' = H; *p*-hydroxybenzoic acid
R = OH, R' = H; protocatechuic acid
R = OCH_3, R' = H; vanillic acid
R = R' = OH; gallic acid
R = R' = OCH_3; syringic acid

Cinnamic acid derivatives

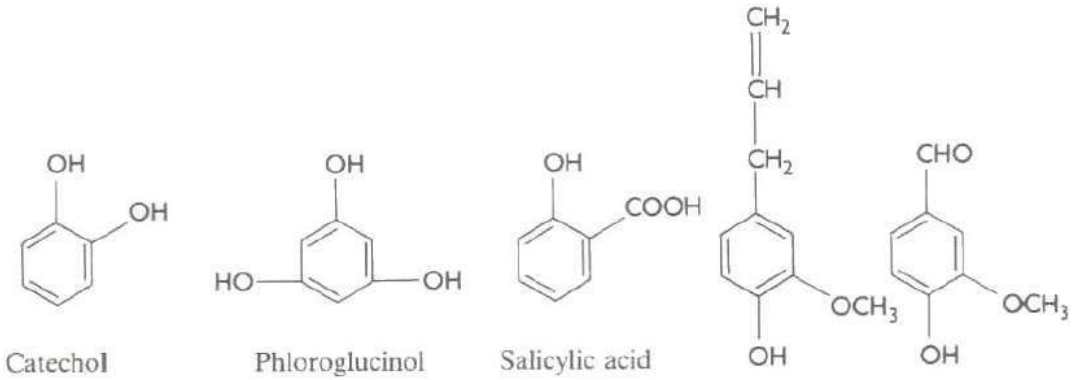


R = R' = H; *p*-coumaric acid
R = OH, R' = H; caffeic acid
R = OCH_3, R' = H; ferulic acid
R = R' = OCH_3; sinapic acid

Simple phenols:

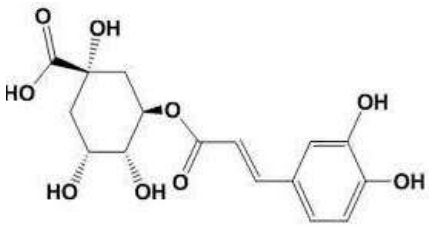
The simple phenols consist of a **singly substituted phenolic ring with alcoholic, aldehydes or carboxylic acid groups**.

These are relatively rare in plants. Phenol itself, **catechol** (a dihydric phenol), resorcinol (a dihydric phenol), **phloroglucinol** (a trihydric phenol) and **pyrogallol** have been reported from relatively few sources. By contrast with the above, hydroquinone is distributed in many families and occurs as arbutin - Hydroquinone-O-β-glucoside.



Phenylpropanoids

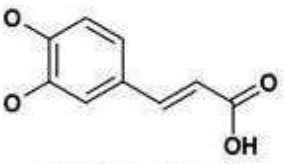
Phenylpropanoids are naturally occurring phenolic compounds having **an aromatic ring to which a three-carbon side chain is attached**. The most widespread are the **hydroxycinnamic acids** and the **4** most common ones are **p-coumaric**, **caffeic**, **ferulic and sinapic acids** that play a essential role in phenolic metabolism.



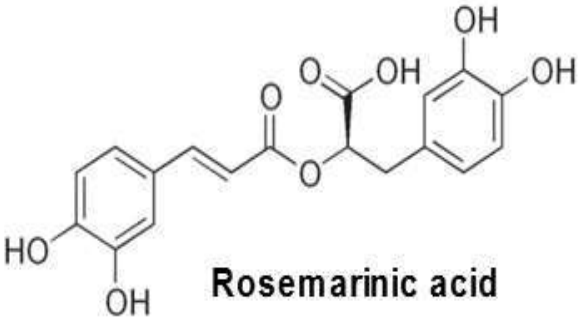
Chlorogenic Acid

Hydroxycinnamic acids usually occur in plants in combined forms as esters.

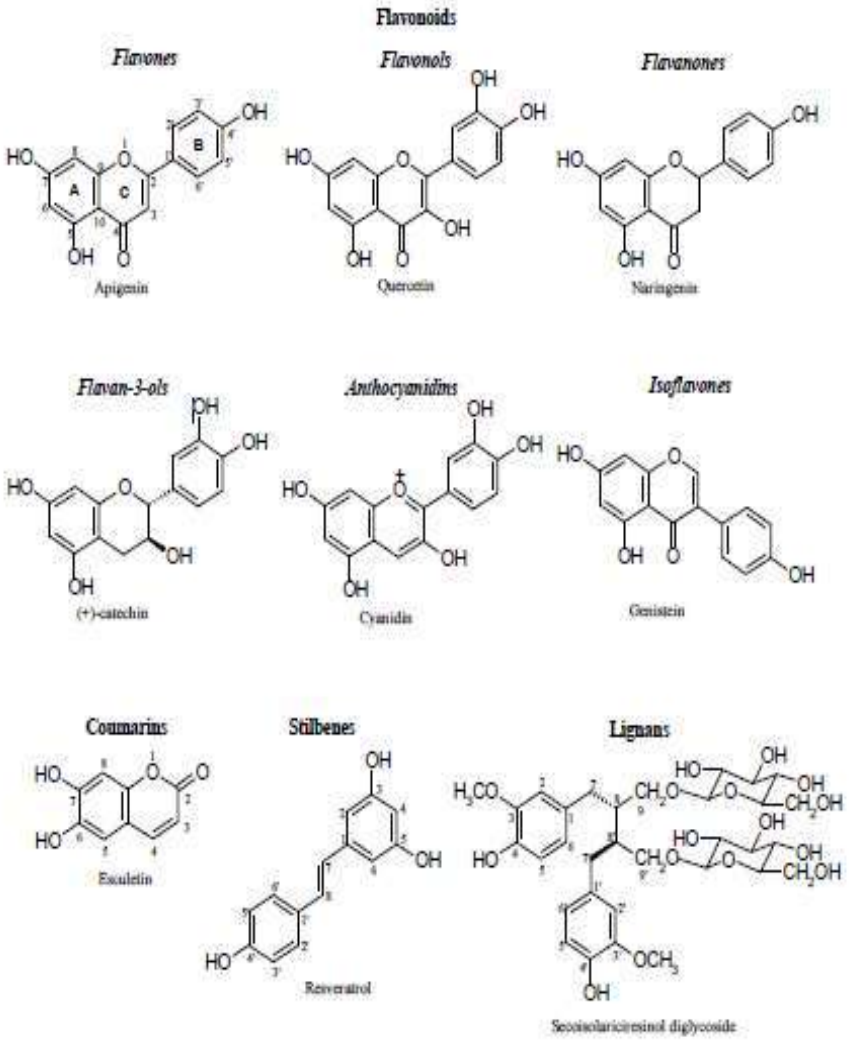
In the pharmaceutical sector, for instance, Caffeic acid derived from *Cyanora scolymus* L. is used to treat digestive disorders. Rosmarinic acid, another phenolic acid derivative from *Rosmarinus officinalis* L. has diuretic activities and antioxidant properties. Moreover, all these compounds show antibacterial, antifungal and antitumor activities.



Caffeic Acid



Rosemarinic acid



Physico-Chemical Properties, Characterization & Extraction

In general, phenols are **soluble in polar organic solvents**; they are soluble in sodium hydroxide and carbonate solutions. Phenolic acids are solubilized by bicarbonates; they can be extracted with organic solvents in slightly acidic conditions. The **glycosides** of these phenolic compounds are classically, **soluble in water.**

All of these compounds are **unstable**. All phenols are **easy oxidized**, especially in alkaline conditions.

Cinnamic derivatives tend to isomerize in aqueous solution under UV.

These compounds are generally **extracted**, preferably from fresh plant material, **with alcohol** or if the extract less lipophylic

substance and **avoid partial esterification** of the phenolic acids, we can make the extraction with an alcohol and water mixture.

The analysis of simple phenolic compounds from a plant is commonly carried out by **TLC or by GC, HPLC**. The TLC solvents are mixtures that contain an acid most of the time (acetic, formic).

The spots are visualized using general reagents for phenols (**ferric chloride, vanillin and HCL, 2,6-dichloroquinone chlorimide in alkaline conditions.**

Separation of the constituents of mixtures can be achieved by classic chromatographic techniques.

Biosynthesis:

Plant phenolic arise from two main aromatization pathways

1. The most common pathway is the one which, via **Shikimic acid**, (synonym: *Ilicium regiosum*) leads from monosaccharide to aromatic amino acid [phenylalanine and tyrosine] then, by **deamination** of this latter, **to cinnamic acids** and their numerous derivatives, including **benzoic acids**, acetophenones, lignans and coumarins.
2. The other pathway begins with **acetate** and **leads to poly-β-ketoesters** of variable length (fatty acids and alcohol's), which afford, by cyclization (Claisen or aldol condensation), products that are often polycyclic, including chromones, isocoumarins, xanthones and quinones.

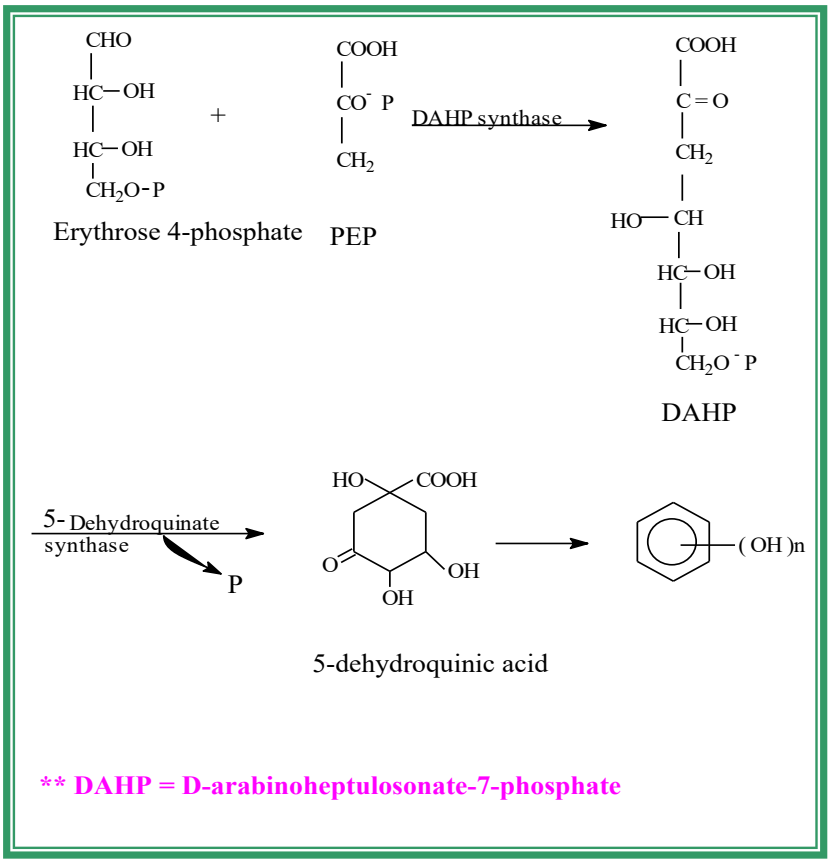
Biosynthetic Origin of the Aromatic Ring [Shikimic Acid Pathway]

Since numerous works and reviews are devoted to this reaction sequence and to the mechanisms involved, we shall only present here a succinct summary of the pathway leading from the product of glycolysis and of the photosynthesis cycle to aromatic amino acids (phenylalanine and tyrosine).

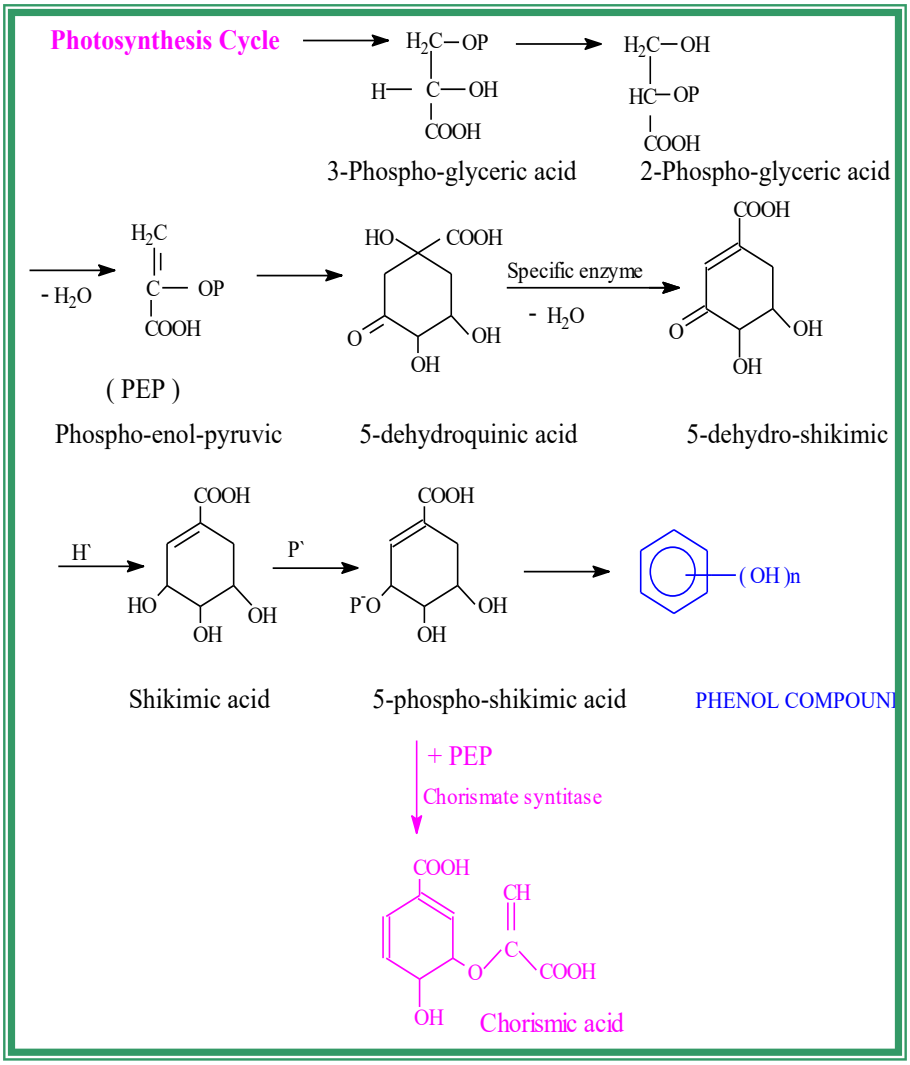
The **first** reaction is the **condensation of phosphoenolpyruvate (PEP) with erythrose 4 phosphate** which **yield** a C_7 compound, 3-deoxy-D-arabinoheptulosonate-7-phosphate (**DAHP**).

The **Cyclization of DAHP to 5-dehydroquinate** is a complex reaction that involves an intermolecular **aldol condensation** subsequent to the elimination of the phosphate group.

An enzyme that forms a transient Schiff base between a lysine residue and the carbonyl group of 5-dehydroquinate, and includes a stereospecific cis elimination of a water molecule catalyzes the dehydration of 5-dehydroquinate.



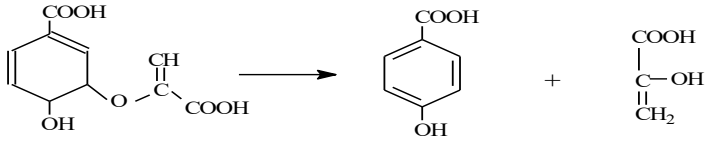
Following the reduction of 5-dehydroshikimate and shikimate phosphorylation, **condensation with another molecule of PEP** yields enol ether, 3-enol-pyruvyl-shikimate-5-phosphate, this leads, via an unusual trans 1,4-elimination, to **chorismate**.



Chorismate acid holds **a key position** in metabolism and has multiple destiny, such as:

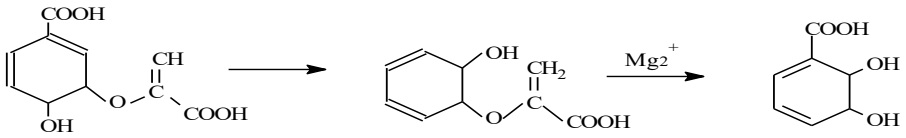
1. Hydroxylation and dehydration to isochorismate, which arise phenol acids in C6-c1 (**salicylic acid**).
2. Claisen-type pericyclic re-arrangement to prephenate. This pathway leads, via phenylpyruvate, to **phenylalanine and tyrosine.**
3. **Amination** and anthranilate formation. (Anthranilate is the required intermediate of the biosynthesis of tryptophan, which is the **starting point of the formation of all indole alkaloids**).
4. **Benzoic acids** and their derivatives formation.

1. Formation of P-hydroxy benzoic acid



Chorismic acid

2. Formation of Salicylic acid



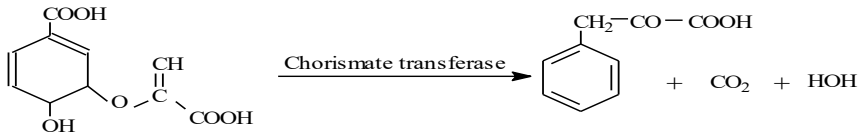
Isochorismic acid

2,3dyhydro-2,3dy(OH) benzoic acid

2,3 Dy(OH) benzoic acid

Salicylic acid

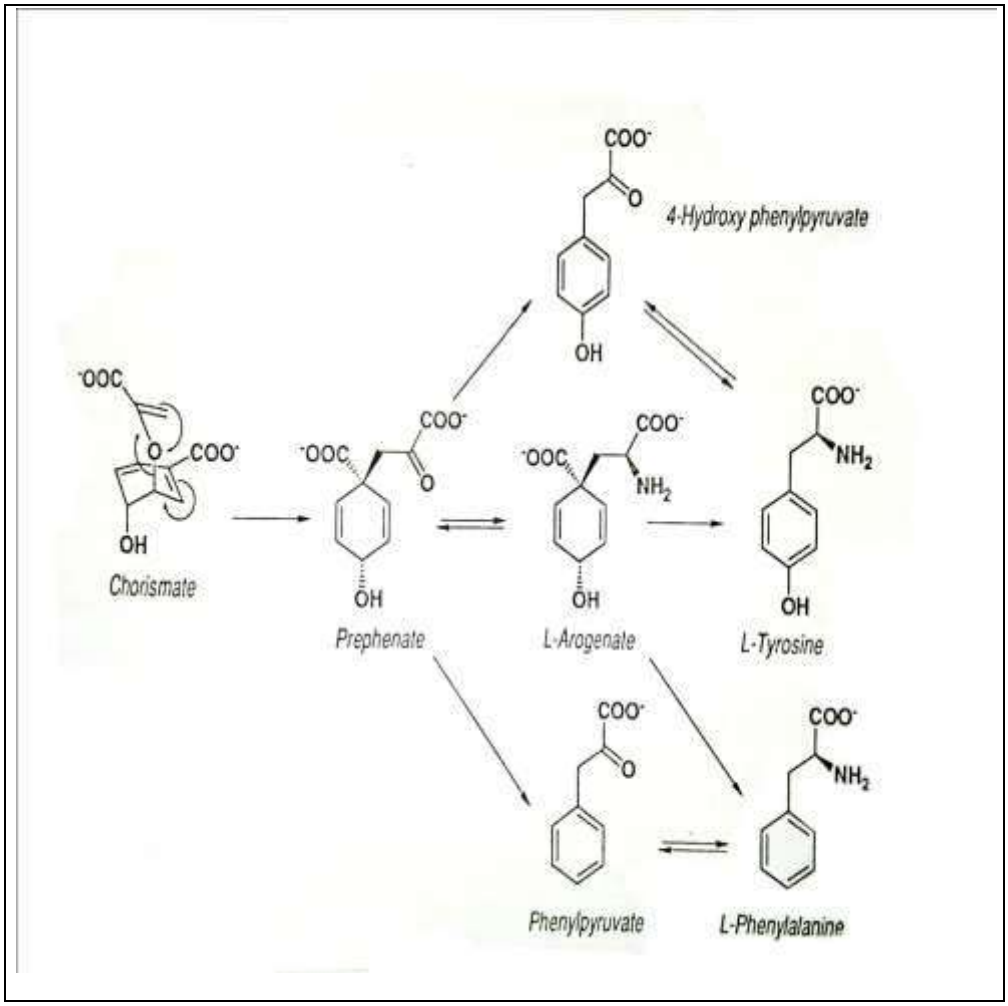
3. Formation of Phenylalanine

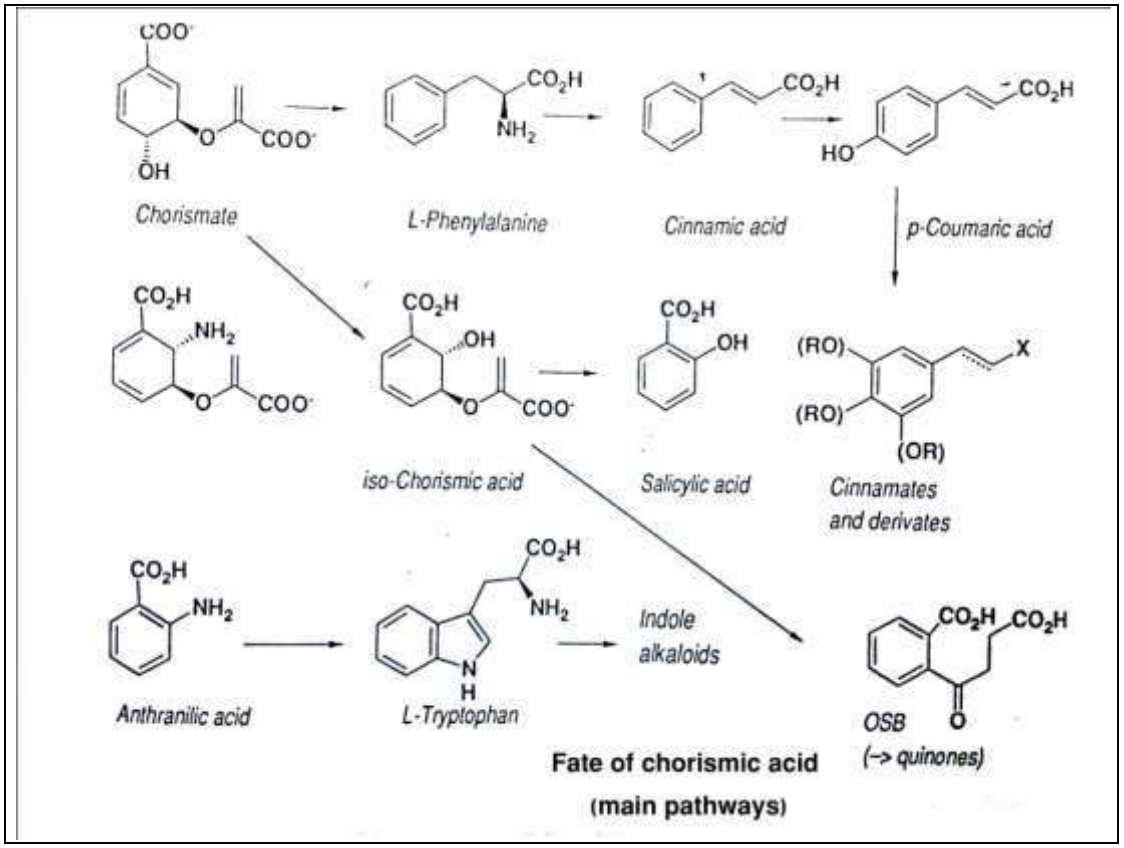


Phenyl pyruvic acid

Phenylalanine

Pericyclic rearrangement of chorismate: formation of aromatic amino acids:




Chorismate
L-Phenylalanine
Cinnamic acid
p-Coumaric acid
iso-Chorismic acid
Salicylic acid
Cinnamates
and derivates
Anthranilic acid
L-Tryptophan
Indole
alkaloids
OSB
(-> quinones)
Fate of chorismic acid
(main pathways)

Pharmacological Applications & Uses

Phenolic compounds have **two main actions**:

The **first** is **urinary antiseptic** properties of arbutin, and

the **second** is **anti-inflammatory** properties of salicylates.

