SECONDARY METABOLYTES
Phenolics, Terpenoids, Steroids, Alkaloids

Prof. Dr. Ali Hikmet Meriçli

PHENOLICS

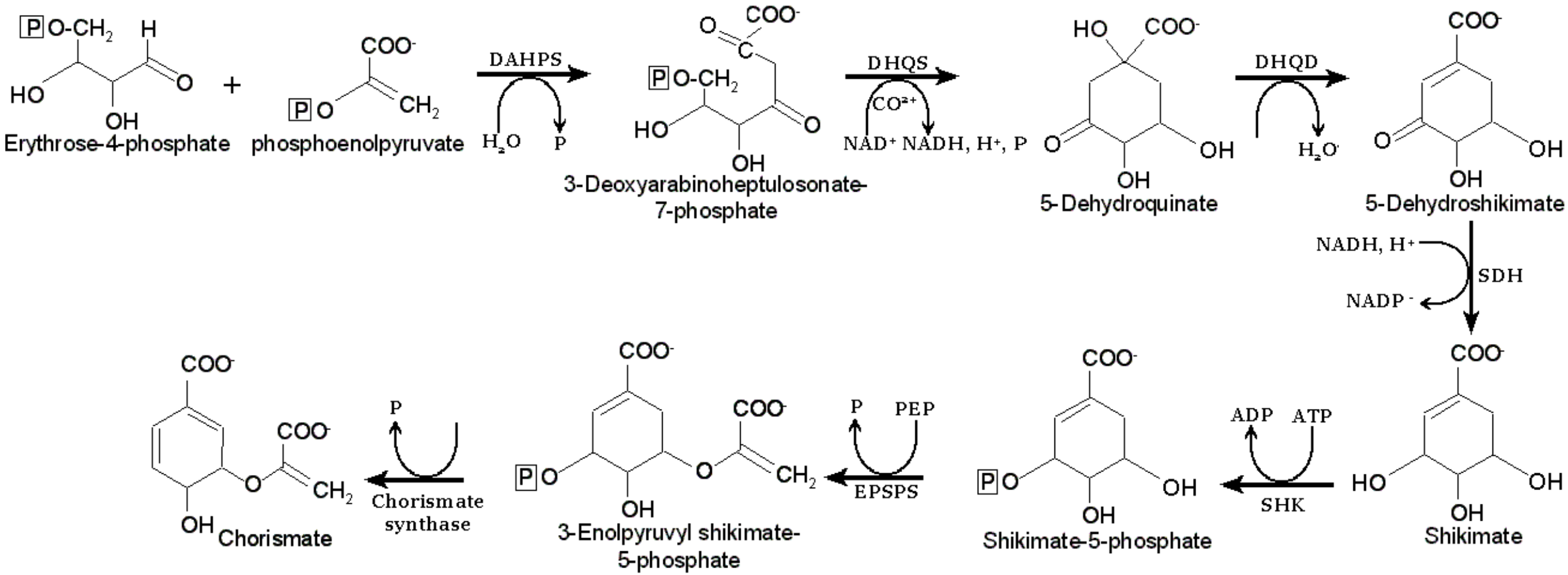
Prof. Dr. Ali Hikmet Meriçli

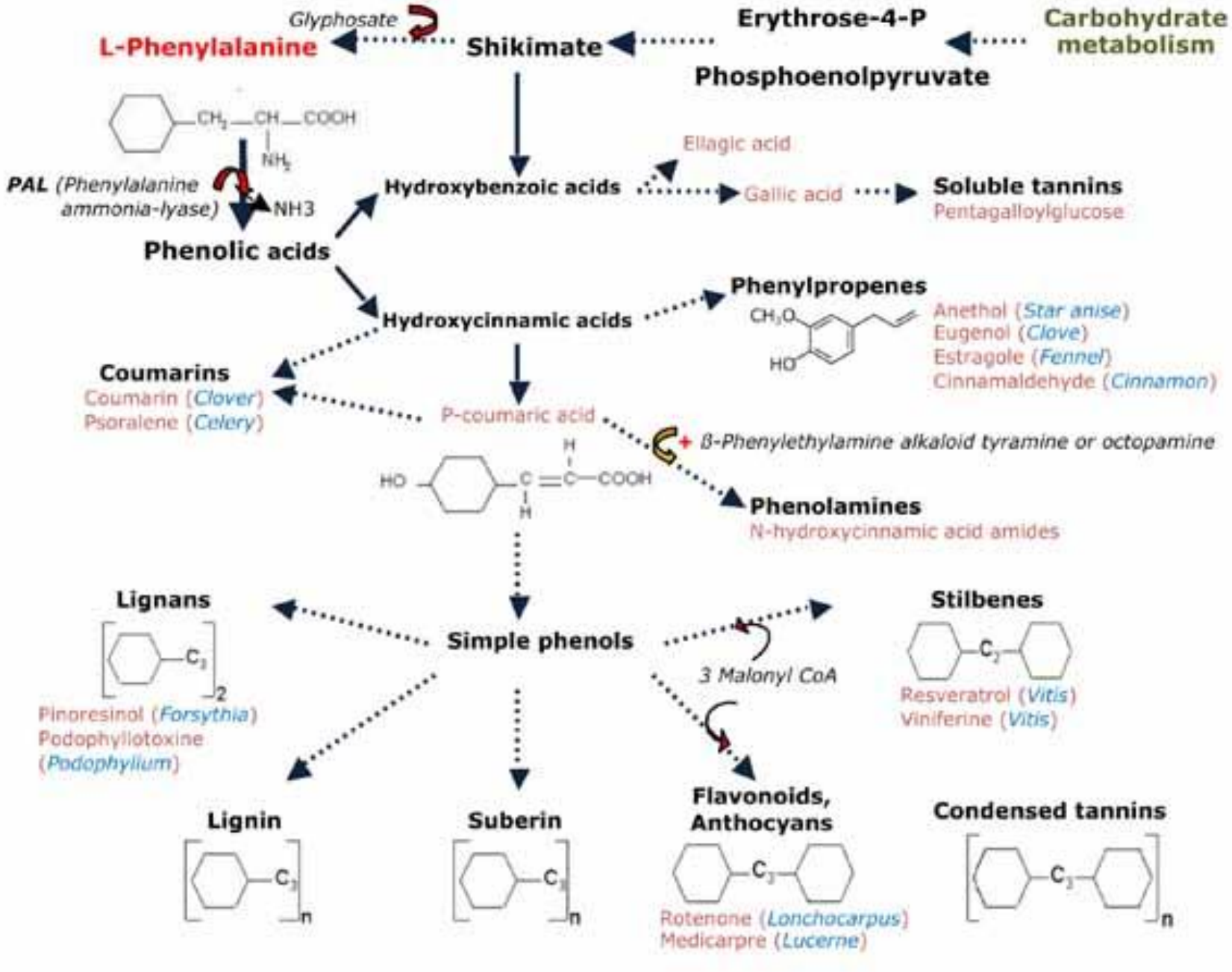
Generalities

Phenolics form a vast group of substances which 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, a purely chemical definition of phenols is insufficient to characterize plant phenolics: it would include secondary metabolites which possess these structural elements, but which evidently belong to quite different phytochemical groups. For example many alkaloids (e.g., boldine, morphine) and a fair number of terpenes (e.g., thymol, gossypol, carnosol), within their structure, an aromatic ring and phenolic hydroxyl group.

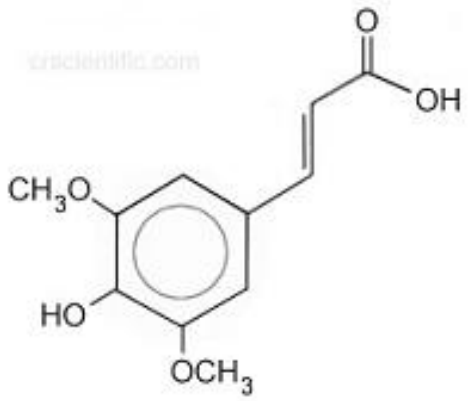
Plant phenolics arise from two main aromatization pathways:

- The most common pathway is the one which, via shikimate (shikimic acid), leads from monosaccharides to aromatic amino acids (phenylalanine and tyrosine), then, by deamination of the latter, to cinnamic acids and their numerous derivatives, including benzoic acids, acetophenones, lignans, lignins, and coumarins.
- The other pathway begins with acetate and leads to poly-β-ketoesters of variable lenght – polyketides – which afford, by cyclization, products that are often polycyclic, including chromones, isocoumarins, orcinols, depsides, depsinones, xanthones, and quinones.