Glycosidic **phenylpropanoids esters have interesting anti-inflammatory** potential activity such as verbascoside, which **inhibit 5-lipoxygenase** in human granulocytes.

Simple phenol-Containing Drugs

Arctostaphylos uva-ursi (L).

Ericaceaeae family

Uva ursi, bearberry, kinnikinnick and manzanita as common names

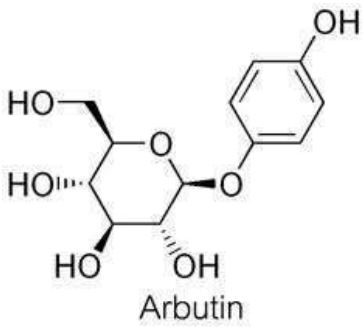
CHARACTERISTICS

The leaves have a **bitter**, **astringent** taste. They are distinguished from the cranberry by the reticulate vein structure and non-glandular spots beneath.

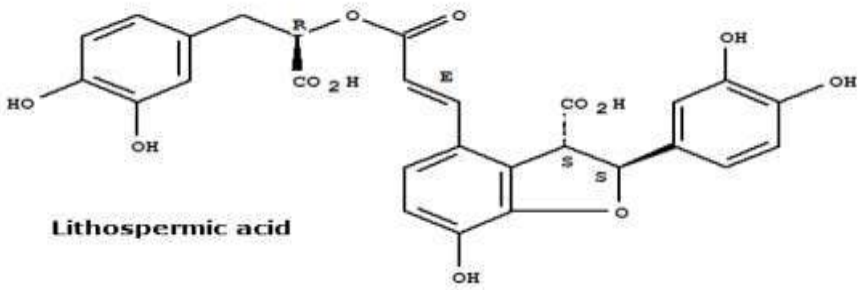
The arbutin content is highest in December and January and also when the leaves are dried rapidly.

PHYTOCHEMICALS

- **Hydroquinone glycosides**: **arbutin**
- **Phenol carboxylic acids:** including **gallic acid, p-coumaric acid, syringic acid, salicylic acid, p hydroxybenzoic acid, ferulic acid, caffeic acid, lithospermic acid** (dimeric caffeic acid)

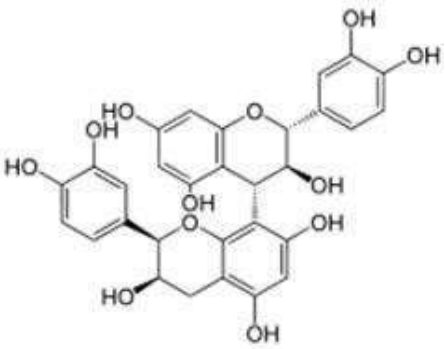


Arbutin

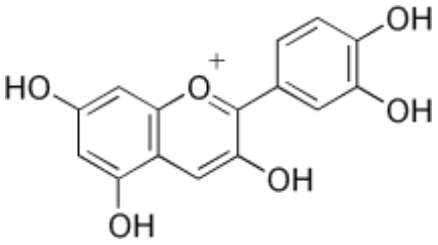


Lithospermic acid

- **Tannins** (15-20%): **Gallo tannins**, **condensed tannins**, chiefly **proanthocyanidins** and their monomerics, including **cyanidin**, delphinidin



Proanthocyanidins



Cyanidin

- **Iridoide**: monotropein (0.025%)
- **Flavonoids**
- **Enzymes:** including a beta-glucosidase (arbutase), and
- **Triterpenes.**

EFFECTS

Uva-Ursi is used for **inflammatory disorders** of the efferent **urinary tract**.

The tannins in Uva-Ursi act as an **astringent**, and the phenol glycoside's and their aglyca have an **antibacterial effect.**

The antimicrobial effect is associated with the aglycon hydroquinone **released from arbutin** (transport form) or arbutin waste products **in the alkaline urine.**

The drug has urine-sterilizing properties that are attributed to bacteriostatic hydroquinones, conjugates of glucuronic acid and sulfuric acid.

The maximum antibacterial effect is expected 3 to 4 hours after administration.

Indication

Patients with urinary tract infection (UTI)

CONTRAINDICATIONS

The drug is contraindicated in **pregnant women**, **nursing** mothers and **children under 12 years of age**.

DRUG INTERACTIONS

Uva-Ursi preparations **should not be administered with any substance that causes acidic urine** since this reduces the antibacterial effect. Because the urine disinfecting effect of the hydroquinones released in the urinary tract only occurs in **an alkali environment**, the simultaneous administration of **medication or food that increase uric acid levels in the bladder is to be avoided**.

OVERDOSAGE

Over dosage can lead to inflammation and irritation of the bladder and urinary tract mucous membranes. Liver damage is conceivable in connection with administration of the drug over extended periods, particularly with children, due to the possible hepatotoxicity of the hydroquinones released.

HOW SUPPLIED

Capsules—150 mg, 455 mg, 505 mg

DAILY DOSE

400mg

Cynara scolymus L

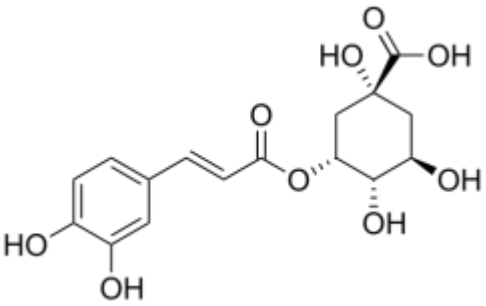
Asteraceae family

Artichoke

DESCRIPTION

Medicinal Parts: The medicinal parts are the dried whole or cut basal leaves and the dried or fresh herb from the artichoke.

PHYTOCHEMICALS: ARTICHOKE LEAF

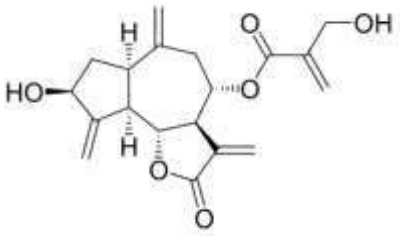


Neochlorogenic acid

Caffeic acid derivatives: **chlorogenic** acid, **neochlorogenic** acid, cryptochlorogenic acid, **cynarin**

Sesquiterpene lactones: Cynaropicrin, dehydrocynaropicrin, grossheimin, cynaratriol.

PHYTOCHEMICALS: ARTICHOKE ROOT



Cynaropicrin

Caffeic acid derivatives, including **chlorogenic acid sesquiterpene lactones**, are not contained in the rhizome.

Health benefits of Artichoke

High in Antioxidants

Artichokes have more **antioxidants** than any other vegetable and they ranked seventh in a study of the antioxidant levels of 1,000 different foods. Some of the powerful **antioxidants components** in artichokes are **quercertin, rutin, anthocyanins, cynarin, luteolin, and Silymarin**.

Cancer Prevention and Treatment

Studies done with artichoke leaf extract have found that they **induce apoptosis (cell death) and reduce cell proliferation** in many different forms of cancer, including prostate cancer, leukemia, and breast cancer.

Increased Bile Flow

The pulp of artichoke leaves contains a polyphenol antioxidant called **cynarin** which increases bile flow.

Good for the Liver

Artichokes are very beneficial to the liver. Studies have found they may even **regenerate liver tissue**. Artichokes have long been used in folk and alternative medicine as a treatment for liver ailments and the scientific studies are now proving them to be correct.

Better Digestion

Artichokes help the digestive system. They are a **natural diuretic**, they aid digestion, improve gallbladder function and, as mentioned above, they are of great benefit to the liver.

Cholesterol Reduction

Ingredients in artichoke leaves have been shown to reduce cholesterol by inhibiting HMG-CoA reductase. **They raise good cholesterol** (HDL) and **lower bad cholesterol** (LDL).

High in Fiber

One large artichoke contains a quarter of the recommended daily intake of fiber. A medium artichoke has more fiber than a cup of prunes.

Source of Vitamins & Minerals

- Fresh artichoke is an excellent source of vitamin **folic acid**; provide about 68 µg per 100 g (17% of recommended daily allowance). Folic acid acts as a co-factor for enzymes involved in the synthesis of DNA. Scientific studies have proven that adequate levels of folates in the diet during pre-conception period, and during early pregnancy, help prevent neural tube defects in the newborn baby.
- Fresh globes also contain good amounts of anti-oxidant vitamin; **vitamin-C** (Provides about 20% of recommended levels per 100 g). Regular consumption of foods rich in vitamin C helps the body develop resistance against infectious agents and scavenge harmful, pro-inflammatory free radicals from the body.
- It is one of the vegetable sources for **vitamin K**; provide about 12% of DRI. Vitamin K has potential role bone health by promoting osteotrophic (bone formation) activity. Adequate vitamin-K levels in the diet help limiting neuronal damage in the brain; thus, has established role in the treatment of patients suffering from Alzheimer's disease.
- It is also rich in B-complex group of vitamins such as **niacin**, vitamin **B-6** (pyridoxine), thiamin, and pantothenic acid that are essential for optimum cellular metabolic functions.
- Further, artichoke is rich source of minerals like **copper**, **calcium**, **potassium**, **iron**, **manganese** and **phosphorus**. Potassium is an important component of cell and body fluids that helps controlling heart rate and blood pressure

by countering effects of sodium. Manganese is used by the body as a co-factor for the antioxidant enzyme, superoxide dismutase. Copper is required in the production of red blood cells. Iron is required for red blood cell formation.

- Additionally, it contains small amounts of antioxidant flavonoid compounds like **carotene-beta**, **lutein**, and **zea-xanthin**.

INDICATIONS AND Target Patients

- Liver disorder
- Loss of appetite
- Bile disorder
- Hyperlipidemia
- Nerve disorder
- Malnutrition
- Anemia
- Cancer

CONTRAINDICATIONS

Because of the stimulating effect of the drug upon the biliary tract, it should not be administered if there is a bile duct blockage. Colic can occur where the patient suffers from gallstones.

DAILY DOSAGE

The average daily dose is 6 gm of drug; single dose is 500 mg of dry extract.

Rosmarinus officinalis L.

Lamiaceae family

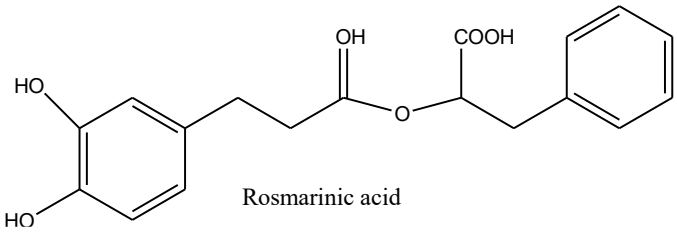
Rosemary

DESCRIPTION

Medicinal Parts: The medicinal parts are the oil extracted from the leaves and the leafy stems, the flowering, dried twig tips, the dried leaves, the fresh leaves, the fresh aerial parts collected during flowering and the flowering branches.

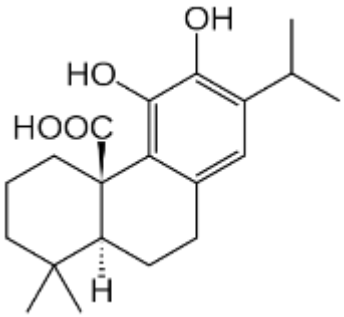
PHYTOCHEMICALS

Caffeic acid derivatives: chief component rosmarinic acid.



Rosmarinic acid

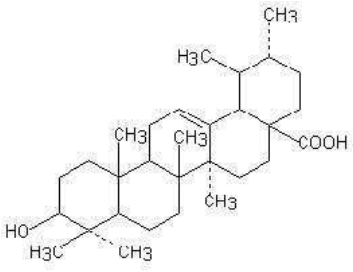
Diterpenes: including Carnosic acid, isorosmanol, rosmadial, rosmaridiphenol, rosmariquinone.



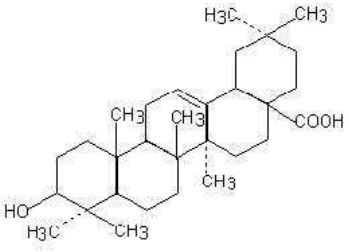
Carnosic acid

Flavonoids: including , diosmin, hesperidin, homoplantiginin, phegopolin

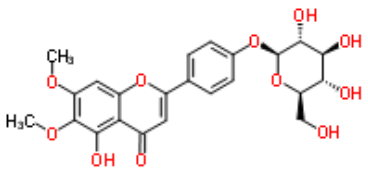
Triterpenes: chief components oleanolic acid, ursolic acid and their 3-acetyl esters



Ursolic Acid

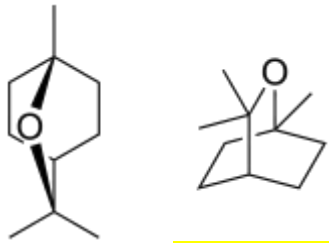


Oleanolic Acid



cirsimarin

Volatile oil (1.0 to 2.5%): chief components 1,8-cineole (Eucalyptol), alpha-pinene , camphor.



1,8 - Cineol

EFFECTS/ Health benefits

- One of the best antimicrobial and antiviral drugs.
- **Improved Memory**
  Rosemary has long been believed to have memory-enhancing properties. In 1529, an herbal book recommended taking rosemary for "weakness of the brain." Today, research has found that rosemary contains a diterpin called **carnosic acid** that has neuro-protective properties that researchers believe may protect against Alzheimer's disease as well as the normal memory loss that happens with aging.
- Researchers from Northumbria University in the United Kingdom found that the amount of 1,8-cineole, a main chemical in rosemary oil, in the blood is linked with **brain performance**.
- **Mood Elevator**
  Smelling rosemary improved test subjects' quality of memory also found that their mood was significantly improved compared to the control group.
- **Migraine Help**
  Rosemary has been a popular natural migraine remedy for centuries. Boil some rosemary in a large pot of water and pour it into a bowl. Place a towel over your head and lean over the pot to inhale the steam for about 10 minutes. Because smelling rosemary has been found to improve memory and mood, this method may also help with memory function and put you in a better state of mind.

- **Pain Relief**

  It not only helps relieve the **pain of migraines**, but essential oil of rosemary can also be applied topically as a natural treatment for **arthritis**, sore muscles, and other joint and muscle pains.

- **Anti-Inflammatory**

  Rosemary contains two potent **anti-inflammatories**, **carnosic acid and carnosol**. One study found that these two compounds inhibited COX-2, an enzyme that causes pain and inflammation in the body. They also inhibited the production of excess nitric oxide, which also plays a role in the inflammatory process.

  The herb parts, especially flower tops contain phenolic anti-oxidant **rosmarinic acid** as well as numerous health benefiting volatile essential oils such as cineol, camphene, borneol, bornyl acetate, α-pinene, etc. These compounds are known to have rubefacient (counterirritant), anti-inflammatory, anti-allergic, anti-fungal and anti-septic properties.

- **Immune Booster**

  Rosemary boosts the immune system thanks to its **antioxidant**, anti-inflammatory, and anti-carcinogenic properties. Because it is healing in so many ways, it boosts the overall health of the body.

- **Rich in Vitamins & Minerals**

  The herb is exceptionally rich in many B-complex groups of vitamin, such as **folic acid**, **pantothenic acid**, **pyridoxine**, **riboflavin**.

  Rosemary herb contains **very good amounts of vitamin A, 2924 IU per 100 g; about 97% of RDA.**

Fresh rosemary leaves are a good source of antioxidant vitamin; **vitamin-C** containing about 22 mg per 100 g, about 37% of RDA. The vitamin is required for the collagen synthesis in the body. Collagen is the main structural protein in the body required for maintaining the integrity of blood vessels, skin, organs, and bones. Regular consumption of foods rich in vitamin C helps the body protect from scurvy; develop resistance against infectious agents (boosts immunity) and help scavenge harmful, pro-inflammatory free radicals from the body.

Rosemary herb parts, whether fresh or dried, are **rich source of minerals** like **potassium**, **calcium**, **iron**, **manganese**, **copper**, and **magnesium**. Potassium is an important component of cell and body fluids, which helps control heart rate and blood pressure. Manganese is used by the body as a co-factor for the antioxidant enzyme, superoxide dismutase.

This herb is an **excellent source of iron, contains 6.65 mg/100 g of fresh leaves (about 83% of RDA)**. Iron, being a component of hemoglobin inside the red blood cells, determines the oxygen-carrying capacity of the blood.

- **Hair Growth**

  There is a possibility that rosemary may **stimulate hair growth**. One study found that people with alopecia, a disorder that causes the hair to fall out, had significant hair regrowth after rubbing rosemary, lavender, thyme, and cedarwood into their scalps for seven months. However, it is not clear whether it was the rosemary or the other herbs that caused the regrowth.

- **Better Circulation**

  Essential oil of rosemary is often applied topically as a **natural remedy for poor circulation**, though there have been no studies to prove this effect.

- **Fresh Breath**

  Rosemary can be used as a **natural mouthwash** and is said to work very well. To make the mouthwash, steep fresh rosemary in a pint of heated water. Strain it and use it as a mouth rinse as often as you like. It will keep in the fridge if covered.

- **Diuretic Properties**

  Rosemary is a **mild diuretic**, which means that it can help get water retention in the body. When rosemary is used regularly, it may help in the increase of urine flow and **help the kidneys function at optimal levels** to help get rid of excess water in the body.

- **Respiratory Health**

  Rosemary is a great natural remedy for respiratory problems. Breathing in the scent of the essential oil may help with congestion due to colds, allergies, respiratory infections, and the flu. You may also boil fresh rosemary in a pot of water, place it in a bowl, and breathe in the steam to help clear the lungs and throat. This will also help with any sinus or head pain associated with respiratory conditions.

INDICATIONS / Target Patients

- Antimicrobial / antiseptic
- Blood pressure problems
- Dyspeptic complaints
- Loss of appetite
- Joint arthritis
- Difficulty in concentration
- Mood swing
- Headache

- Mild Migraine
- Common cold/allergy/sensibility.

CONTRAINDICATIONS

Rosemary preparations should not be used during pregnancy.

DAILY DOSAGE

The daily dose is 4 to 6 gm drug. Tea — 1 cup several times a day.

Benzoic & Cinnamic Ester Containing Drugs

Myroxylon balsamum

Fabaceae family

Tolu Balsam

Other Names

Balsam of Peru, Balsam Tree, Peruvian Balsam, Tolu

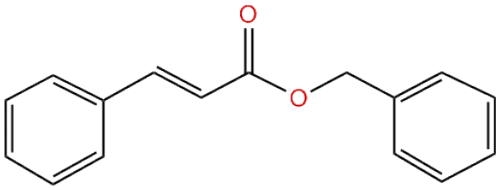
Balsams are defined as oleoresine containing substantial proportions of benzoic acid and cinnamic acid, and their esters.

MEDICINAL PARTS

The medicinal parts are the balsam from the sweltered trunks, the hardened resin balsam that has been extracted from damaged trunks, softened and purified through a process of melting and sweltering.

PHYTOCHEMICALS

Ester mixture (10-20%): made up of benzyl benzoate and benzyl cinnamate. Resins (up to 80%).



Benzyl cinnamate

EFFECTS

The undiluted oil showed antibacterial and fungicidal effects in the diffusion test. The drug also acts as an expectorant. The effect on the respiratory tract appears to work in the field of aromatherapy.

INDICATIONS AND USAGE

Tolu Balsam is used to treat inflammation of the mucous membranes of the respiratory tract.

Echinacea purpurea

Asteraceae family

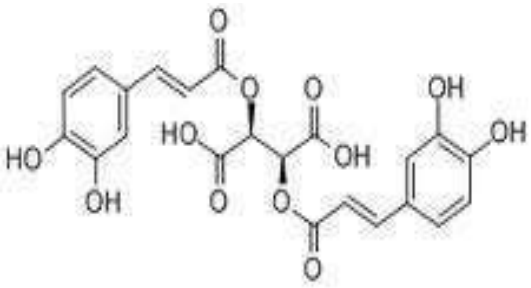
Extracts of Echinacea purpurea (EP, purple coneflower) have been used traditionally in North America for the **treatment of various types of infections and wounds**, and they have become very popular herbal medicines globally.

One of the most popular herbs in the marketplace over the world is the medicinal plant Echinacea. The term refers to several plants in the genus *Echinacea,* derived from the aboveground parts and roots of *Echinacea purpurea* (L.) Moench, *E. angustifolia* D.C., and *E. pallida* (Nutt.) Nutt.

Chemistry

Echinacea purpurea herb contains:

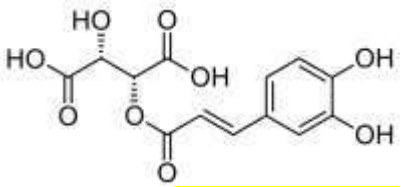
Caffeic acid derivatives: mainly cichoric acid, caftaric acid and chlorogenic acid;



Cichoric acid

Phenylpropanoids:

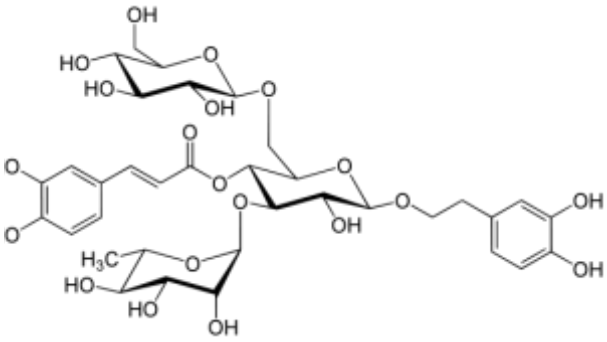
Echinacoside is a natural phenol. It is a caffeic acid glycoside from the phenylpropanoids class



Caftaric acid

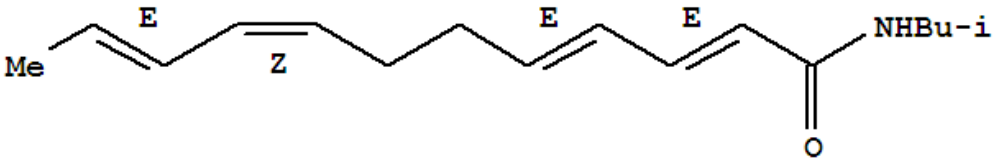
Alkamides:

Mainly isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutyl amides;



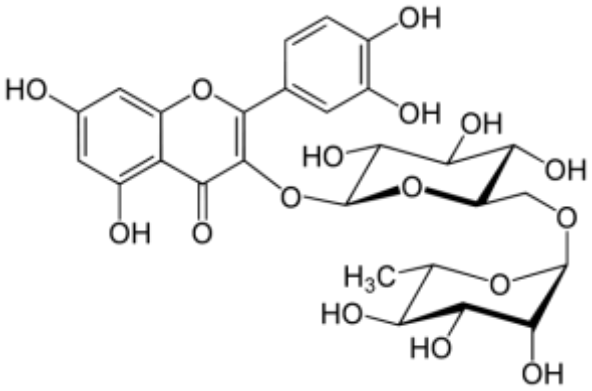
Echinacoside

Polysaccharides, including PS I (a 4-0-methylglucoronylarabinoxylan) and PS II (an acidic rhamnoarabinogalactan), fructans;



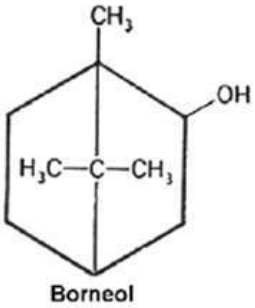
2, 4, 8, 10 Dodecatetraenamide

Flavonoids of quercetin and kaempferol type (e.g., rutoside); 0.080.32%



Rutoside

Essential oil composed of borneol, bornyl acetate, pentadeca-8-en-2-one, palmitic acid, and others.



Borneol

Effect / Heath benefits

1) Echinacea Can Help Prevent Sickness

Echinacea strengthens your immune system by stimulating the production of T-cells. It also increases the ability of your white cells to fend off pathogenic invaders.

2) Echinacea Can Shorten the Symptoms of Illness

Even if you begin taking echinacea after you're already sick, it can help to reduce your recovery time.

3) Echinacea May Be Used as a Topical Disinfectant

Echinacea helps protect your healthy cells from invasion by bacteria and viruses, even if you apply the herb topically. This means you can use it to keep cuts and scratches from getting infected. Not only will it keep the wound from getting infected, but it will speed the healing process. When used externally as a topical disinfectant, echinacea also has analgesic properties.

4) **Echinacea is a Powerful Treatment**

Echinacea is known to be particularly effective in speeding the recovery process of a number of common illnesses. Some illnesses against which Echinacea supplements may be particularly effective include:

- Urinary tract infection
- Sore throat pain
- Enlarged lymph glands
- Upper respiratory infection
- Enlarged prostate
- Vaginal yeast infections
- Bronchitis
- Hay fever
- Sinusitis
- Ear infections
- Gingivitis
- Canker sores

5) Echinacea May Benefit Psoriasis and Eczema

When applied topically to breakouts of psoriasis and eczema, Echinacea has been shown to be an effective treatment.

6) Echinacea is Good for Slow-Healing Wounds

Topically applied, Echinacea can dramatically speed wound healing, so it's often used for the treatment of slow-healing wounds. It also helps to relieve the pain of the wound and can protect slow-healing wounds from infection. Echinacea is also frequently used as a hemorrhoid remedy, and is often added to over-the-counter hemorrhoid medications.

7) Echinacea Helps Heal Sunburn

When applied topically to sunburns, Echinacea's healing properties help speed the recovery process.

8) Echinacea Helps Resolve Recurrent Infections

Echinacea is particularly effective in helping to resolve recurring infections, such as ear infections. When used for a few weeks, Echinacea's immune-boosting compounds accumulate in the body, making its immune-boosting effects cumulative.

9) Echinacea increases the "non-specific" activity of the immune system.

In other words, unlike a vaccine which is active only against a specific disease, Echinacea stimulates the overall activity of the cells responsible for fighting all kinds of infection. Unlike antibiotics, which are directly lethal to bacteria, Echinacea makes our own immune cells more efficient in attacking bacteria, viruses and abnormal cells, including cancer cells.

Echinacea facilitates wound healing, lessens symptoms of and speeds recovery from viruses. Anti-inflammatory effects make it useful externally against inflammatory skin conditions including psoriasis and eczema. It may also increase resistance to candida, bronchitis, herpes, and other infectious conditions.

Indication / Target Patients

- Common cold
- Colds & Flu
- Influenza
- Respiratory tract infection
- Upper respiratory tract infection

- Urinary tract infection (UTI)
- chronic fatigue syndrome (CFS),
- rheumatism,
- migraines,
- acid indigestion,
- pain,
- dizziness,
- rattlesnake bites, and
- Attention deficit-hyperactivity disorder (ADHD).

Precaution:

However, Echinacea can lose its effectiveness over time, and may ultimately damage your immune system by inhibiting the production of T-cells if you make it a permanent part of your health routine. It might not be a good idea to use Echinacea supplements in any form, including tea, daily for longer than eight consecutive weeks.

Drug-Drug interaction:

Echinacea is often taken together with goldenseal. This herbal remedy can help fight the inflammatory and congestive elements of the common cold by soothing conditions in the inner membranes of the nose and throat. It also has some anti-inflammatory and immune boosting abilities, according to researchers. Lots of herbal remedy providers package Echinacea together with goldenseal for a double punch against cold and flu viruses.

Echinacea may alter the actions of other medicines that affect your immune system.

A steroid medicine including **betamethasone** (Celestone), **dexamethasone** (Hexadrol, Decadron, others), **cortisone** (Cortone), **hydrocortisone** (Cortef, Hydrocortone, others), **methylprednisolone** (Medrol, Solu-Medrol, others), **prednisone** (Deltasone, Orasone, others), **prednisolone** (Prelone, Pediapred, others), **triamcinolone** (Aristocort, others), and others; **or**

Cyclosporine (Neoral, Sandimmune), tacrolimus (Prograf), **azathioprine** (Imuran), **methotrexate** (Rheumatrex), or other immune system suppressants.

You may not be able to take Echinacea, or you may require a dosage adjustment or special monitoring during treatment if you are taking any of the medicines listed above.

Side Effects

Depending upon dosage, short-term fever reactions, and nausea and vomiting can occur. In individual cases, immediate allergic reactions are possible.

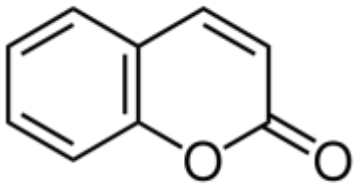
Chapter 3

Coumarins

Introduction

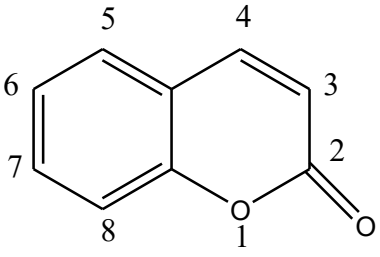
Coumarins be obligated their class name to "Coumarou" the language name of Tonka bean, Fabaceae family, from which coumarin itself was isolated in 1820.

Coumarin is a phytochemical (benzopyrone); a toxin found in many plants, notably in high concentration in the tonka bean, vanilla grass, woodruff, mullein, lavender, licorice, strawberries, apricots, cherries, cinnamon, sweet clover and bison grass having vanilla like flavor and is a oxygen heterocycle as shown in the figure.

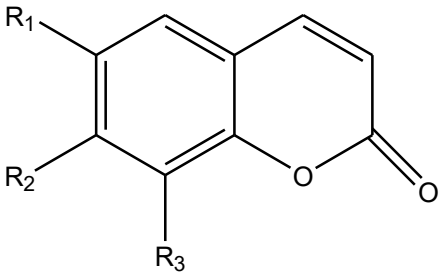


Chemistry & Classification:

Except for a few rare cases, all coumarins are substituted by a hydroxyl group in position 7, Umbelliferone, which is 7-hydroxy-coumarin itself, is the precursor of the 6,7, di and 6,7,8 trihydroxylated coumarins.

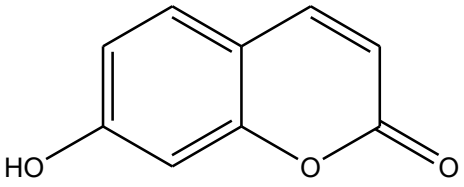


Coumarin

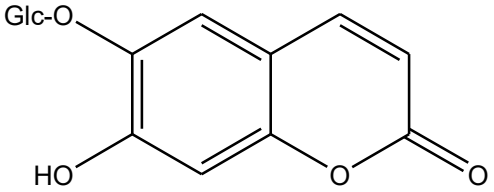


R_1	R_2	R_3	Compound
H	OH	H	Umbelliferone
OH	OH	H	Aesculetin
OCH_3	OH	H	Scopoletin

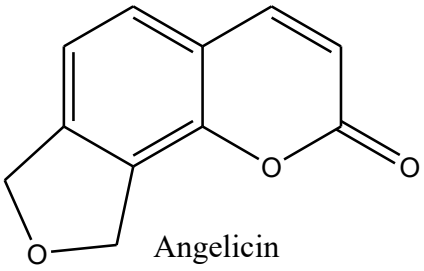
One structural feature which is common to many coumarins is **prenylation**, prenylation on the ring in the 6 or 8 position of umbelliferone. Prenylation is also the origin of polycyclic coumarins, furano and pyrano coumarins, linear (Psoralen) and angular (angelicin, visnadin) coumarins.



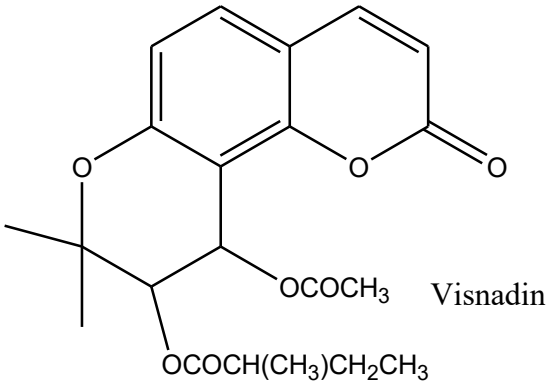
Umbelliferone



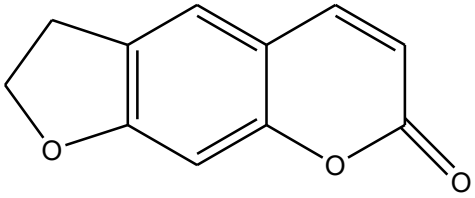
Aesculin



Angelicin



Visnadin



Psoralen

Biosynthesis:

1. **Simple coumarins**

Coumarins arise from the metabolism of phenylalanine via cinnamic acid, p-coumaric acid. The specificity of the process resides in:

- the 2'-hydroxylation,
- photocatalyzed isomerization of the double bond
- spontaneous lactonization.

2. **Formation of Furano & Pyranocoumarins**

Prenylation

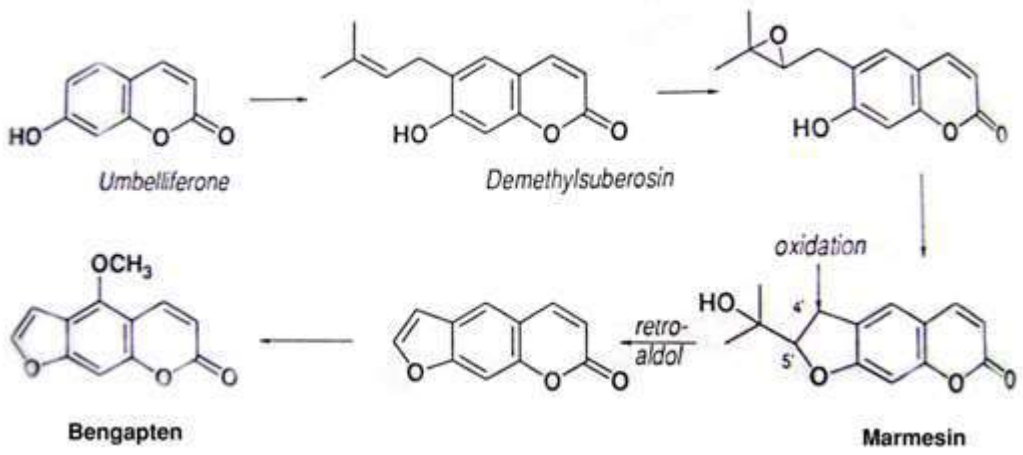
of the benzene ring by **d**i**m**ethyle**a**llyl **p**yro**p**hosphate (DMAPP) in the 6 or 8 position of a 7 hydroxy-coumarin is the origin of the extra ring which characterizes these molecules. Prenylation in 6 position yield the so called "linear" furano-and pyranocoumarins; in the 8 position it give the "angular" homologs.

The cyclization of 6 or 8-isoprenylcoumarin is probably due to nucleuophilic attack by the hydroxyl group in the 7- position on the epoxide formed by oxidation of the double bond of the isopentenyl residue.

The proposed mechanism for the formation of furanocoumarins includes two successive steps:

1. Stereospecific oxidation in the 4' position and
2. elimination of the hydroxyisopropyl residue in the 5' position by retroaldol condensation.

Substitution in the 5 or 8 position or in both positions of furanocoumarins occurs later and is catalyzed by oxidases and O-methyl transferases.



Properties, Extraction & Characterization

Coumarins in the **free state** are **soluble** in **alcohols and in organic solvents** such as ether and chlorinated solvents, with which they can be extracted. Their **glycosides** are more or less soluble in water.

Coumarins have a **characteristic UV** spectrum which is heavily influenced by the nature and position of substituents, and by alkalinization KOH, $NaOCH_3$.

When examined under UV light, TLC spots from coumarin containing drugs have colors which are **enhanced in the presence of ammonia**, and range from **blue to yellow and purple**.

Pharmacological Properties & Uses

Aescluin is said to be a venous tonic and vascular protective agent and is sometimes referred to as a "**vitamin P factor**". Some furanocumarins are photosensitizer; therefore they are indicated for the therapy of **psoriases** and **vitiligo**. **Visnadin**, a pyranocoumarin isolated from khella, has been extracted and marketed for its coronary vasodilator effect and presented as having a favorable action on senile cerebral insufficiency.

Coumarin Containing Drugs

Aesculus hippocastanum

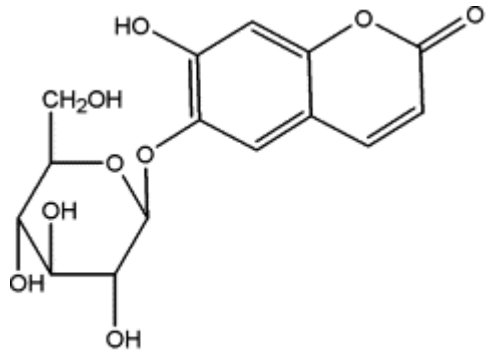
Horse Chestnut

MEDICINAL PARTS

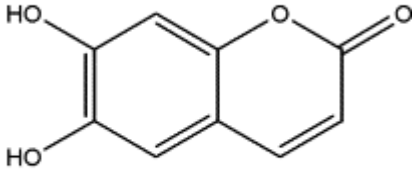
The medicinal parts are the dried Horse Chestnut leaves; the oil extracted from the peeled fruit capsules (seeds) and dried chestnut seeds.

PHYTOCHEMICALS

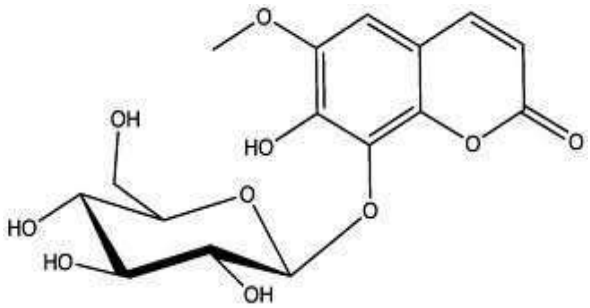
- ***Hydroxycoumarins:***
  chief component is aesculin, in addition fraxin and scopolin



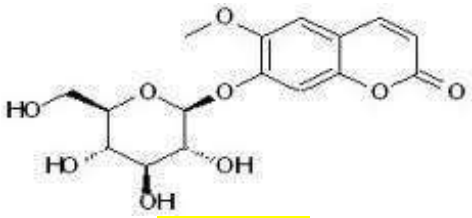
aesculin



aesculetin

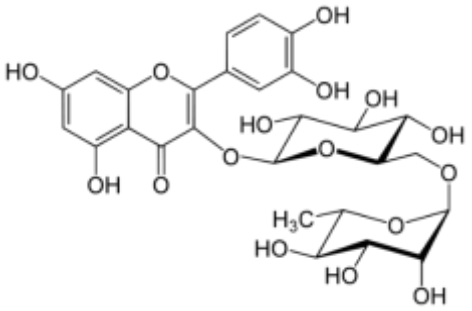


Fraxin

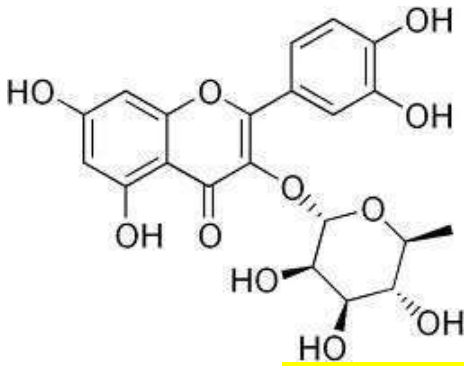


Scopolin

- ***Flavonoids:*** including rutin, quercitrin, and isoquercitrin



Rutin

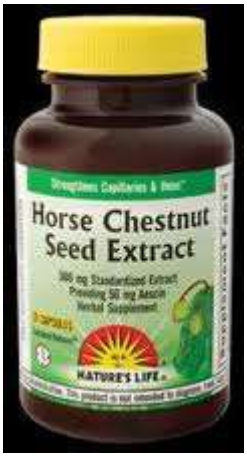


Quercitrin

- ***Triterpene saponins*** &
- ***Tannins.***

EFFECTS / Health benefits

- Improve Vein Health and Flexibility
- Treat Varicose Veins
- Improve Fertility
- Improve Circulation
- Neuron Protection
- Minimizes Leg Cramping
- Stop Diarrhea
- Provide Hemorrhoid Relief
- Prevent Inflammation
- Cancer Fighting Properties



INDICATIONS / Target Patients

Venous conditions (chronic venous insufficiency). Treatment of symptoms found in pathological conditions of the veins of the legs (**chronic venous insufficiency**), for example pain and a sensation of heaviness in the legs, nocturnal cramps in the calves, pruritis and swelling of the legs.

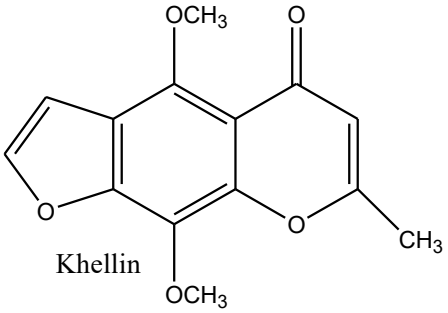
DRUG INTERACTIONS

Horse Chestnut leaf has a coumarin component and may interact with warfarin, salicylates and other drugs with anti-coagulant properties.

Ammi Visnaga

Apiaceae family

Khella



Khellin

MEDICINAL PARTS

The medicinal part is the fruit.

PHYTOCHEMICALS

- ***Furochromones:*** particularly khellin, visnagin, khellol and khellol glucoside
- ***Pyranocoumarins:*** particularly visnadin and samidin
- ***Flavonoids:*** including quercetin and isohamnetin and their 3- sulfates
- **Volatile oil** &
- **Fatty oil.**

EFFECTS / Health benefits

- There are several respiratory benefits of khella. It is said to help treat **asthma, bronchitis, spastic coughs, and emphysema**. The khellin constituent present in khella is said to be an effective bronchio-dilator and it is also said to have antispasmodic abilities.
- It may help **to prevent atherosclerosis** by helping to raise good cholesterol levels and by preventing arterial plaque formation.
- Khella may help to **relieve bladder and urinary tract constriction and spasms.** It may also relieve urinary colic.
- Khella is said to have **antispasmodic** properties making it a good remedy for a variety of spasms. It can help with spastic menstruation, abdominal cramps, spastic coughs, and painful periods.
- This herb may be beneficial for the **health of the gallbladder and bile duct.** It may promote the discharge of gallstones and gallbladder colic.

- The khellin component, when combined with sun exposure, may help to treat the skin disease known as **vitiligo**, in which the skins' pigment-carrying melanocytes are lost. It may also be beneficial in treating inflammation, psoriasis, minor burns and wounds, and certain dermatological problems.

Side Effects and Warnings

There are a few side effects associated with this herb, such as **decreased visual acuity, nausea, and vomiting**. Other adverse reactions may include **headache, vertigo, insomnia, anorexia, an elevation in liver function** test results, **constipation**, **itching**, and weak **phototoxic activity**.

Patients should also avoid prolonged exposure to ultraviolet radiation and sunlight. It is also very important to talk to a doctor before taking khella, especially if the patient is taking other herbs or medications, or has any medical conditions or ailments.