Erythrose-4-phosphate
phosphoenolpyruvate
DAHPS
H2O
P
3-Deoxyarabinoheptulosonate-7-phosphate
DHQS
CO2+
NAD+ NADH, H+, P
5-Dehydroquinate
DHQD
H2O
5-Dehydroshikimate
NADH, H+
NADP-
SDH
Shikimate
ADP
ATP
SHK
Shikimate-5-phosphate
P
PEP
EPSPS
3-Enolpyruvyl shikimate-5-phosphate
P
Chorismate synthase
Chorismate

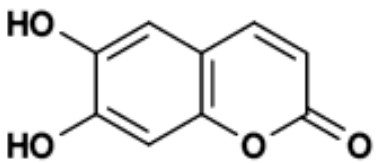


Shikimate pathway



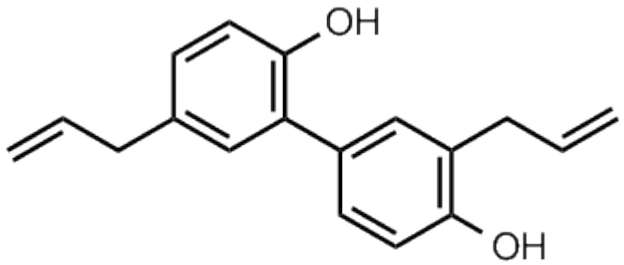
Sinapic acid

PHENYLPROPANOIC ACID



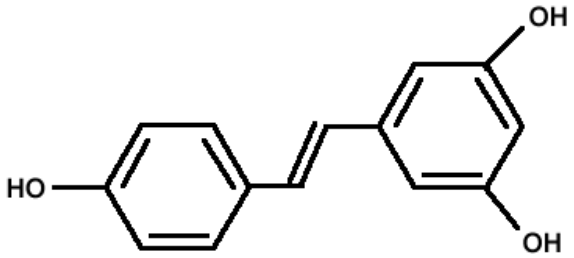
Aesculetin

COUMARIN



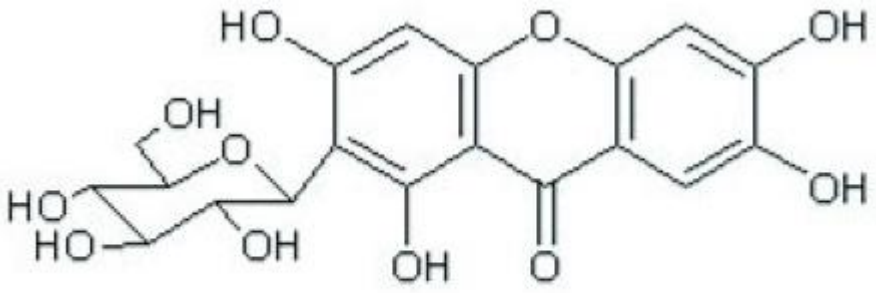
honokiol

NEOLIGNAN



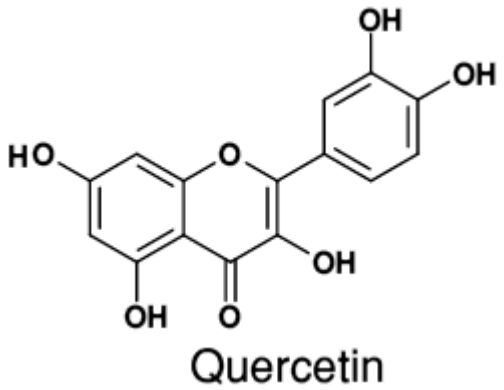
Resveratrol

STILBENE



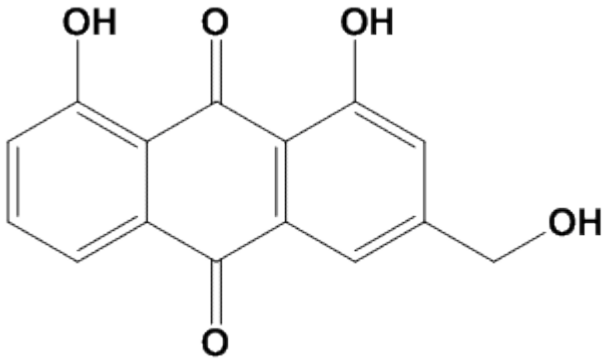
Mangiferin

XANTHONE



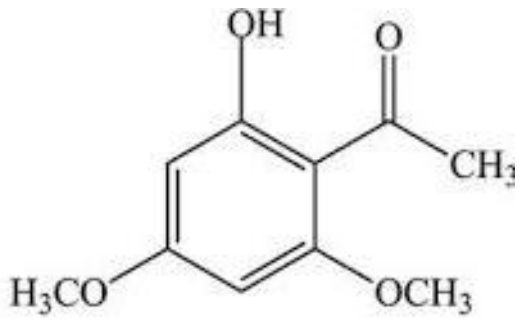
Quercetin

FLAVONOL



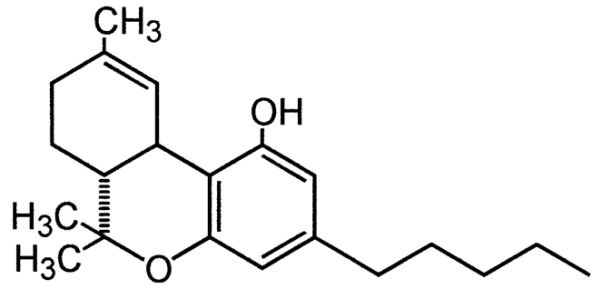
Aloe-Emodin

ANTHRAQUINONE



xanthoxylin

BENZOPHENONE



∆-9-tetrahydrocannabinol (THC)

CANNABINOID

HOMOLYTIC CLEAVAGE

Oxidation of the phenolate ion is fascile and yields a phenoxy radikal which is stabilized by resonance and highly reactive. This ease of oxidations has consequences in the domains of analytical chemistry (e.g., color reactions with ferric chloride), pharmaceutical technology (instability, incompatibilities with metals), and practical applications (antioxidant and radical scavering properties).

ACIDITY OF PHENOLS

Phenolate ion stabilization by resonanace explains the acidity of these molecules: consequently, they are soluble in alkaline hydroxide solutions. It also explains why they are so highly reactive.

CHARACTERIZATION OF PHENOLICS