Angelica sinensis

Apiaceae family

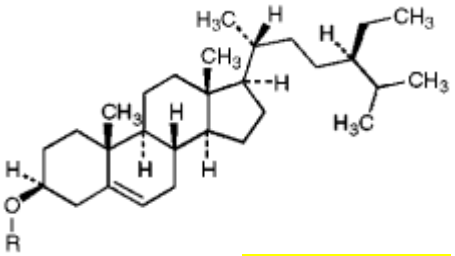
Dong Quai

MEDICINAL PARTS

The medicinal parts are the seed, whole herb and root.

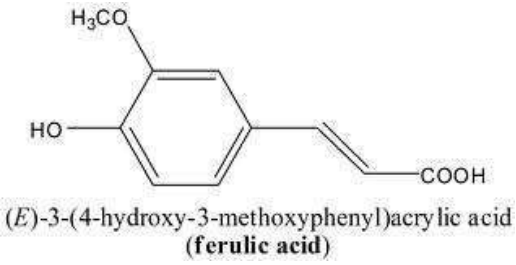
PHYTOCHEMICALS

- **Furanocoumarins:** including bergaptene, xanthotoxin, scopoletin, umbelliferone
- **Caffeic acid derivatives:** including chlorogenic acid
- **Ferulic acid**
- **β-sitosterol**
- **Polysaccharide**
- **Lignan**



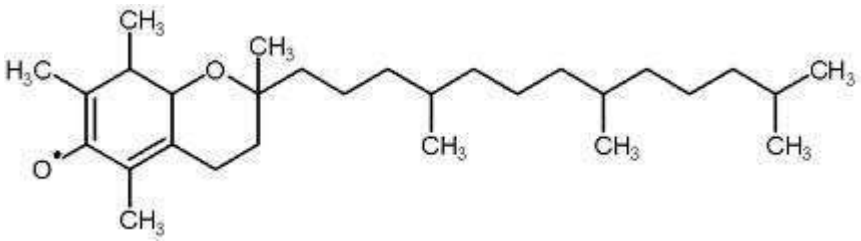
β-sitosterol

- **Flavonoids**
- **Volatile oil:** chief components are alpha- and beta-phellandrenes, alpha-pinenes, macrocyclic lactones, including penta- and heptadecanolide.



(*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid
(ferulic acid)

- **Vitamin E, Vitamin B_{12}, iron, folinic acids.**



Vitamin E

EFFECTS /Health benefits

- The root acts as an antispasmodic, cholagogue and stimulatory for secretion of gastric juices.
- Balancing & reinforcing the female hormone system.
- Inflammatory effect
- Ischemia and Neurodegeneration
- Wound healing
- Cytotoxic and genotoxic effects (Safrole-2′,3′-oxide (SAFO))
- Antibacterial and anti-inflammatory activity
- Diabetes
- Cerebral infarction
- Immunomodulatory functions
- Anti-tumor effects
- Dementia
- Subarachnoid hemorrhage
- Anticoagulative activities
- Hypertension

Nutritional Role of Dong Quai

Dong Quai **has hormone-like compounds** which help minimize estrogen problems related to the menstrual cycle. It has natural chemicals called coumarins that dilate blood vessels and increase blood flow to the organs and also serve to reduce inflammation and muscle spasms. This dilation of blood vessels can also help to lower blood pressure. Since Dong Quai is rich in iron, it helps build red blood cells.

MECHANISM OF ACTION

- Have **tonic effects on the uterus**, initially causing **contractions followed by relaxation**.
- When **estrogen levels are high**, displays an overall estrogen-decreasing effect, accounting for its use in the treatment of **menstrual discomforts and PMS**.
- During menopause**, declines in estrogen** levels facilitate its action as a mild estrogenic agonist, used in the treatment of **hot flashes and vaginal dryness**.
- **Coumarins** act as **anti-coagulant activity**; they dilate the blood vessels, stimulate the central nervous system, and increase the blood flow throughout the body.

INDICATION/Target patients

- Painful menstruation (Dysmenorrhea),
- Menopausal difficulties.
- Female infertility
- For uterine health
- For perimenopause, menopause, and premenstrual syndrome (PMS)
- For blood pressure and blood sugar
- For anemia
- For vaginal dryness and hot flashes
- For anti-inflammatory properties
- For blood vessels and blood flow to organs

CONTRAINDICATION

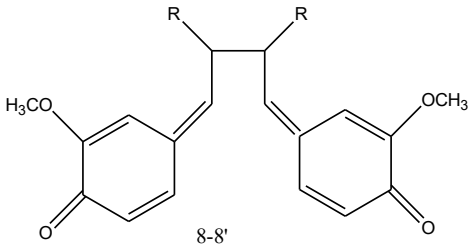
Pregnancy

PRECAUTIONS

The blood-thinning properties of Dong Quai (Angelica) may cause menstrual bleeding to increase.

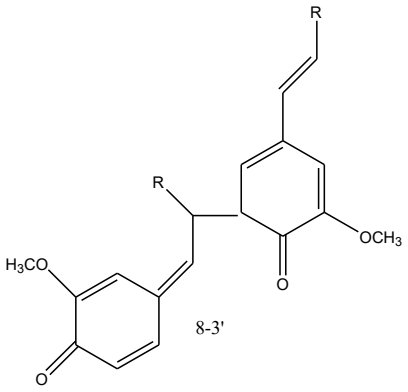
Chapter 4

Lignans, Neolignans



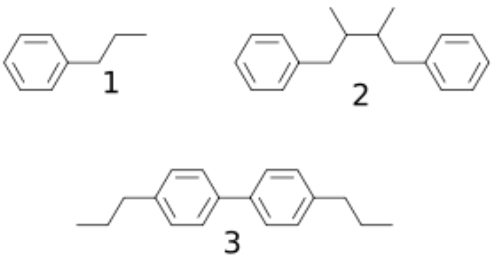
The term **lignan** usually designates compounds whose skeleton **results from bonding between the β carbons of side chain of two units derived from 1-phenylpropane (8-8′ bond).**

Neolignans are also **condensation products of phenylpropanoids units, but the actual bond varies and involves no more than one β carbon (8-3′, 3-3″, 8-O-4″).**



Lignans are one of the major classes of phytoestrogens, which are estrogen-like chemicals and also act as **antioxidants**.

Plant lignans are polyphenolic substances derived from phenylalanine via dimerization of substituted cinnamic alcohols, known as monolignols, to a dibenzylbutane skeleton **2**. This reaction is catalysed by oxidative enzymes and is often controlled by dirigent proteins. Many natural products, known as phenylpropanoids, are built up of C_6-C_3 units (a propylbenzene skeleton **1**) derived from cinnamyl units just as terpene chemistry builds on isoprene units. Structure **3** is a neolignan.



Food Sources

Flax seed and sesame seed are among the **highest** known **sources of lignans.**

Other sources of lignans include cereals (rye, wheat, oat and barley - rye being the richest source), pumpkin seeds, soybeans, broccoli, beans, and some berries.

Broccoli

Pharmacological Properties

Lignans possess **cytotoxic and antimitotic properties**, only the semisynthetic derivatives of podophyllotoxin are exploited in therapeutics. Plant lignan compounds are converted in the intestine to form of lignans (enterolignans) the human body can assimilate. Some studies have reported **a positive association between high levels of lignans in the body with reduced risks of prostate cancer, ovarian cancer, breast cancer, osteoporosis, and cardiovascular disease.**

Drugs Containing Lignans & Related Compounds

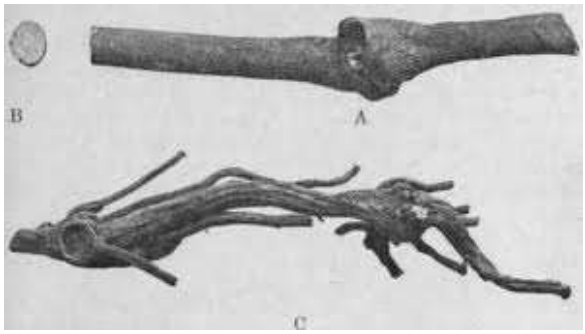
Podophyllum peltatum

Berbidaceae family

May Apple

MEDICINAL PARTS

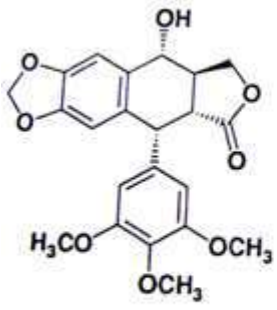
The medicinal parts are the dried rhizome and the resin extracted from it.



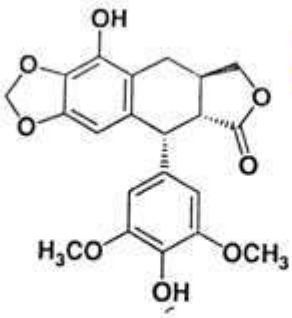
PHYTOCHEMICALS

***Podophyllin*:** mixture of ethanol-soluble extractive material from the root

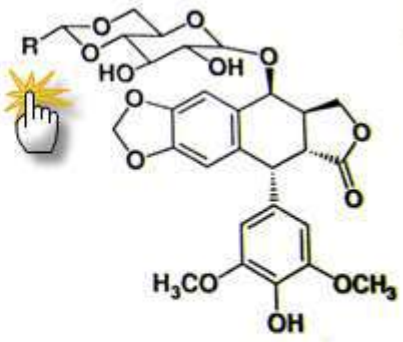
***Lignans*:** chief components podophyllotoxin (20%), including as well, alpha-peltatin (5%), beta-peltatin (10%), 4'-dimethyl podophyllotoxin, dioxypodophyllotoxin



Podophyllotoxin



α—Peltatin



R = CH_3, Etoposide
R = thienyl, Teniposide

EFFECTS

The drug is antimitotic, podophyllotoxin and peltatins inhibit the growth of experimental tumors induced in the mouse.

Etoposide phosphate (brand names: **Eposin**, **Etopophos**, **Vepesid**) is an inhibitor of the enzyme topoisomerase II. It is used as a form of chemotherapy for malignancies such as Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, non-lymphocytic leukemia,

and glioblastoma multiforme. It is often given in combination with other drugs. It is also sometimes used in a conditioning regimen prior to a bone marrow or blood stem cell transplant.

Silybum marianum L.

Asteraceae family

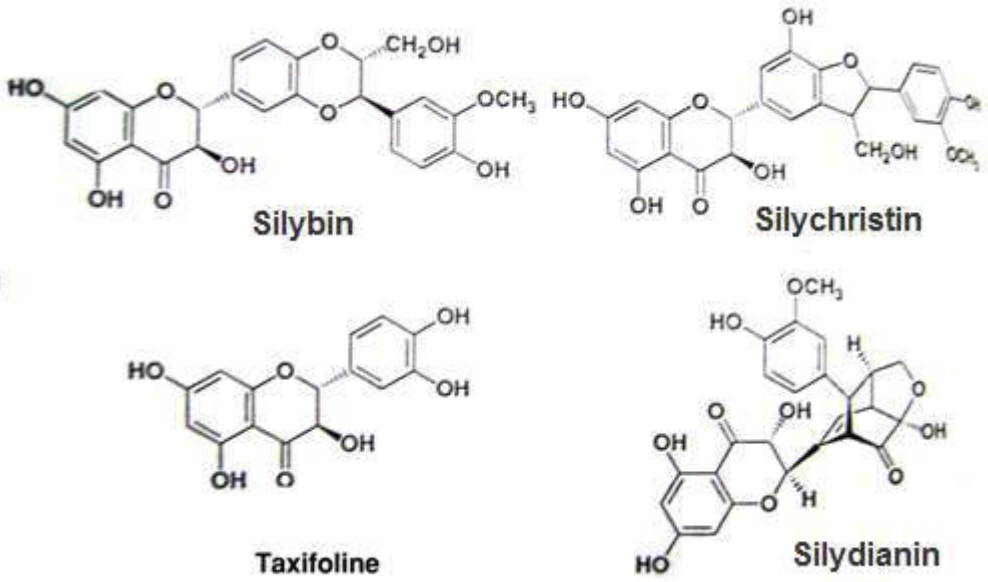
Milk Thistle

MEDICINAL PARTS

The medicinal parts of the plant are the ripe seeds.

PHYTOCHEMICALS: MILK THISTLE SEED

- ***Silymarin*** (**flavonolignan mixture**, 1.5-3%): **chief components silybin A, silybin B** (mixture known as **silibinin**), isosilybin A, isosilybin B, silychristin, silydianin
- ***Flavonoids***: apigenin, chrysoeriol, eriodictyol, naringenin, quercetin, taxifolin
- ***Fatty oil*** (20-30%)



EFFECTS: MILK THISTLE SEED

Hepatoprotective Effects

The hepatoprotective activity of the seed is from silymarin, in **particular, silychristin and silydianin**.

The compounds seem to inhibit the entrance of toxins and block toxin binding sites through alteration of the liver cell's outer membrane.

The hepatoprotective effect of **silibinin (silymarin),** also involves different functions of the Kupffer cells. Silibinin decreases production of superoxide by the Kupffer cells.

Silibinin also inhibits leukotriene formation by the Kupffer cells

Silymarin increases glutathione production by the liver, intestines and stomach. Glutathione is used for detoxification cells in the liver.

Silibinin decreases hepatic and mitochondrial glutathione oxidation induced by iron overload and is a mild chelator of iron.

PROTECTIVE EFFECTS

The seed exerts an anti-inflammatory effect through inhibition of leukotriene production by silymarin.

Silibinin and silychristin demonstrated remarkable stimulatory effects on proliferation rate, biosynthesis of protein and DNA, and activity of the enzyme lactate dehydrogenase in kidney cells, Silibinin reduces intracellular and secreted forms of prostate-specific antigen (PSA) levels and inhibits cell growth via a Gl arrest in cell cycle progression in hormone-refractory prostate carcinomas. Silibinin-induced Gl arrest decreases the kinase activity of cyclin-dependent

LIVER REGENERATIVE EFFECTS

Silymarin stimulates RNA polymerase I in the cell nucleus of the hepatocytes, resulting in an increase of ribosomal protein synthesis and the regenerative ability of the liver.

This mechanism is of particular importance in the antidote effect against death-cap mushroom poisoning since the poison which it

contains, alpha-Amanitin, inhibits this enzyme in the cell nucleus. The drug also has a **cholagogic effect**.

High cholesterol

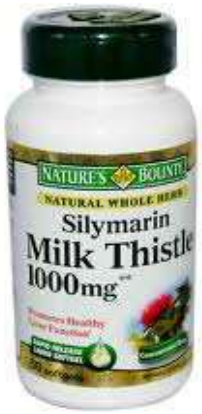
One animal study found that silymarin (an active compound in milk thistle) worked as effectively as the **cholesterol-lowering drug**, with the additional benefit of substantially **increasing HDL** cholesterol.

Cancer

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.

INDICATIONS / Target Patients



Dyspeptic complaints

Liver and gallbladder complaints

The drug is used for toxic liver damage, adjunctive treatment in chronic inflammatory liver disease and hepatic cirrhosis.

Viral hepatitis

Cardiovascular with high cholesterol level

DRUG INTERACTIONS

The concomitant use of silymarin and butyrophenones or phenothiazines results in a reduction of lipid peroxidation (Palasciano, 1994). Silymarin has an antagonistic effect with yohimbine and phentolamine when given siflffulaneously (Di Carlo, 1993).

HOW SUPPLIED

Capsules—70 mg, 100 mg, 140 mg, 150 mg, 175 mg, 180 mg, 500 mg, 540 mg, **1000 mg,** 1050 mg.

Schizandra chinensis

Schizandraceae (Magnoliaceae) family

Schizandra

MEDICINAL PARTS

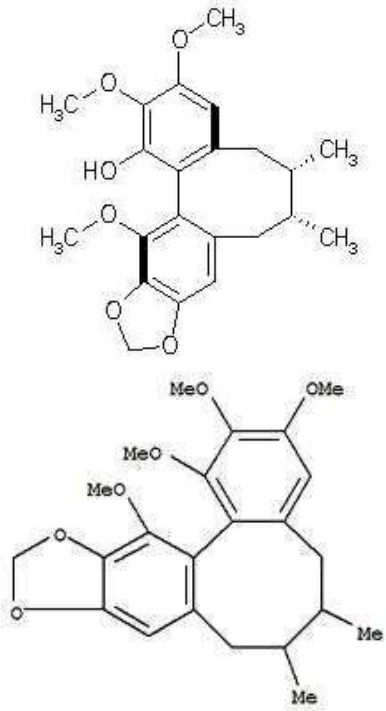
The medicinal parts of the plant are the ripe fruits. The schizandra fruit has a sweet, salty, bitter, hot and sour taste. This explains the Chinese name wu wei zi meaning five taste fruit. The Schizandra seeds are bitter and pungent. Besides the phytochemicals, schizandra is also rich in minerals, vitamins and essential oils.

PHYTOCHEMICALS

Gomisin, Schizandrin, Lignans, β-Sitosterol.

EFFECT

its berries are used in traditional Chinese medicine, where it is considered one of the 50 fundamental herbs. They are most often used in dried form, and boiled to make a tea. Medicinally it is used as a tonic and restorative adaptogen with notable clinically documented liver



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Schizandrin

protecting effects. The primary hepatoprotective (liver protecting) and immuno-modulating constituents are the lignans schizandrin, deoxyschizandrin, gomisins, and pregomisin, which are found in the seeds of the fruit.

CONTRAINDICATION

It should not be used by pregnant women.

Linum usitatissimum

Lineaceae family

Flaxseed

MEDICINAL PARTS

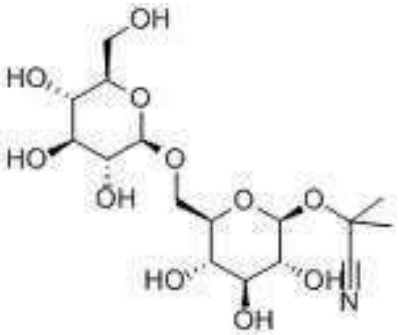
The medicinal parts are the stem as a sterile linen thread, the oil extracted from the seeds, the dry ripe seeds, the linseed cakes and the fresh flowering plant.

PHYTOCHEMICALS

Mucilages (3-10%, in the epidermis, high swelling capacity): including arabinoxylans, galactans, rhamnogalacturonans

Lignans: secoisolariciresinol-diglucoside

Cyanogenic glycosides (0.05-0.1%): linustatin and neolinustatin (yielding under optimal conditions 30-50 mg HCN per100 gm)



Linustatin

Fatty oil (30-45%): chief fatty acids linolenic acid (40-70%), linoleic acid (10-25%), oleic acid (13-30%)

Proteins (20-27%)

Phenylpropane derivatives: including among others, linusitamarine

EFFECT

Flax seeds come in two basic varieties: (1) brown; and (2) yellow or golden. Most types have similar nutritional characteristics and equal amounts of short-chain omega-3 fatty acids. The exception is a type of yellow flax called Linola or solin, which has a completely different oil profile and is very low in omega-3.

Flax seeds contain high levels of **lignans** and Omega-3 fatty acids. Lignans may benefit the heart; possess anti-cancer properties and studies performed on mice found reduced growth in specific types of tumors. Flax seed may also lower cholesterol levels, especially in women.

CONTRAINDICATIONS

Flaxseed is contraindicated in the following conditions: ileus, stricture of the esophagus and in the gastrointestinal area, acute inflammatory illnesses of the intestine, of the esophagus and of the stomach entrance.

Glycine soja

Soybean

MEDICINAL PARTS

The medicinal parts are the soya lecithin extracted from the soya bean, the soya oil and the soya seed.

PHYTOCHEMICALS

Phospholipids (45-60%): in particular phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol

Fatty oil (30-35%)

Steroids: Phytosterols (2-5%)

EFFECTS

The phospholipids extracted from soya lecithin was shown to have lipid-reducing properties in animal experiments and clinical trials.

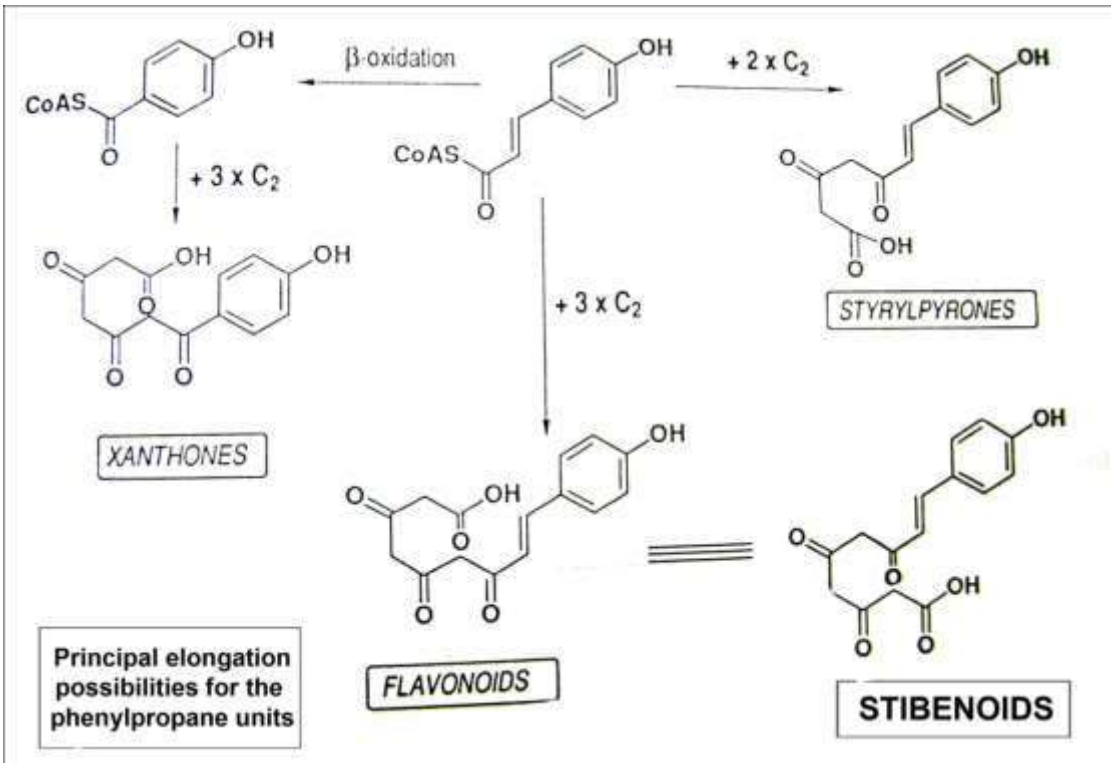
DAILY DOSAGE

The average dose is 3.5 gm of phospholipids (phosphatidylcholine).

Chapter 5

Shikimate: Phynylpropane chain

The elongation of compounds of the Ar-C_3 type by the stepwise addition of two carbon units is a common process in plants: it is the origin of stylpyrones (Ar-C_3 + 2 × C_2), stilbenoids, flavonoids and isoflavonoids (Ar-C_3 + 3 × C_2).



Diarylheptanoids & Arylalkanones

These compounds, including curcuminoids, gingerols, and their derivatives, are specific to several genera of the family Zingiberaceae. They are the coloring substances of turmeric and the pungent principles of ginger.

Curcuma domestica

Zingiberaceae family

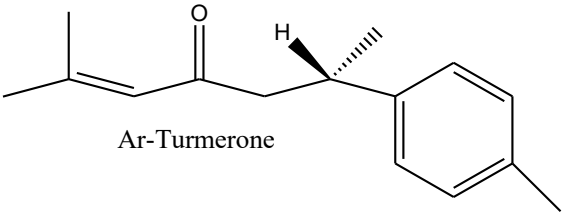
Turmeric

MEDICINAL PARTS

The medicinal parts are the stewed and dried rhizome.

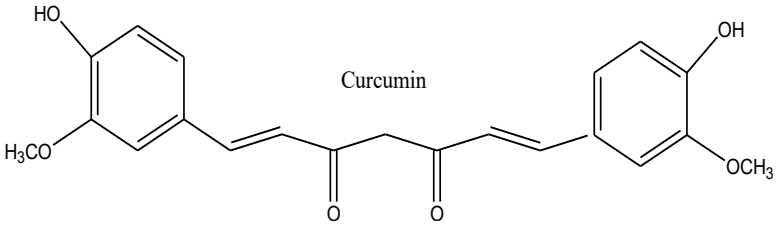
PHYTOCHEMICALS

Volatile oil *(3-5%):* alpha- and beta-tumerone (aroma source), artumerone, alpha- and gamma-atlantone, curlone, zingiberene, curcumol



Ar-Turmerone

Curcuminoids *(3-5***%**), **(coloring principles)***:* including **curcumin**, demethoxy curcumin, bidemethoxy curcumin



Starch *(30-40%)*: (arabino-galactan)

EFFECTS

Turmeric has antihepatotoxic, antihyperlipidemic and anti-inflammatory effects. It is also antioxidative (inhibits lipid peroxide formation in the liver), antitumor and antimicrobial (in particular, the sesquiterpene derivatives). It has insect repellent and antifertile effects. It also inhibits prostaglandin formation, in vitro.

INDICATIONS AND USAGE

- Dyspeptic complaints
- Loss of appetite
- Anti-inflammatory
- Antimicriobial

CONTRAINDICATIONS

General: The drug should not be used by people with obstructed biliary ducts; those with gallstones.

Pregnancy: Turmeric should not be used during pregnancy.

DAILY DOSAGE

The average dose is 1.5 to 3 gm of drug. The powder should be taken 2 to 3 times daily after meals; the tea (2 to 3 cups) should be taken between meals. The tincture dose is 10 to 15 drops 2 to 3 times daily.

Zingiber officinales R.

Zingiberaceae family

Ginger

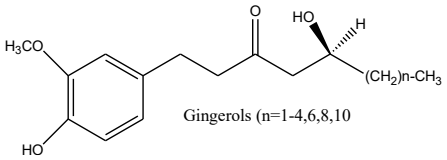
MEDICINAL PARTS

The medicinal part is the root.

PHYTOCHEMICALS

Volatile oil *(2.5-3.0%*): chief components vary greatly, depending upon country of origin: (-)-zingiberene and arcurcumene, beta-bisabolene and ar-curcumene, neral and geranial, D-camphor, beta-phellandrene, geranial, neral and linalool, (E)-alpha farnesene, important as aroma carrier zingiberol (mixture of cis- and trans-beta-eudesmol).

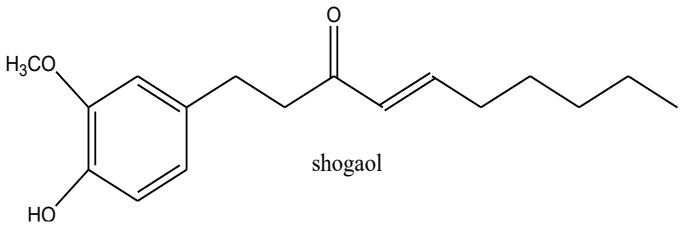
Aryl alkanes



Gingerols (n=1-4,6,8,10

Gingerols: chief components [6]-gingerol (pungent substances), [8]-gingerol, [10]-gingerol

Shogaols: chief components [6]-shogaol (pungent substane), [8]-shogaol, [10]- shogaol (artifacts formed during storage. arising from the gingerols)



shogaol

Gingerdiols

Diarylheptanoids: including among others, gingerenone A and B.

EFFECTS / Health Benefits

Compounds isolated from the Ginger rhizome have been studied in numerous in vitro and animal experiments. Other studies show that Ginger root is positively inotropic. antithrombotic; has anti-oxidant, anti-migraine and anti-lipidemic effects, and promotes secretion of saliva, gastric juices and bile.

Anti-Emetic Effects

The components in Ginger that are responsible for the antiemetic effect are thought to be the **gingerols and shogaols.**

The anti-emetic effect of Ginger is thought to be due to local gastrointestinal actions.

Anti-Inflammatory Effects

The anti-inflammatory effect of Ginger is thought to be due to inhibition of cyclooxygenase and 5-lipoxygenase, results in reduced leukotriene and prostaglandin synthesis.

Miscellaneous Effects

In humans, Ginger increases the tone and peristalsis of the intestine. The root of *Zingiber officinale* has also shown immune system stimulation and platelet aggregation inhibitory activity.

INDICATIONS AND USAGE

- Loss of appetite
- Travel sickness
- Dyspeptic complaints

CONTRAINDICATIONS

- Because of its cholagogic effect, the drug should not be taken in the presence of gallstone conditions.
- Ginger has been found to inhibit thromboxane synthesis, therefore it should not be used by patients who are at risk for hemorrhage.

DRUG INTERACTIONS

More than one in-vitro study confirms an antithrombotic effect. It is recommended that patients taking anticoagulants or those with bleeding disorders avoid the use of large doses of Ginger.

HOW SUPPLIED

Capsules — 100 mg, 400 mg, 420 mg, 460 mg, 470 mg, 500mg, 550 mg, 1000 mg

Fluid Extract — 1:1

Oil — 100%

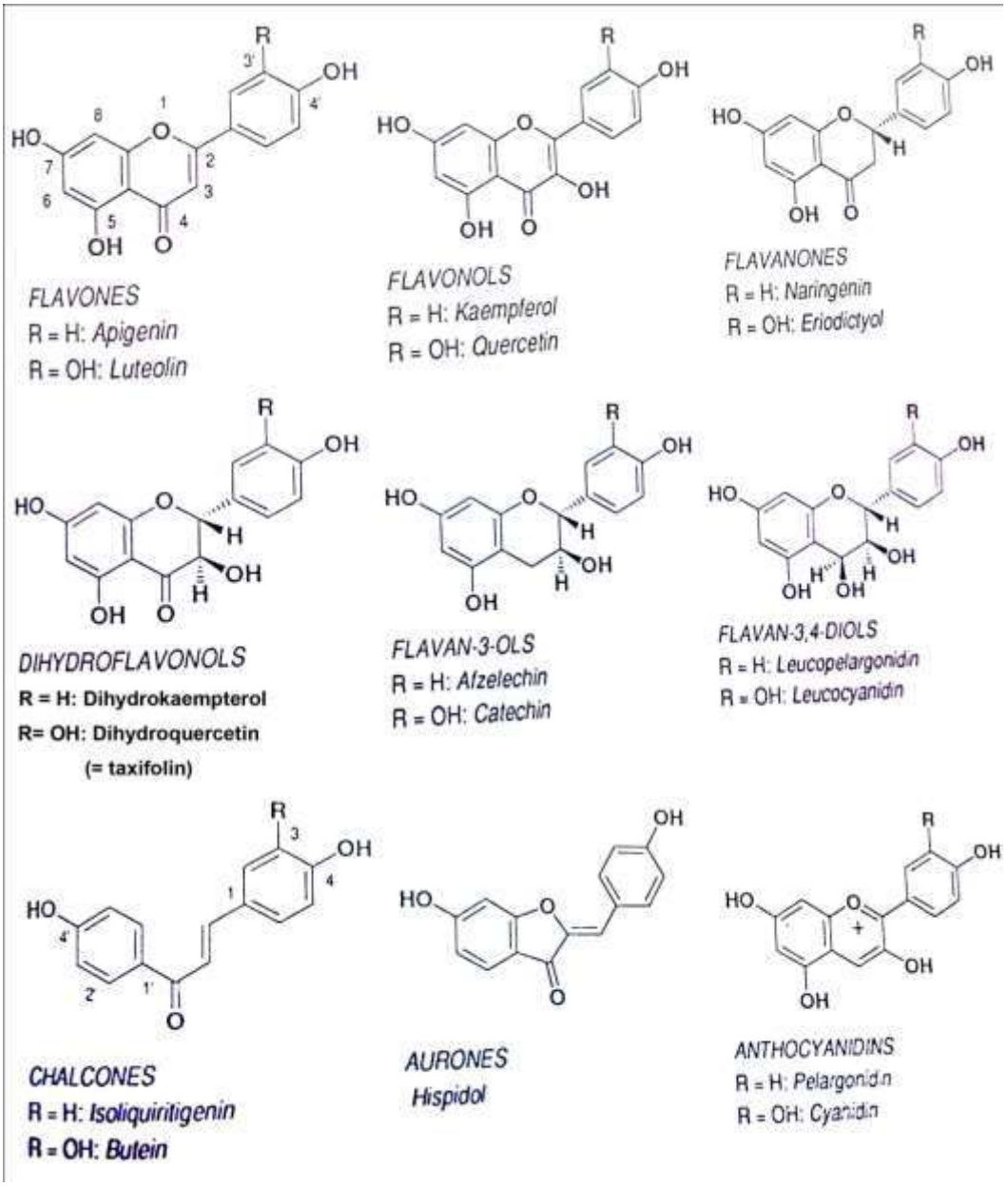
Tea Bags

Chapter 6

Flavonoids

Flavonoids in the sense of the term are virtually universal plant pigments. They are responsible for the color of flowers, fruits and sometimes leaves. For example, there are yellow Flavonoids (chalcones, aurones & yellow flavonols), and red, blue or purple anthocyanins.

All Flavonoids have a common biosynthetic origin, and therefore possess the same basic structural element, namele the 2-phenylchromane skeleton.



Occurrence

Flavonoids are common in Bryophytes (O-& C-glyccosides flavones, biflavonoids, proanthocyanins), Gymnosperms (proanthocyanins, flavones, flavonol) and in Angiosperms where the structural diversity of Flavonoids is maximal.

Flavonoids Functions in Plants

The flavonoids are a remarkable group of plant metabolites. No other class of secondary product has been credited with so many—or such diverse—key functions in plant growth and development.

Anthocyanins and 3-Deoxyanthocyanins

- Defence
- Protection from Solar Ultraviolet
- Photoprotection
- Antioxidant Activity
- Anthocyanins as a Generalized Stress Response

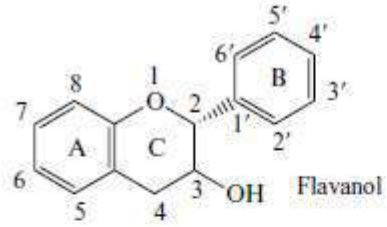
Colorless Flavonoids

- Stress Protection
- Heavy Metal Tolerance
- Oxidative Stress
- Reproduction
- A Role as Chemical Messengers

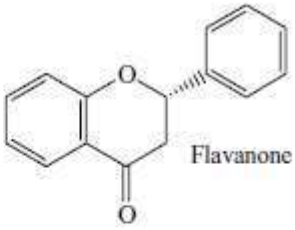
Chemical Structure & Classification

There are 6 classes of Flavonoids, biosynthesis frequently places at least three phenolic hydroxyl groups in the 5, 7, and 4’ positions of the aglycone, however, one of these may also be absent.

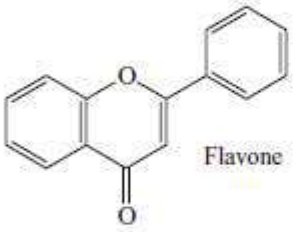
1. Flavones, Flavonols.
2. Flavanones and Dihydroflavanols.
3. Biflavonoids.
4. Chalcones, Aurones.
5. Glycosylflavonoids.
6. *C*- Glycosylflavonoids.



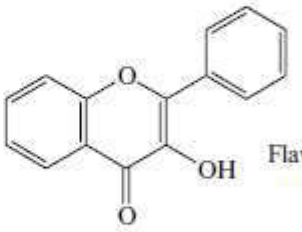
Flavanol



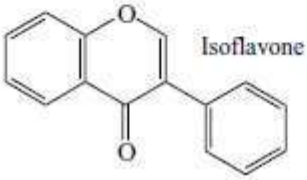
Flavanone



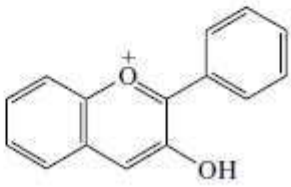
Flavone



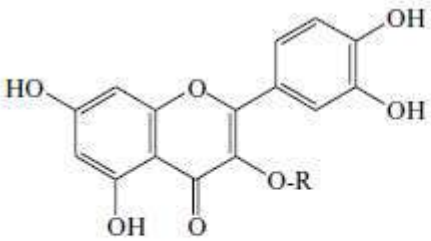
Flavonol



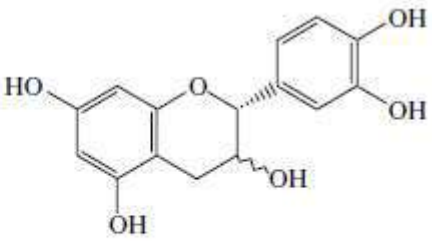
Isoflavone



Anthocyanin (pigment)



R = H (quercetin)
R = β-D-Glc (isoquercitrin)
R = α-L-Rha-1,6-β-D-Glc (rutin)

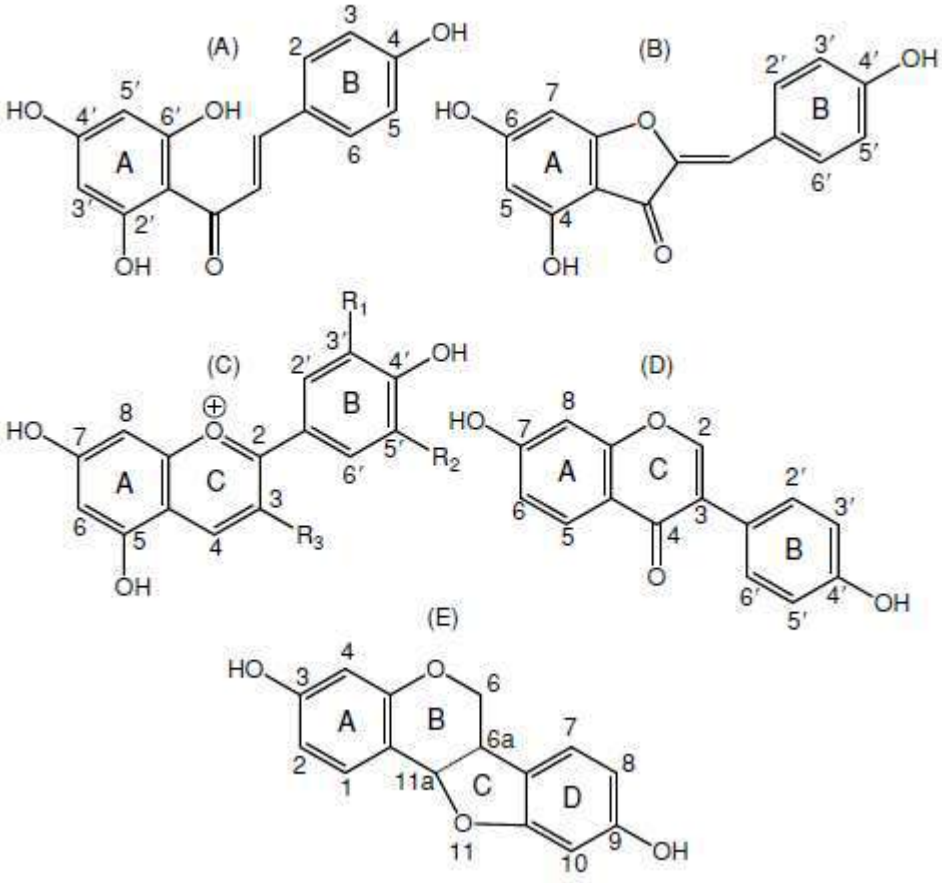


Catechin (*3S*), epicatechin (*3R*)

The main flavonoid classes

Flavonoid Biosynthesis

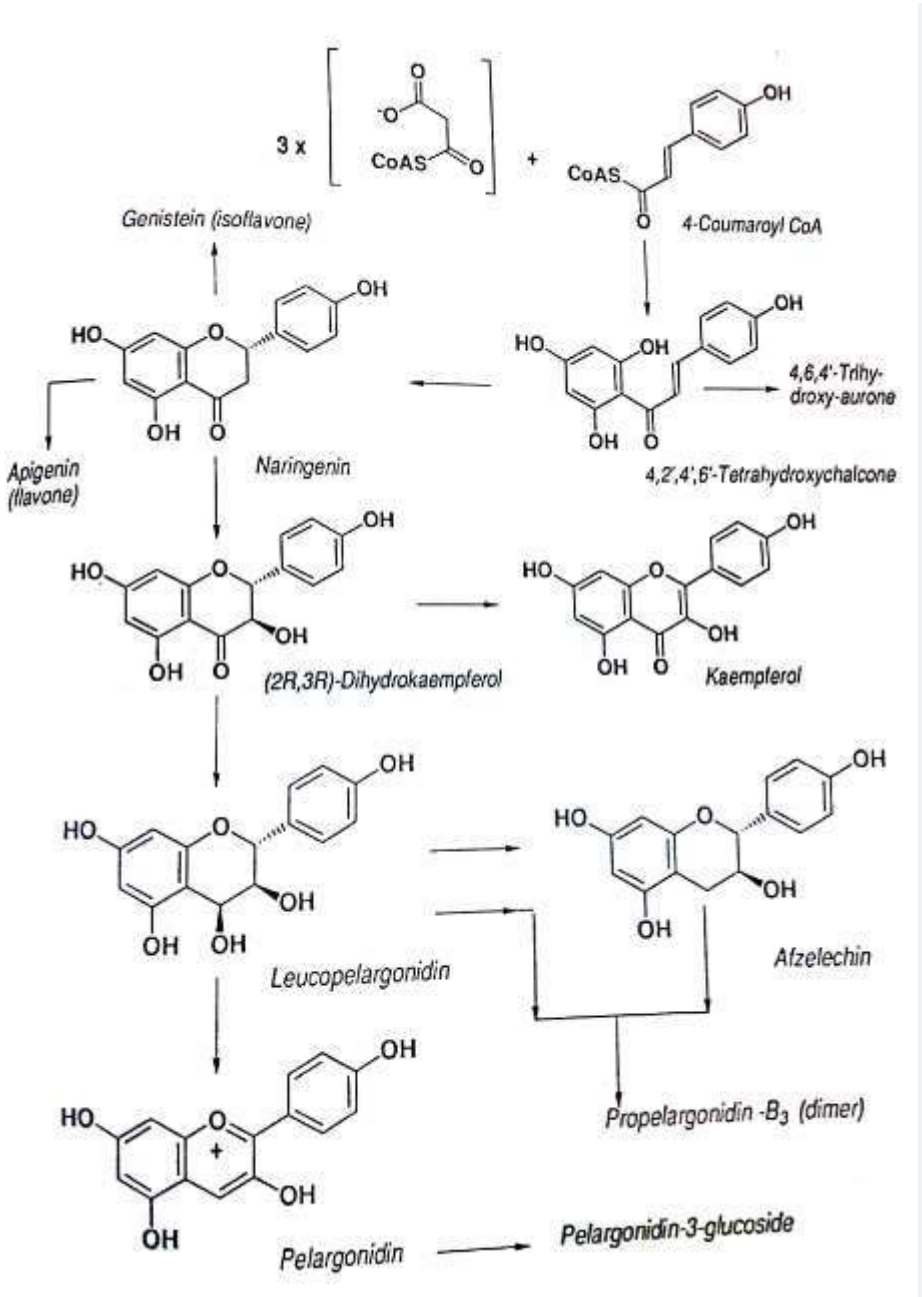
The flavonoid pathway is part of the larger phenylpropanoids pathway, which produces a range of other secondary metabolites, such as phenolic acids, lignins, lignans, and stilbenes. The key flavonoid precursors are phenylalanine, obtained via the shikimate and arogenate pathways, and malonyl-CoA, derived from citrate produced by the TCA cycle. There are many branches to the flavonoid biosynthetic pathways, with the best characterized being those leading to the colored anthocyanins and proanthocyanidins (PAs) and the generally colorless flavones, flavonols, and isoflavonoids.



Base structures of a chalcone (A), an aurone (B), the main anthocyanidins (C), an isoflavonoid (D), and a pterocarpan (E).

Biosynthesis of Flavonoid Precursors

The first flavonoids, the chalcones, are formed from HCA-CoA esters, usually 4-coumaroyl-CoA, in three sequential reactions involving the ''extender'' molecule malonyl-CoA.



The other flavonoids (Flavonols, proanthocyanidins, anthocyanins) no longer have carboxyl group in 4 position. They all arise from a trans-dihidro-cis-dihydroxyflavonol (leucoanthrocyanidin), itself a reduction product of dihydroflavonol.

Physico-Chemical Properties, Separation & Extraction

Flavonosides are **water soluble and soluble in alcohols**, aglycones, for the most part, **soluble in polar organic solvents**, when they have at least one free phenolic group, they **dissolve in alkaline** hydroxide solutions.

Lipohhilic flavonoids can washed with hexane and then extracted by solvents of medium polarity (dichlormethan).

The glycosides can be extracted by acetone or by alcohols mixed with water.

The separation and purification of the different flavonoids is based on the usual chromatographic techniques.

Although several color reactions allow the characterization of aglycones and glycosides.

The classic quantitation methods are colorimetric or spectrophotometric and HPLC.

Extraction

Flavonoids (particularly glycosides) can be degraded by enzyme action when collected plant material is fresh or non-dried; **it is thus advisable to use dry, lyophilized, or frozen samples**.

When dry plant material is used, it is generally ground into a powder.

For **extraction**, the solvent is chosen as a function of the type of flavonoid required.

Polarity is an important consideration here. **Less polar flavonoids** (e.g., isoflavones, flavanones, methylated flavones, and flavonols) are **extracted with chloroform**, dichloromethane, diethyl ether, or ethyl acetate, while flavonoid glycosides and **more polar** aglycones are **extracted with alcohols** or alcohol–water mixtures.

Glycosides have increased water solubility and aqueous alcoholic solutions are suitable. The bulk of extractions of flavonoid-containing material are still performed by simple direct solvent extraction.

Flavan-3-ols (catechins, proanthocyanidins, and condensed tannins) can often be **extracted directly with water**.
However, the composition of the extract does vary with the solvent — whether water, methanol, ethanol, acetone, or ethyl acetate.
Anthocyanins are **extracted** with **cold acidified methanol**. The acid employed is usually acetic acid (about 7%) or trifluoroacetic acid (TFA) (about 3%). The use of mineral acid can lead to the loss of attached acyl groups.

Biological Properties

The main property attributed to flavonoids is a **"vitamin P factors"** or "P factor" activity, potentially active on veins; they increase capillary permeability and fragility.
Flavonoids are often anti-inflammatory which is compatible with what is known of their interactions in the metabolism of arachidonic acid (apigenin) and can be antiallergic, hepatoprotective (isobutrin, flavanolignanes), antispasmodic (flavonoids of thyme) and they can be diuretic, decrease blood cholesterol level, antibacterial, antiviral and antioxidant.

Therapeutic Uses

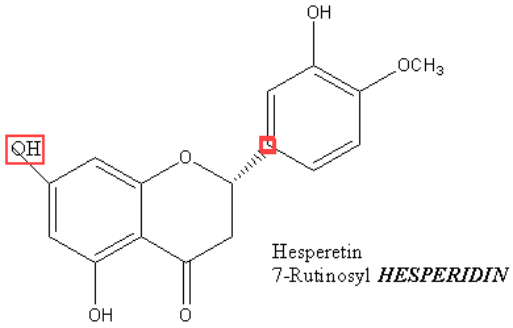
- To treat capillary and venous disorder.
- Vascular protective agents.
- Venous tonic.
- To treat capillary fragility disorder.
- To treat dysfunctions linked to the acute attack of piles.
- To treat metrorrhagias.
- To treat circulatory disorder of the retina.

Flavonoids Containing Drugs

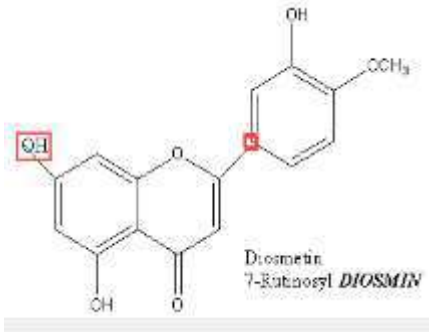
Citroflavonoids

Citrus from Rutaceae family

These are very abundant in pericarp and are mainly flavonone glycosides (hesperidine, naringin)



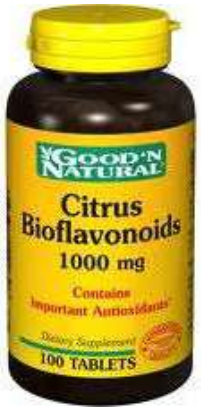
Hesperetin
7-Rutinosyl ***HESPERIDIN***



Diosmetin
7-Rutinosyl ***DIOSMIN***

and flavone glycosides (diosmin, rutin). Citrus is indicated in the treatment of leg symptoms of chronic functional and organic venous insufficiency, fullness, pains and nocturnal cramps.

The daily administration dose is 1g/day for 8-10 weeks.



Rutin: quercetin 3-rutinoside

Sophora japonica

Fabaceae Family

Japanese Pagoda

PHYTOCHEMICALS

Flavonoids: including rutin, sophorine

Polysaccharides: galactomannans

Quinolizidine alkaloids (0-0.04%):

including among others

cytisine, N-methyl cytisine, matrine, sophocarpine

Fatty oil

Proteins

Toxic lectins

EFFECTS

The active agent, rutin, increases the permeability of the capillaries.

Ginkgo biloba

Ginkgoaceae Family

Ginkgo, Maidenhair Tree

MEDICINAL PARTS

The medicinal parts are the fresh or dried leaves, and the seeds separated from their fleshy outer layer.

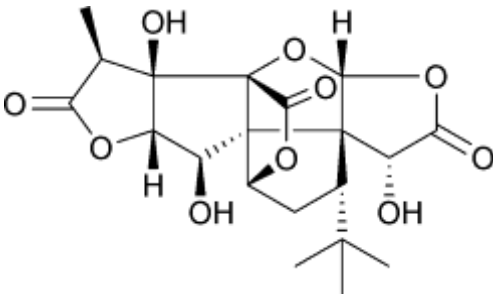
PHYTOCHEMICALS

Flavonoids (0.5-1. 8%): including monosides, biosides and triosides of quercetin, isorhamnetins, 3-0- methylmyristicins, & kaempferol, to some extent estered with p-coumaric acid

Biflavonoides (0.4-1.9%): for example, amentoflavone, bilobetin, 5-methoxybilobetin, ginkgetin, isoginkgetin

Proanthocyanidins (8-12%)

Trilactonic diterpenes (0.06-0.23%): ginkgolide A, B, C



Ginkgolide B

EFFECTS

Ginkgolide B is a potent inhibitor of platelet-activating factor (PAF), which is important for the induction of arachidonate-independent platelet aggregation. Ginkgolide B blocks the binding to PAF to its receptor resulting in an antagonistic effect (Chung, 1987). This effect will inhibit PAF-induced bconchoconstriction and airway hyperactivity, along with T-lymphocyte proliferation and cytokine production.

PAF induces inflammation and changes in vascular permeability. Ginkgo biloba exerts ischemic protective and antioxidant effects through the flavonoids. This occurs through a free scavenger action and prevention of lipid peroxidation. Lipid peroxidation is involved in producing tissue and vascular damage, and neuronal loss, which may lead to dementia.

Other effects consist of spasmolytic properties through direct action on alpha-adrenoceptors and smooth muscle relaxing properties.

Passiflora incarnate

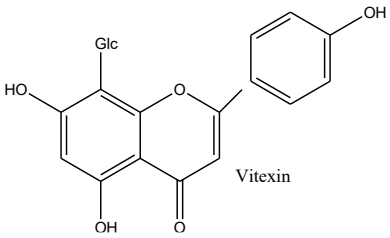
Passifloraceae Family

Passion Flower

MEDICINAL PARTS

The medicinal parts are the whole or cut dried herb and the fresh aerial parts. The yellow pulp from the berry is edible. Several other related species also have edible fruits or healing properties.

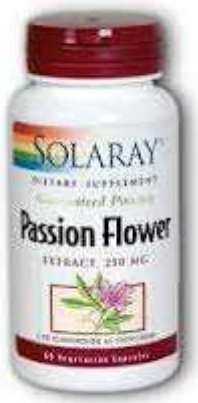
PHYTOCHEMICALS



Flavonoids (up to 2.5%): in particular C-glycosyl-flavones, including among others isovitexin-2"-o-glucoside, schaftoside, isoschaftoside, isoorientin, vitexin, saponarin.

Cyanogenic glycosides: gynocardine (less than 0.1%)

Volatile oil (trace)



EFFECT

Sedative or spasmolytic effects could not be definitively proven.

USES

- *To treat abnormalities of the cardiac rhythm in the adult and*
- *To treat the symptoms of nervousness in adults and children, particularly minor sleeplessness.*

Thymus vulgaris

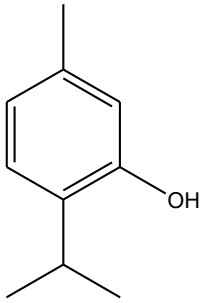
Lamiaceae family

Thyme

MEDICINAL PARTS

The medicinal parts are the oil extracted from the fresh, flowering herb: the dried leaves; the striped and dried leaves; and the fresh aerial part of the flowering plant.

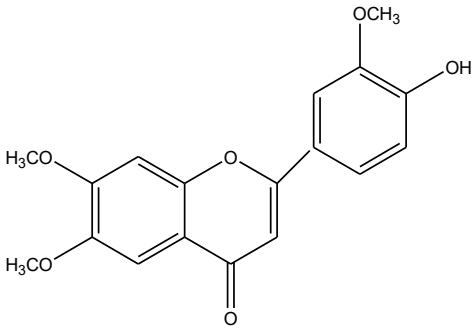
PHYTOCHEMICALS



Thymol

Volatile oil *(LO-2.5%):* chief components thymol (20-55%), p-cymene (14-45%), carvacrol (1-10%), gamma-terpinene (5-10%), borneol (up to 8%), linalool (up to 8%).

Caffeic acid derivatives*:* rosmarinic acid (0.15-1.35%).



5,4'-Dihydroxy-6,7,3'-trimethoxyflavone

Flavonoids*:* including among others, luteolin, apigenin, naringenin, eriodictyol, cirsilineol, salvigenin, cirsimaritin, & thymonine, thymusine, partially present as glycosides.

Triterpenes*:* including among others, ursolic acid (1.9%), oleanolic acid (0.6%)

EFFECTS

Thyme is a bronchial antispasmodic, an expectorant, anti-inflammatory agent and an antibacterial agent.

INDICATIONS AND USAGE

- Cough
- Bronchitis

Achillea millefolium

Asteraceae family

Yarrow

MEDICINAL PARTS

The dried flower clusters and above-ground parts of the herb are used medicinally.

PHYTOCHEMICALS

Flavonoids: including apigenine-7-O-glucoside, luteolin-7- O-glucoside, rutin.

Volatile oil *(0.2-1.0%):* chief components (rendered through steam distillation) are chamazulene.

Sesquiterpene lactones*:* Mainly guaianolides including, achillicin, 8-alpha-angeloyloxy-10-epi-artabsin.

Some sesquiterpenes are transformed through steam distillation into chamazulene (proazulenes).

Polyynes*:* including pontica epoxide

Alkamids*:* including tetradeca-4,6-diin-10,12-dien acetyl isobutylamides

Betaine*:* including L-stachydrine, L-hydrostachydrine (betonicine)

EFFECTS

The herb has a cholagogue (stimulates the flow of bile) effect due to the guaianolide and germacranolide content.

The flavonoid content exerts a spasmolytic effect, while the proazulene fraction has an anti-edema and anti-inflammatory effect. The effect probably results from the interaction of various structured bonds with the chamazulene and flavonoids.

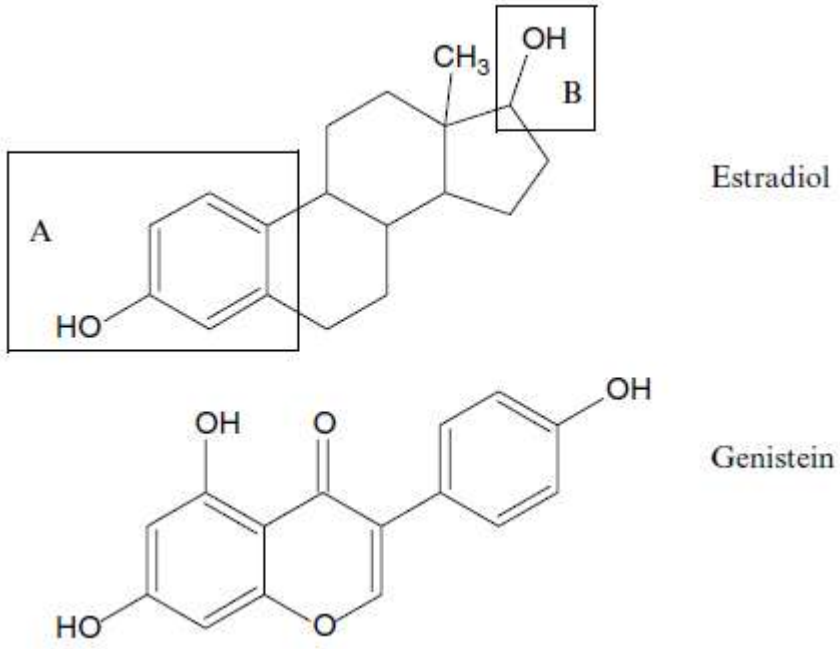
INDICATIONS AND USAGE

- Loss of appetite
- Dyspeptic complaints
- Liver and gallbladder complaints

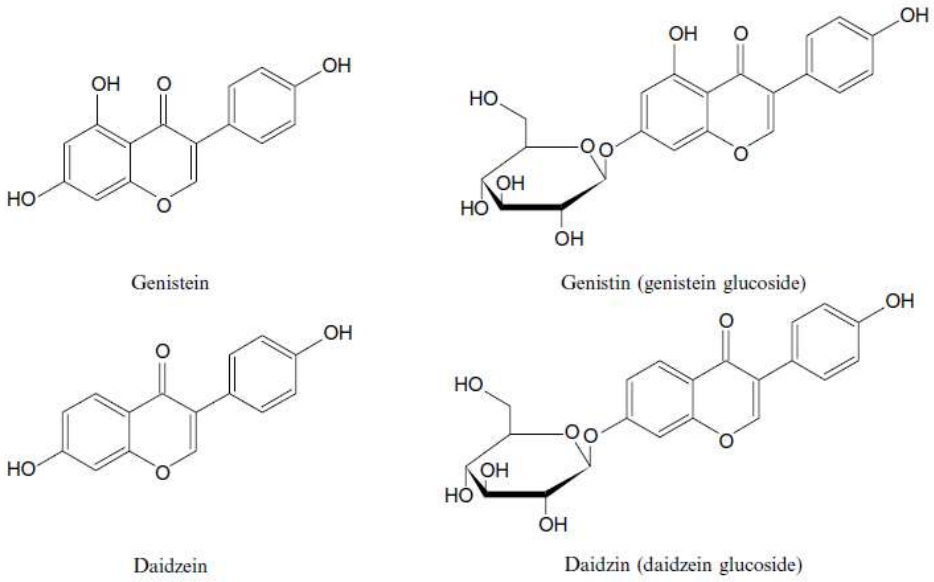
Chapter 7

ISOFLAVONOIDS

Isoflavonoids phytoestrogens such as the soy isoflavones genistein and daidzein are plant derived non-steroidal estrogen mimics, often referred to as phytoestrogens.



The structural relationship between phytoestrogens and 17β-estradiol



Chemical structures of the main soy (genistein and daidzein) isoflavonoids (aglycones and glucosides)

Soy foods are made from soy beans and include both fermented and non-fermented foods. Non-fermented soy foods contain isoflavones mostly present as β-glycosides, some of which are esterified with malonic acid or acetic acid. Fermented soy foods such as miso or tempeh contain mostly unconjugated isoflavones.
The possible role of Isoflavonoids in the prevention of cancer and in particular hormone dependent cancers such as breast and prostate cancer is currently extensively investigated.

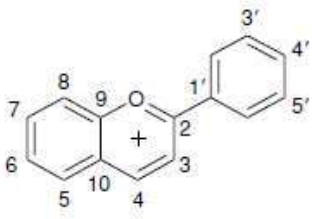
Chapter 8

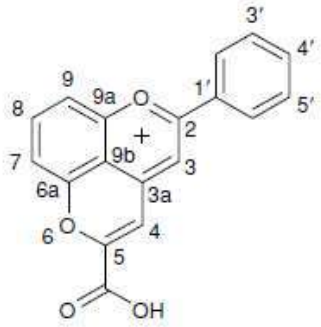
The Anthocyanins

The anthocyanins constitute a major flavonoid group that is responsible for cyanic colors ranging from salmon pink through red and violet to dark blue of most flowers, fruits, and leaves of angiosperms.

These pigments occur as glycosides (anthocyanins) and their aglycone (anthocyanidin) are derived from the 2 - phenylbenzopyrylium (flavylium cation).

The Numbering of the Structure on the Left is Used for all Anthocyanins; the Numbering for the Pyranoanthocyanins is Given in the Structure on the Right.

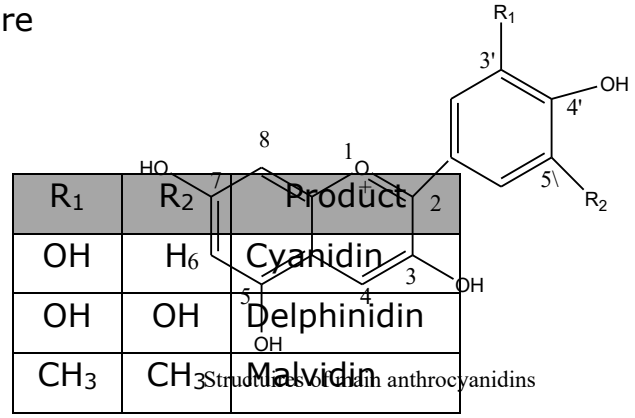




Structure & Biosynthetic Origin of Anthocyanins

Anthocyanidins occur in acidic medium as cations, They are always hydroxylated in the 3 position and, most often, penta (3, 5, 7, 3′, 4′) or hexasubstituted (3, 5, 7, 3′, 4′, 5′)by hydroxyl groups which may be free, methylated, or engaged in Glycosidic bond.

The most common aglycones are presented as follow:



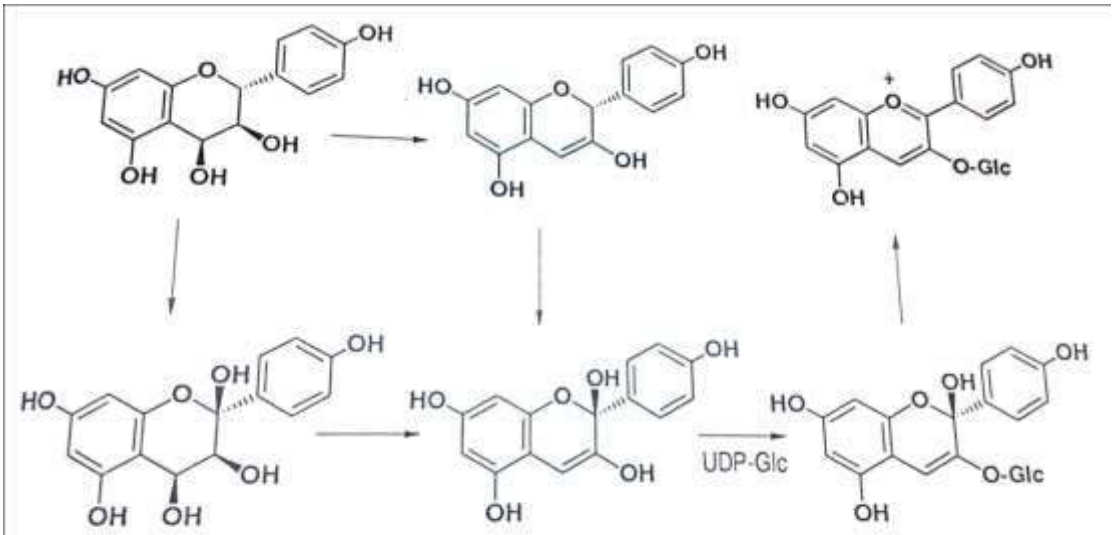
R_1	R_2	Product
OH	H_6	Cyanidin
OH	OH	Delphinidin
CH_3	CH_3	Malvidin

Structures of main anthrocyanidins

The 3 hydroxyl group is always linked to a sugar. Many anthrocyanins are acylated by phenylpropanoic acids, which esterify one or several hydroxyl groups on the saccharides.

Biosynthetic Origin

Anthocyanins arise from the general metabolism of flavonoids.



Possible biosynthetic origin of anthocyanins

Physico-chemical properties, extraction

Anthrocyanins are soluble in water and alcohols, and insoluble in polar organic solvents. They are generally **extracted** with an **alcohol** in the presence of **small amount 0.1-1% of HCl,** to

1. Avoid esterification of the free carboxyl group of acylated anthrocyanins by diacid, and to
2. Prevent their deacylation.

In **strong acid medium**, the cation is **red and stable**, in **weak acid** medium the cation loss one or two protons and this lead to anhydro-base **blue** in color. **Hydrating** the molecule (in 2-position) leads to carbinol, which is **colorless**.

Anthocyanins solutions are very unstable, and they can only be kept under nitrogen, at low temperature and in the dark.

The separation of anthrocyanins is achieved by chromatographic techniques (TLC, HPLC).

Pharmacological Activity

Anthocyanins decrease capillary permeability and fragility. Other activity: antiedema, regeneration of visual purple and coloring agents.

Anthocyanins Containing Drugs

Vaccinum myrtillus

Ericaceae family

Blueberry

DESCRIPTION

Blueberries are flowering plants of the genus Vaccinium (a genus which also includes cranberries and bilberries) with dark-blue berries.

PHYTOCHEMICALS

Blueberries are rich in anthocyanins, proanthocyanidins, resveratrol, flavonols, quercetin, tannins, water, sugars, and organic acids.

NUTRIENT VALUE

Blueberries have a diverse range of micronutrients, with notably high levels of the essential dietary mineral manganese, vitamin B6, vitamin C, vitamin K and dietary fiber.

INDICATIONS

- Vascular protective & antiedemic.
- Inhibit collagen induced platelet aggregations.
- Anti-inflammatory agent & Antioxidant agent.

Ribes nigrum

Grossulariaceae

Black Currant

MEDICINAL PARTS

The medicinal parts are the leaves collected after the flowering season and dried, **the fresh ripe fruit** with the tops and stems and the fresh leaves collected in summer.

PHYTOCHEMICALS: BLACK CURRANT FRUITS

Ascorbic acid (vitamin C, 0.1 to 0.3%)

Anthocyans*:* chiefly cyanidin-3-O-rutinoside and delphinidin-3-O-rutinoside.

Phenol caroboxylic acid derivatives*:* caffeoyi-, p-cumaroyl and feruloyl-quinic acids; p-cumaroyl and feruloyl glucoses

Flavonoids*:* chief components isoquercitrin, myricetin glucoside, rutin

Fruit acids *(3.5%):* malic acid, citric acid, isocitric acid

Invert sugar

EFFECTS:

The extract of the drug that contains anthocyane has a hypotensive and spasmolytic effect in animal experiments. In addition, an antimicrobial and xanthine-oxidase and lipoperoxidase inhibiting effect has been proven.

INDICATIONS AND USAGE

Black currant dried berries are used for bladder complaints, venous insufficiency, hemorrhoids, bruising and petechiae.

Chapter 9

TANNINS

Generalities

Seguin first applied the term ''tannin'', in 1796 to denote: *'' the substances present in plant extracts that able to combine with proteins of animal hides prevent their putrefaction and convert them into leather''*.

Based on this definition tannin is '' a substance that is detected qualitatively by a tanning test (the goldbeater's test) and is determined by its adsorption on standard hide powder''.

Many tannins occur as glycosides. The characteristic behavior of tannins derives from the presence of a considerable number of Phenolic groups within a molecule of moderate size.

In fact, the astringent and antiseptic activities of tannins, as well as their effects towards alkalis and iron salts, are attributed to this polyphenolic nature.

These properties are basis of the classic definition of tannins: "***water soluble phenolics of molecular weight between 500 and 3000 which in addition to displaying the classic reactions of phenols can precipitate alkaloids, gelatin, and other proteins".***

Major sources of commercial tannins, as used in the leather industry, are obtained from chestnut and myrobolans trees. Pharmaceutical tannin is prepared from oak galls.

Some plants contain tannins in addition to the principal therapeutic constituents. This may complicate extraction or produce incompatibities with other drugs (many alkaloids, for example, are precipitated by tannins). The removal of tannins from the extracts is thus recommended.

Certain drugs contain only one type of tannin. Others may contain than one type e.g. tea, hamamelis leaves and bark contain both hydrolyzable and condensed tannins.

Types of Tannins

The major types of tannins are:

A. True Tannins

- These are complex Phenolic compounds of high molecular weights ranging from about 1000 to 5000. they display the general properties of tannins and are precipitated by gelatin in 1% solution.
- The tannins can be sub classified into **hydrolysable tannins**, **condensed tannins** and **complex tannins**.
- Two types of hydrolazable tannins are distinguished the **gallitannins** and the **ellagitannins**.

B. Pseudo- Tannins

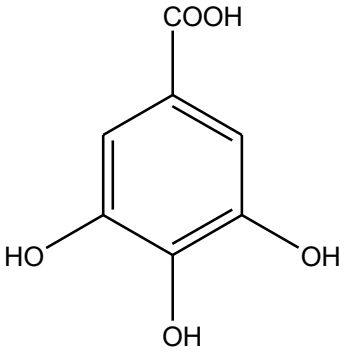
These are simple phenolics that give some of the tests for tannins buy are not precipitated gelatin in 1% solution.

A: True Tannins

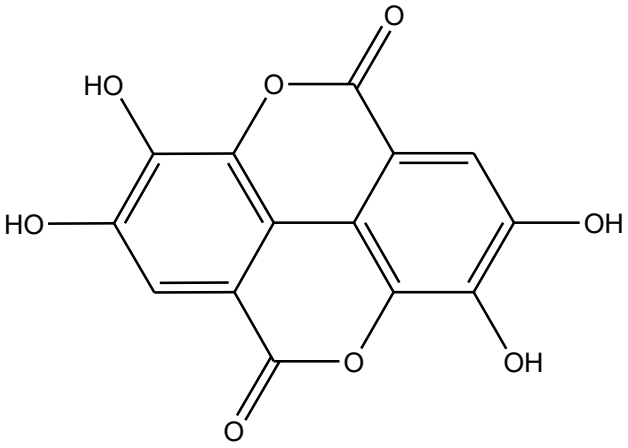
A-1: Hydrolysable tannins

- These may be hydrolyzed by acids or enzymes such as tannase.
- They are formed from several molecules of phenolic acids such as gallic and hexahdroxydiphenic acids which are united by ester linkages to a central glucose molecule.
- Like gallic acid their solutions turn blue with iron salts.
- They were formerly known as pyrogallol tannins, because on dry distillation gallic acid and similar components are converted into pyrogallol.
- Two principal types of hydrolysable tannins are gallitannins and ellagitannins which are, respectively, composed of gallic acid and hexahydiphenic acid units.
- Ellagic acid (the depside of gallic acid) can arise by lactonization of hexahdroxydiphenic acid during chemical hydrolysis of the tannin, thus the term ellagitannins is a misnomer.

- C-glucosidic ellagitannins are common in a number of families including the Myrtaceae, Hamamelidaceae, Punicaceae and Rosaceae.



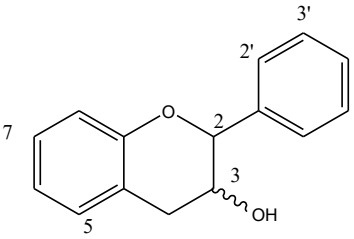
Gallic Acid



Ellagic Acid

A-2: Condensed tannins (proanthocyanidins)

- Unlike hydrolyzable tannins these are not readily hydrolyzable to simpler molecules and they do not contain a sugar moiety.
- They are related to flavonoid pigments and have polymeric flavan-3-ol-structures (usually di-and trimers).



Flavan 3 ol

- Catechins which also occur with the tannins and flavan-3,4-diols (Lecoanthocyanidins) are intermediates in the biosynthesis of the polymeric molecules.
- On treatment with acids or enzymes condensed tannins are converted into red insoluble compounds known as Phlobaphenes.
- Phlobaphenes give the characteristic red color to many drugs such as red cinchona bark, which contain these phlobatannins and their decomposition products.
- On dry distillation they yield Catechol and these tannins are therefore sometimes called Catechol tannins.

A-3:Complex tannins

These represent a group of tannins that are biosynthesized from both hydrolysable tannin (mostly a C-glucoside ellagitannins) and condensed tannin. The union occurs through a C-C bond between the C-1 of the glucose unit of the ellagitannins and the C-6 the flavan-3-ol derivative.

B: Pseudotannins

Pseudotannins are polyphenolic compounds of lower molecular weight than true tannins. They do not respond to the goldbeater's skin test. Examples are gallic acid, catechins and chlorogenic acid.

Physical properties

- Tannins are non-crystallizable compounds.
- They are soluble in water forming colloidal solutions with reaction and sharp astringent taste.
- They are soluble in dilute alkalis, alcohol, glycerol and acetone, nut only sparingly soluble in other organic solvents.
- Their solutions precipitate heavy metals, alkaloids, glycosides and protein (e.g. gelatin).

Extraction

Tannins are generally **extracted with a water and acetone** mixture (methanol is to be avoided because The optimal yield is obtained from the fresh tissues, or from the frozen or lypophilized tisseues, because the dried drugs, part of tannins is irreversibly combined to other polymers. After eliminating the acetone, the pigments and lipids are removed from the aqueous solution by a solvent extraction (chloroform).

Next an ethyl acetate extraction of the aqueous solution separates the dimeric proanthocyanidins and most gallitannins. The polymeric proanthocyanidins and high molecular weight gallitannins remain in the aqueous phase.

Tests for identification of tannins

Goldbeater's skin test (skin tanning test):

Goldbeater's skin is a membrane prepared from the intestine of the ox, soak a small piece of goldbeater's skin in 25% HCL; rinse with distilled water and place in the solution to be tested for 5 min. wash with distilled water and transfer to a 15 % solution of ferrous sulphate. **A brown or black color on the skin denotes the presence of true tannins.**

Medicinal and biological properties

- Tannin-containing drugs precipitate proteins and have been traditionally used as styptics **(stop hemorrhage)** and internally for the protection of inflamed surfaces of mouth and throat.
- They play an important role in the **treatment of burns**. They from a mild antiseptic protective layer on the surface of the injured skin below which regeneration of new tissue takes place.
- They act as **anti-diarrheals**, although not recommended in this respect ad they usually hinder elimination of bacterial toxins from the body.
- Tannins have been employed as **antidote in poisoning by heavy metals**, alkaloids and certain glycosides due to their precipitation as tannates.
- Tannin solutions have also been used as **laboratory reagents** for detection of these constituents.
- Recently tannins as most polyphenols were proved to have a potent **antioxidant effect**.
- Studies on the **antitumour** effect of tannins proved that a strong activity is obtained with ellagitannins having galloyl groups at the O-2 and O-3 positions of the glucose core(s), as in the tellimagrandins.

- Certain tannins were proved to have anti-HIV activities.

Economical importance

- Tannins are **used in leather industry** to transform raw animal skin to leather due to their ability to cross-link with proteins.
- Tannins are used in **food industry** to improve acceptance of many beverages and foods when a degree of astringency is required.

USES

Tannic acid is the major source of pharmaceutical tannin. It is used as an astringent and styptic.

Tannins Containing Drugs

Quercus infectoria

Fagaceae

Oak

MEDICINAL PARTS

The medicinal part of the plant is the leaf.

PHYTOCHEMICALS

Tannins (60 to 70%): gallotannins, particularly hexa- and heptagalloyl-glucoses.

Phenol carboxylic acids: gallic acid (3%), ellagic acid (2%).

EFFECTS

The astringent quality of the drug can be explained by the tannins it contains. The dry extract exhibits analgetic, hypoglycemic and sedative-hypnotic efficacy.

Hamamelis virginiana

Hamamelidaceae Family

Witch Hazel

MEDICINAL PARTS:

The medicinal parts are the plant's hamamelis water, which is distilled from various plant parts; the bark; the fresh and dried leaves; the fresh bark of the roots and branches; and the dried bark of the trunk and branches.

PHYTOCHEMICALS: WITCH HAZEL BARK

Tannins (up to 12%): including hamamelitannin, monogalloyl hamameloses.

Catechins: including (+) catechin, (+) gallocatechin, (-) epicatechin gallate(III), (-) epigallocatechin gallate(III).

PHYTOCHEMICALS: WITCH HAZEL LEAF

Tannins (5%): including hamamelitannin.

Catechins: including (+) catechin, (+) gallocatechin, (-) epicatechin gallate(III), (-) epigallocatechin gallate(III).

Volatile oil (0.01 to 0.5%): steam distillate, consisting chiefly of aliphatic carbonyl compounds, aliphatic alcohols & aliphatic esters.

Flavonoids: including quercitrin, isoquercitrin

EFFECTS:

Witch Hazel bark & leaves is astringent, anti-inflammatory and locally hemostatic.

INDICATIONS AND USAGE

- Hemorrhoids
- Inflammation of the mouth and pharynx (leaf only)
- Inflammation of the skin
- Venous conditions
- Wounds and bums

Crataegus laevigata

Rosaceae Family

Hawthorn

MEDICINAL PARTS

The medicinal parts are generally white thorn flowers, leaves, fruit, and various mixtures of different plant parts.

PHYTOCHEMICALS

Flavonoides (1.8%): hyperoside, rutin, vitexin

Oligomeric **proanthocyanidins** (2.4%)

Biogenic amines, including tyramine

Triterpenes (0.6%): including oleanolic acid, ursolic acid, 2- alpha-hydroxy oleanolic acid (crataegolic acid)

EFFECT

The active principles are proanthocyanidins and flavonoids. They cause an increase in coronary blood flow due to dilatory effects resulting in an improvement of myocardial blood flow. The drug is positively inotropic and positively chronotropic. The cardiotropic effect of Crataegus is said to be caused by the increased membrane permeability for calcium as well as the inhibition of phosphodiesterase with an increase of intracellular cylco-AMP concentrations. Increased coronary and myocardial circulatory perfusion and reduction in peripheral vascular resistance were observed.

High doses may cause sedation. This effect has been attributed to the oligomeric procyanidins (Anonym, 1994).

INDICATIONS AND USAGE

Hawthorn is used for senile heart, chronic cor pulmonale, and mild forms of bradycardia arrhythmias.

Alchemilla vulgaris

Rosaceae Family

Lady's Mantle

MEDICINAL PARTS

The medicinal part is the herb collected in the flowering season and dried.

PHYTOCHEMICALS

Bitter principles

Flavonoids

Tannins

EFFECTS

Lady's Mantle herb has astringent properties, due to the presence of tannins. It has also been shown to inhibit tumor growth.

INDICATIONS AND USAGE

- Diarrhea

Rubus fruticosus

Rosaceae Family

Blackberry

Medicinal Parts

The medicinal parts are the leaves, roots and berries.

PHYTOCHEMICALS

Fruit acids: including citric acid, isocitric acid

Flavonoids

Tannins (8 to 14%): gallo tannins, dimeric ellagitannins

EFFECTS

Blackberry leaf has astringent and antidiarrheal effects due to the high tannin content.

INDICATIONS AND USAGE

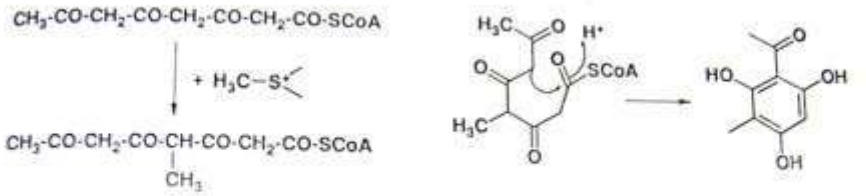
- Diarrhea.
- Inflammation of the mouth and pharynx.

Chapter 10

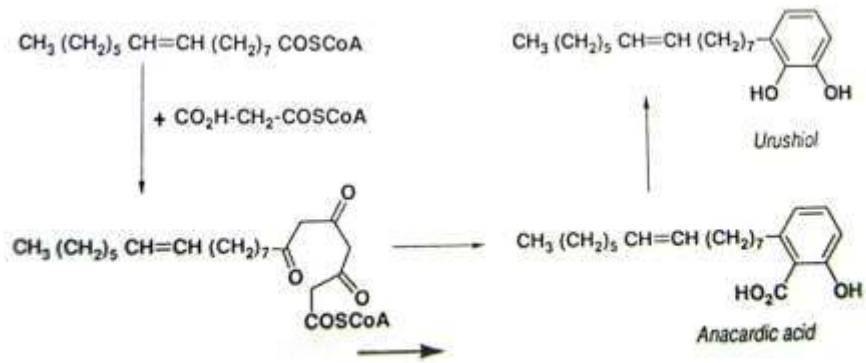
Polyketide

Biosynthetic Generalities

Acetic acid in its activated form of acetyl-*S*-coenzyme A, hold a central position in the biosynthesis of a diverse group of complex molecules: a series of Claisen condensations between two carbon units yield polyketomethylene chains, which lead by reduction to fatty acids, and by further cyclization to many classes of aromatic compounds. A variation, characterized by an aldol condensation, leads, via 3-hydroxy-3methylglutaric acid and mevalonic acid, to the world of terpenes.



Formation of methylphloracetophenone ; its dimerization leads to usnic acid (see generalities)



Polyketides Containing Drugs

Juglans cinerea

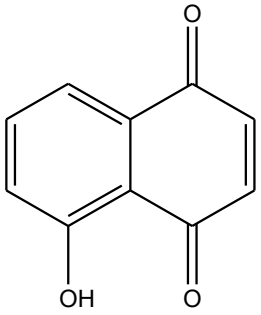
Butternut/ Black Walnut

Medicinal Parts

The medicinal parts are the bark of the tree and root.

PHYTOCHEMICALS

- Fatty oil (unsaturated fatty acids)
- Tannins
- Juglone



Juglone

Effects / Health Benefits

- The nuts are **rich source of energy** and contain health benefiting nutrients, minerals, **antioxidants** and vitamins that are essential for optimum health.
- They are rich in **monounsaturated fatty acids** (about 72%) like **oleic acid** and an excellent source of all important **omega-3** essential fatty acids like **linoleic acid, alpha-linolenic acid** (ALA) and **arachidonic acids**.
- Regular intake of walnuts in the diet helps **to lower total as well as LDL and increases HDL levels in the blood.**
- In addition, they are an excellent source of **vitamin E,** especially rich in gamma-tocopherol; contain about 21 g per 100 g (about 140% of daily-required levels). Vitamin E is a powerful lipid soluble antioxidant, required for maintaining the integrity of cell membrane of mucus membranes and skin by protecting it from harmful oxygen-free radicals.
- These nuts are packed with many important **B-complex groups** of vitamins such as **riboflavin**, **niacin**, **thiamin**, **pantothenic acid**, **B-6**, and **folates**.

- They also very are rich source of minerals like **manganese, copper**, **potassium**, **calcium**, **iron, magnesium**, **zinc**, and **selenium**.

Lawsonia inermis

Henna

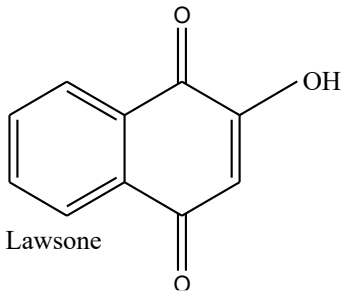
MEDICINAL PARTS

The medicinal parts are the pulverized leaves, the fruit and the bark.

PHYTOCHEMICALS

Naphthalene derivatives (1,4-naphthaquinones): in particular lawsone (2-hydroxy-l,4-naphthaquinone), arising during dehydration of the leaves out of the precursor 1,2,4-trihydroxynaphthalen-4-beta-D-glucoside

Tannins



Lawsone

EFFECTS

The drug is an astringent and a diuretic, and has an antibacterial effect.

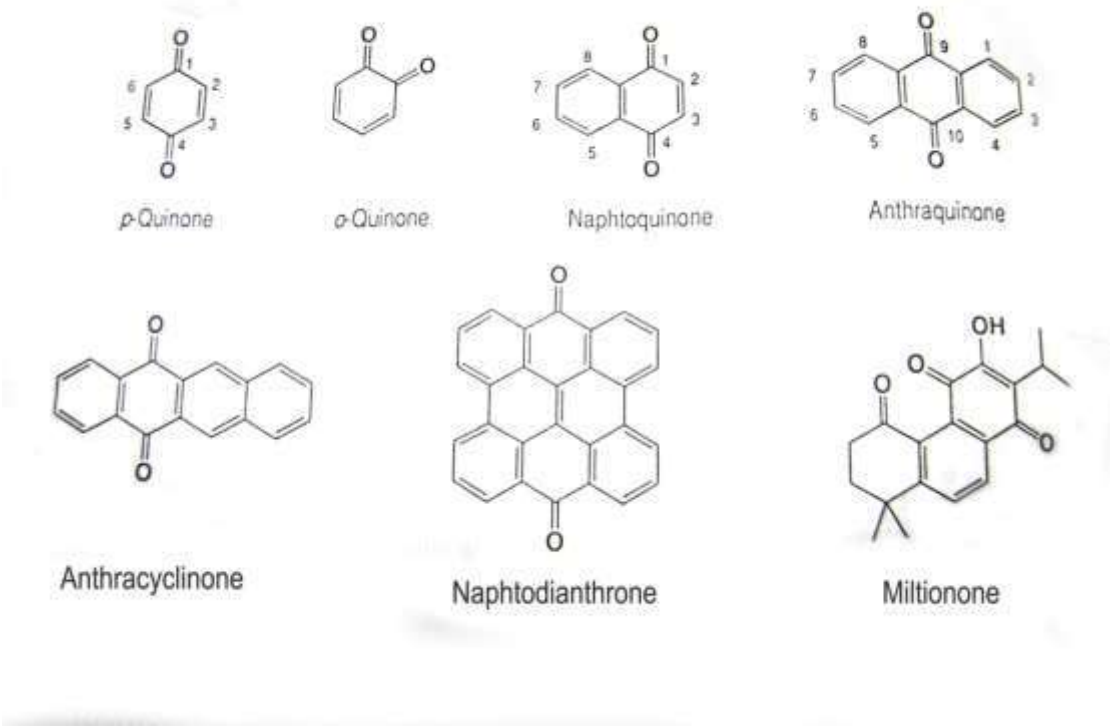
INDICATIONS AND USAGE

The drug is used externally for eczema. scabies, fungal infections and ulcers.

Chapter 11

QUINONES

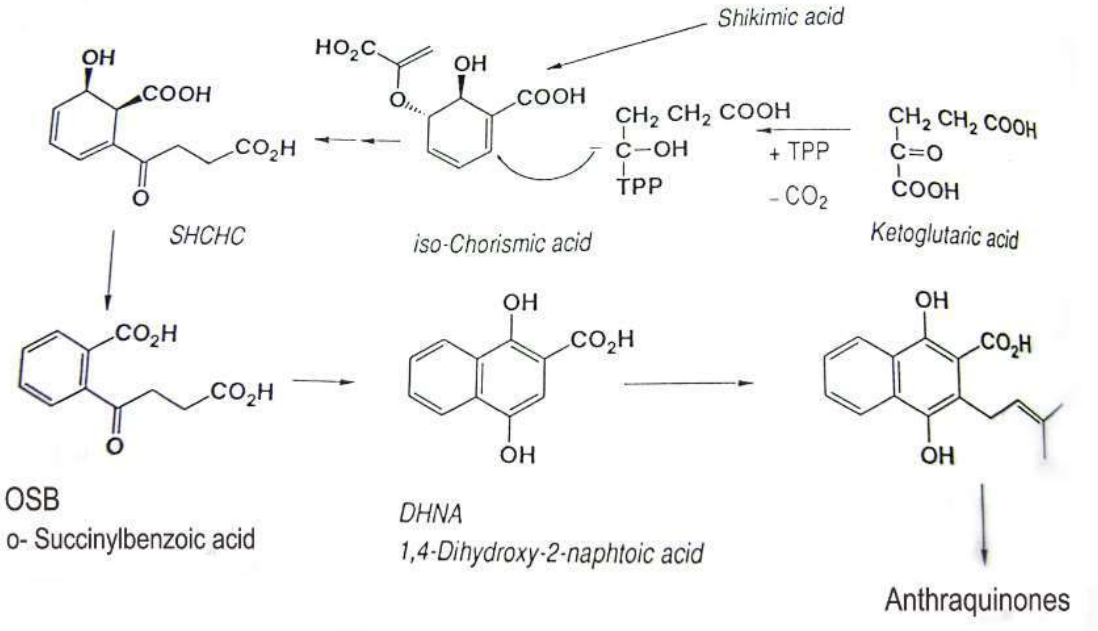
Quinones are oxygen containing compounds which are essentially the oxidized homologs of aromatic derivatives, and are characterized by a 1,4 diketo-cyclohexa2,5-diene pattern (*para*-quinones), or, possible, by a 1,2 diketo-cyclohexa-3,5-diene pattern (*ortho*-quinones). In naturally occurring quinones, the dione is conjugated to an aromatic nucleus (benzoquinones) or conjugated to a condensed polycyclic aromatic system: naphthalene (naphthaquinones), anthracene (anthraquinones), anthracyclinones and so on.



Biosynthesis

Mevalonic & Chorismic acid Pathway

This pathway is the most common in higher plants, is that of O-Succinyl Benzoic acid (OSB). This acid arises from the reaction of isochorismic acid with α-ketoglutaric acid in the presence of thiamine pyrophosphate. It is then acylated by coenzyme A, and cyclized to 1,4-dihydroxy-2naphthoic acid (*DHNA*), the immediate precursor of naphthaquinones; this pathway can be shown to lead to anthraquinones.



Properties, Extraction, Separation & Characterization

There are mild **oxidation reagents,** free quinones are practically **insoluble in water**, can **be extracted by the common organic solvents**, and their separation requires the common chromatographic techniques. **Glycosides extraction is achieved with water or with rather dilute hydro-alcoholic solutions.**

Various color reactions can be used to characterize quinones. The main one is **Bornträger's reaction**, obtained by dissolving the quinone **in alkaline aqueous medium**; the solution develops in a

vivid (brilliant) color which ranges, depending on the structure and the substitutes of the quinone, from orangy-red to purplish-violet. Quinones quantitation is often done by spectrophotometry, and based on one of the colored reactions such as Bornträger's reaction.

Pharmacological properties

The reduced form of 1.4-benzoquinone (hydroquinone) occure as glycoside (arbutin) is strong urinary antiseptic.
Many naphthaquinones are antibacterial and anti fungicidal.
Drugs containing 1,8 dihydroxyanthraquinone derivatives are laxative and purgative and have been used for this activity for centuries (Senna, Rhamnus, & Rheum)
Synthetic hydroquinone has dermatological applications.

Quinone Containing Drugs

Hyderoxyanthraquinone Glycosides

Cassia angustifolia Vahl.

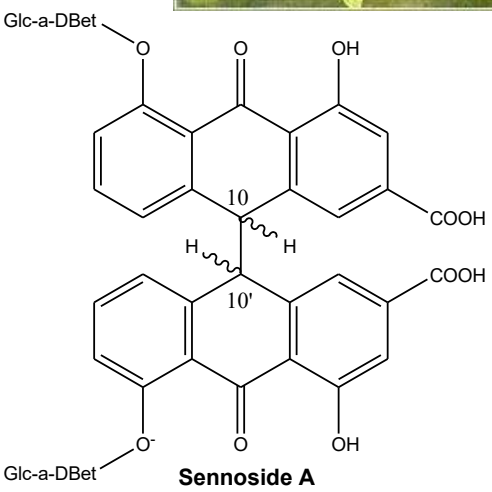
Cassia senna L.

Caesalpiniaceae

MEDICINAL PARTS

The medicinal part is the leaves.

PHYTOCHEMICALS



Sennoside A

The active principles of both drugs are glycosides with 1,8-dihydroxyanthraquinon-type aglycones.

Anthracene derivatives (2.5-3.5%): chief components sennosides A, Al and B, as well as sennosides C and D.

Naphthacene derivatives: including 6-hydroxymusizin glucoside (0.85% in Cassia senna), tinnevellin-6-glucosides (0.3% in Cassia angustifolia).

Flavonoids

Polysaccharides

Naphthalene derivatives.

EFFECTS

Laxative Effects ™

Senna is an anthranoid-type stimulating laxative. The laxative effect is due to the action of sennosides and their active metabolite, rhein anthrone, in the colon. The laxative effect is realized by inhibition of water and electrolyte absorption from the large intestine, which increases the volume and pressure of the intestinal

contents. This will stimulate colon motility resulting in propulsive contractions.

In addition, stimulation of active chloride secretion increases water and electrolyte content of the intestine. These changes in active electrolyte transport are dependent on calcium in the serosal surface (Donowitz, 1984; Yamauchi, 1993). The laxative action of Senna is partially via stimulation of colonic fluid and electrolyte secretion, and this secretion is mediated by stimulation of endogenous prostaglandin E2 formation (Beubler. 1988: Yamauchi, 1993).

INDICATIONS AND USAGE

• Constipation

Senna is used for constipation and for evacuation of the bowel prior to diagnostic tests of the gastrointestinal and colorectal area.

CONTRAINDICATIONS

- The herb is not to be administered in the presence of intestinal obstruction, acute inflammatory intestinal diseases or appendicitis.
- Children & Geriatrics.
- Pregnant & nursing woman

PRECAUTIONS AND ADVERSE REACTIONS

Spasmodic gastrointestinal complaints can occur as a side effect to the drug's purgative effect or from overdosage.

Electrolyte Abnormalies: Long-term use leads to loss of electrolytes, in particular potassium ions. As a result of hypokalemia, hyperaldosteronism, albuminuria, hematuria, inhibition of intestinal motility, and muscle weakness may occur.

DRUG INTERACTIONS

Digitalis Glycosides — with prolonged use or abuse of Senna, loss of potassium may potentiate digitalis toxicity.

Antiarrythmics — Loss of potassium associated with prolonged use of Senna may potentiate arrhythmias when given concomitantly with antiarrhythmic medications.

Estrogen — the serum level of estrogen is decreased when given concomitantly with Senna due to the effect of intestinal transit on the absorption of estrogens (Lewis,1998).

Indomethacin (NSAIDS) — Indomethacin given concomitantly with Senna pod extract had a dose-dependent inhibition of net fluid transport due to~ the v inhibition of prostaglandin E2, which decreases the therapeutic effect of the Senna (Beubler, 1985).

Nifedipine (calcium channel blocker) — Therapeutic effects induced by rhein anthrone also involve the calcium channel which can be blocked by nifedipine, but not verapamil (Yamauchi, 1993).

Rhamnus purshianus

Frangula purshianus
Cascara sagrada

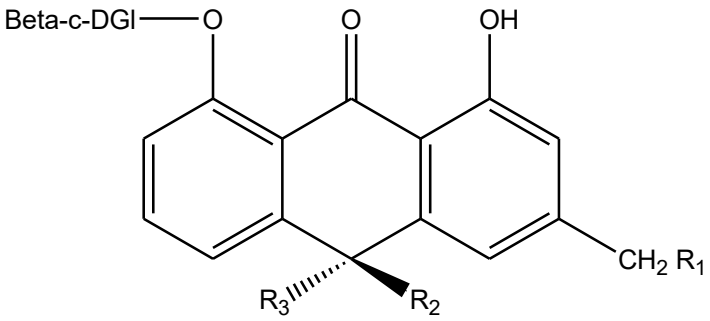
Rhammnaceae

MEDICINAL PARTS

The medicinal parts are the dried bark of the trunk and branches and the fresh bark of the trunk and branches.

PHYTOCHEMICALS

Cascara barks contains 6 to 9% hydroxyl anthraquinon glycosides. The chief constituents are O-glycosides of C-glycosides, namely cascarosides A, B, C and D.



R1 = OH, R2 = Beta-D-Glc, R3=H	Cascaroside A
R1= OH, R2 = H, R3 = Beta-D-Glc	Cascaroside B
R1 = H, R2 = Beta-D-Glc, R3 = H	Cascaroside C
R1 = H, R2 = H, R3 Beta-D-Glc	Cascaroside D

EFFECTS

The bark contains anthracene derivatives and their aglycones which have an anti-absorptive and hydrogogic effect. The anthracene derivatives induce active secretion of electrolytes and water in the intestinal lumina and inhibit the absorption of electrolytes and water from the colon by stimulating propulsive contractions. This results in accelerated intestinal passage time. In this manner, the increased water and subsequent volume of the intestinal content raise pressure and stimulate intestinal peristalsis.

INDICATIONS AND USAGE

• Constipation

CONTRAINDICATIONS

The drug is not to be used with intestinal obstruction, acute inflammatory intestinal diseases, appendicitis or with children under 12 years of age. The drug is not to be administered during pregnancy or while nursing.

Aloe barbadensis/capensis/vera

Aloe

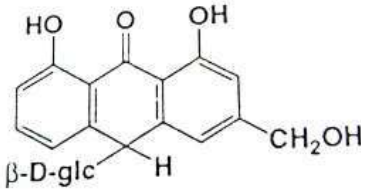
Liliaceae

MEDICINAL PARTS

The medicinal part of the plant is dried juice of the leaves.

PHYTOCHEMICALS

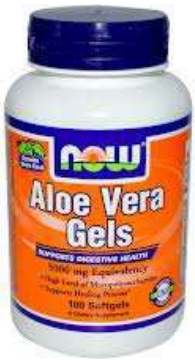
The drug contains 15 to 40% hydroxyl-anthraquinone derivatives, which are aloe-emodin-anthrone-10-C-glycosides: aloin, hydroxyaloins and aloinoside. Aloin is the active principle and chief constituent. Aloin which is a mixture of aloin A and B.



Aloins A, B

EFFECTS

Laxative Effects



Aloe anthranoids such as 1,8-dihydroxy-anthracene derivatives exert a laxative effect. The laxative action is due to anti-absorption osmotic properties. The compounds induce active secretion of electrolytes and water in the lumen of the bowel. Absorption of electrolytes and water from the colon is inhibited resulting in a volume increase. The volume increase of the bowel content leads to an increase in pressure and stimulates intestinal peristalsis.

Antibacterial/Antiviral Effects

Aloe-emodin exerts dose-dependent growth inhibition of *H. pylori* through inhibition of arylamine N-acetyltransferase (NAT) activity (Wang. 1998). Aloe-emodin has shown antibacterial effects on four strains of methicillin-resistant Staphylococcus aureus (Hatano, 1999).

INDICATIONS AND USAGE

- ***Constipation***

CONTRAINDICATIONS

Aloe is contraindicated in cases of intestinal obstruction, acutely inflamed intestinal diseases (e.g., Crohn's disease, ulcerative colitis), appendicitis and abdominal pain of unknown origin.

DRUG INTERACTIONS

Cardiac glycosides **and** ***antiarrhythmic*** drug—Chronic use of Aloe can lead to potassium loss, which can increase the actions of cardiac glycosides and antiarrhythmic drugs.

Thiazide diuretics, licorice and corticosteroids. There is an increase in the possibility of potassium deficiency when Aloe is used along with these agents.

Pregnancy**:** Aloe should not be used during pregnancy.

Pediatric Use: Aloe should not be prescribed to children under 12 years of age.

Naphthodianthrone & Diterpenoid Quinone Containing Drugs

Hypericum perforatum

Saint John's Wort

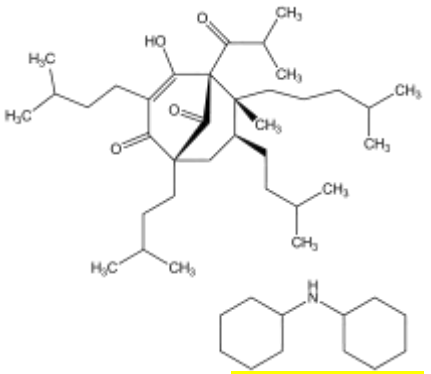
Clusiaceae Family

MEDICINAL PARTS

The medicinal parts include the fresh buds and flowers separated from the inflorescences, the aerial parts collected during the flowering season and dried, and the entire fresh flowering plant.

It was named for Saint John because it blooms around June 24, the day celebrated as his birthday. 'Wort' is an old English word for plant.

For centuries, St Johns wort was used to soothe the nerves and to heal wounds, burns and snakebites.

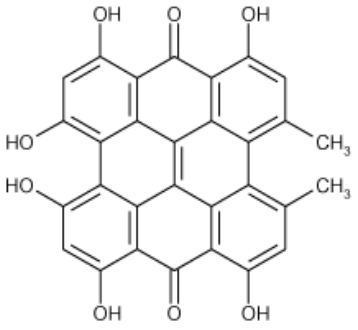


Hyperforin

PHYTOCHEMICALS

Acylphloroglucinols: hyperforin (the active principle) with small quantities of adhhyperforin.

***Anthracene derivatives*:** favoring naphthodianthrones, especially hypericin, pseudohypericin.

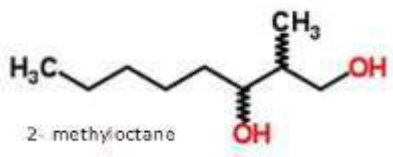


Hypericin

***Flavonoids*:** in particular hyperoside, quercitrin, rutin, isoquercitrin, and also biflavonolids including amentoflavone

Xanthones: 1, 3, 6 ,7-tetrahydroxy-xanthone

***Volatile oil*:** chief components aliphatic hydrocarbons, including, among others, 2-methyloctane, undecane, furthermore dodecanol, mono- and sesquiterpenes:



including, among others, alpha-pinene, caryophyllene, additionally also 2-methyl-3-but-3-en-2-ol.

Oligomers

***Procyanidines* and other catechin tannins**

***Caffeic acid derivatives*:** including chlorogenic acid.

Effects / Health benefits

- Treat anxiety.
- Treats depression.
- Helps to fight off viral and bacterial infections.
- May help to treat premenstrual syndrome (PMS) and fibromyalgia.
- Helps to fight hot flashes.
- Helps to relieve chronic pain.
- Soothes hemorrhoids.

INDICATIONS / Target patients

- Postmenopausal
- Anxiety
- Depressive moods
- Inflammation of the skin
- Blunt (dull) injuries
- Wounds and burns

CONTRAINDICATIONS

Simultaneous use of a MAO inhibitor: St. John's Wort contains some weak monoamine oxidase inhibitor (MAOI) properties that may add to the effects of other MAOI drugs, therefore theoretically increasing the risk for hypertensive crisis.

PRECAUTIONS AND ADVERSE REACTIONS

General: No health hazards are known in conjunction with the proper administration of designated therapeutic dosages.

The tannin content of the drug can lead to digestive complaints, such as feeling of fullness or constipation.

DRUG INTERACTIONS

MAOI**,** such as tranylcypromine, phenelzine, may lead to increased effects and possible toxicity (hypertensive crisis).

Tannic acids present in St. John's Wort may inhibit the absorption of iron (Miller, 1998).

Concomitant use with other **photosensitizers**, such as tetracyclines, sulfonamides, thiazides, quinolones, piroxicam and others should be avoided (Miller, 1998).

Hypericum extract has been reported to **significantly prolong narcotic-induced sleeping times and to antagonize the effects of reserpine** (Okpanyi, 1987).

Cyclosporine — Decreased serum concentrations have occurred with use of St. John's Wort (Bon, 1999).

St. John's Wort has been proven to induce the cytochrome P450 enzyme system, the major pathway for cyclosporine metabolism.

Ethinyloestradiol and **desogestrel** (combined oral contraceptive) Breakthrough bleeding has occurred with concomitant use of St. John's Wort (Bon, 1999).

Hypericin causes a reduction in barbiturate-induced sleeping times (Ozturk, 1992).

Theophylline — the herb has decreased theophylline levels on a patient stabilized on theophylline therapy (Nebel, 1999).

St. John's Wort (600-900 mg/day) taken concomitantly with **sertraline** (50-75 mg/day) after 2 to 4 days, resulted in a presumed serotonin syndrome consisting of dizziness, nausea, vomiting, headache, epigastric pain, anxiety, confusion, and/or feelings of restlessness and irritability.

Chapter 12

Orcinols & Phloroglucinols

Cannabis sativa

Cannabis / hashish / Marijuana

Cannabaceae

Cannabis sativa, also known as hemp, is a species of Cannabis. It is a dioecious, annual herb. It has been used by humans throughout recorded history for its fiber, for its psychological and physiological potential as a source of drug material, and for the nourishment and oil of its seeds.

MEDICINAL PART

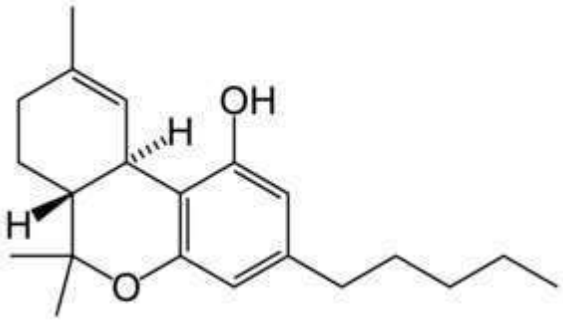
The medicinal parts are the twig tips of the female flowers, with either flowers or fruit attached the flower-bearing twigs that have been dried; the ripe hemp fruit and various homeopathic preparations of the fresh dried plant-parts.

PHYTOCHEMICALS

Cannabinoids: chief active agent 9-tetrahydrocannabinol (9-THC = 1-THC), in addition to 60 additional cannabinoids

Volatile oil: of a very complex composition, with, among other things beta-caryophyllenes, humules, caryophyllene oxide, alpha pinenes, beta-pinenes, limonene, myrcene, betaocimene

Flavonoids: including canniflavone-1, canniflavone-2.



Δ9-THC

EFFECT

Psychotropic action: In most subjects the effect is registered following an oral dose of 20 mg d-9-tetrahydrocannabinol or after inhaling a cigarette with 2% d-9-tetrahydrocannabinol.

The symptoms are mood swings, reduction in drive, inability to think clearly, confusion, lack of concentration, impairment of short term memory and perception of time. Sensory impressions become heightened or experienced differently.

Complex tasks become more difficult, the capacity to understand or empathize is impaired. Negative reactions such as anxiety, panic and psychosis can occur.

Cannabinoids Receptors

There are currently two known types of Cannabinoids receptors, **CB1 and CB2.**

CB1 receptors are found primarily in the brain, specifically in the basal ganglia and in the limbic system, including the hippocampus. They are also found in the cerebellum and in both male and female reproductive systems.

CB1 receptors are essentially absent in the medulla oblongata, the part of the brain that is responsible for respiratory and cardiovascular functions. ***Thus, there is not a risk of respiratory or cardiovascular failure as there is with many other drugs.***

CB1 receptors appear to be ***responsible for the euphoric and anticonvulsive*** effects of cannabis.

CB2 receptors are almost exclusively found in the immune system, with the **greatest density in the spleen**.

CB2 receptors appear to be responsible for the anti-inflammatory and possible other therapeutic effects of cannabis.

Tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) are the most prevalent natural cannabinoids and have received the most study.

THC is the primary psychoactive component of the plant. Medically, it appears to moderate pain and to be neuroprotective. THC has a greater affinity for the CB1 receptor than for the CB2 receptors. Its effects are perceived to be more cerebral.

CBD is not psychoactive, and appears to moderate the euphoric effects of THC. It may decrease the rate of THC clearance from the body, perhaps by interfering with the metabolism of THC in the liver. Medically, it appears to relieve convulsion, inflammation, anxiety, and nausea. CBD has a greater affinity for the CB2 receptor than for the CB1 receptor. It is perceived to have more effect on the body.

TOXICITY

THC has a LD50 value of 1270 mg/kg (male rats) and 730 mg/kg (female rats) administered orally dissolved in sesame oil.

If this were scaled up to an adult human, the lethal dose would be between approximately 50 and 86 g for a 68 kg person. This would be equivalent to 1-1.8 kg of marijuana with a 5% THC content (roughly average) taken orally (much more if smoked). It is important to note, however, that toxicity studies in animal models do not necessarily correlate to human toxicity.

Humulus lupulus

Hops

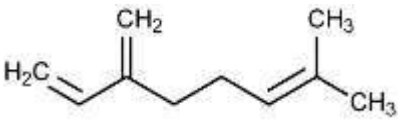
Cannabinaceae

MEDICINAL PARTS

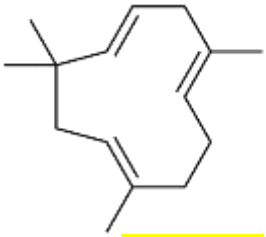
The medicinal parts are the glandular hairs separated from the infructescence, the whole dried female flowers, the fresh cones (preferably with few seeds) collected before the seeds ripen and the fresh or dried female inflorescence.

PHYTOCHEMICALS

Volatile oil: very complex in makeup, chief components myrcene, humulene, beta-caryophyllene, undecane- 2-on, furthermore 2-methyl-but-3-en-ol (particularly following storage, as breakdown product of the acylphloroglucinols).



Myrcene

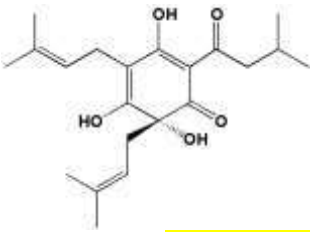


Humulene

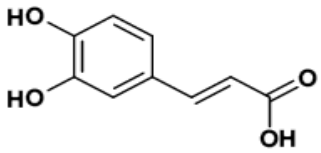
Alpha-bitter acids: humulone.

Flavonoids: rutin, quercitrin, astragalin.

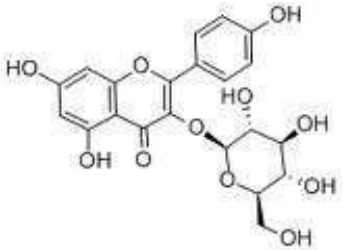
Phenolic acid: including, among others, ferulic acid, caffeic acid and their derivatives, for example, chlorogenic acid.



Humulone



Caffeic Acid



Astragalin

Effects / Health & Benefits

The female flowers of the *Humulus lupulus* L. plant, hops are often used to
treat arthritis, fibromyalgia, insomnia, diabetes, and menopausal symptoms.

Hops and Menopause

Test-tube research shows that 8-prenylnaringenin (a substance found in hops) may act as a phytoestrogen (a natural chemical known to mimic the action of estrogen). Since levels of estrogen are known to decline during menopause, some women take hops in order to soothe menopausal symptoms.

Hops and Insomnia

Combination hops with valerian may help treat insomnia. Many published studies, found that the use of valerian on its own or in combination with hops helped improve sleep quality and lessened the amount of time it takes to fall asleep.

Hops have phyto-estrogen.

Researchers from King's College, UK, identified a potent phytoestrogen in hops, 8-prenylnaringenin, which has an activity greater than other established plant estrogens. 8-Prenylnaringenin competed strongly with 17ss-estradiol for binding to both the alpha- and ss-estrogen receptors. Its strong estrogenic activity was also reflected in its relative binding affinity to estrogen receptors from rat uteri. This phytoestrogen can also be detected in beer containing hops, but the levels are low

Uses

Used as a bittering agent in beer, hops are thought to deliver sedative effects.

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