Some phenolic compounds are directly visible, such as flower anthocyanins, and others can be visualized under ultraviolet light or by color reactions. General reagents for phenols abound: ferric chloride, phosphomolybdate-phosphotungstate, vanillin, and other aldehydes in the presence of hydrochloric acid, 4-diazoniobenzenesulfonate followed by sodium carbonate, 4-nitrophenyldiazonium tetrafluoroborate followed by sodium acetate, and 2,6-dichloroquinone chlorimide (Gibbs reaction and formation of indophenolates).

Phenols and Phenolic Acids

GENERALITIES

The term phenolic acid applies to all organic compounds with at least one carboxyl group and one phenolic hydroxyl group.

SIMPLE PHENOLS

Simple phenols (e.g., catechol, guaiacol, phloroglucinol) seldom occure naturally, except hydroquinone which is found in several families (Ericaceae, Rosaceae).

PHENOLIC ACIDS DERIVED FROM BENZOIC ACID

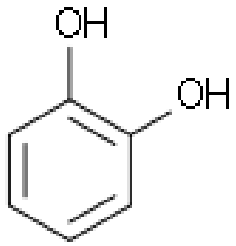
C_6-C_1 Phenolic acids that are hydroxylated derivatives of benzoic acid are quite common in the free state, as well as combined into esters or glycosides. Gallic acid and its dimer (hexahydroxy diphenic acid) are constituents of hydrolyzable tannins.

PHENOLIC ACIDS DERIVED FROM CINNAMIC ACID

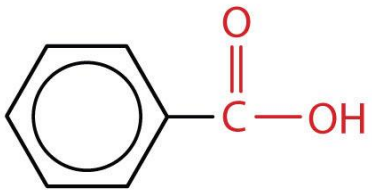
Most C_6-C_3 phenolic acids (4-coumaric, caffeic, ferulic, sinapic acids) are very widely distributed. Others occur rarely in the free state, and are very often found esterified:

- Esters of aliphatic alcohols (e.g., feruloyltartaric acid)
- Esters of quinic acid (chlorogenic acid, widely distributed) and depsides (rosmarinic and lithospermic acids), spesific to the Lamiaceae and Boraginaceae

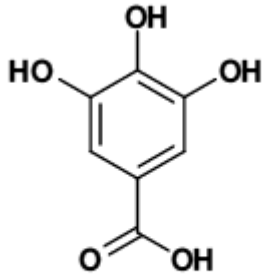
Note also that these acids frequently esterify the hydroxyl groups of many secondary metabolites : **flavonoids, anthocyanins, alkanols, saponins, and even although less commonly, alkaloids.**



Catechol

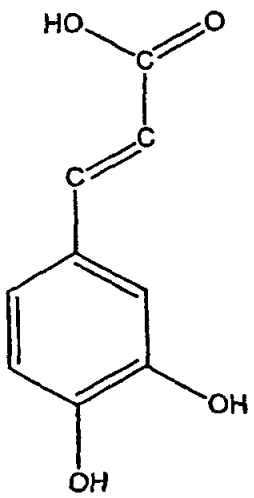


Benzoic acid

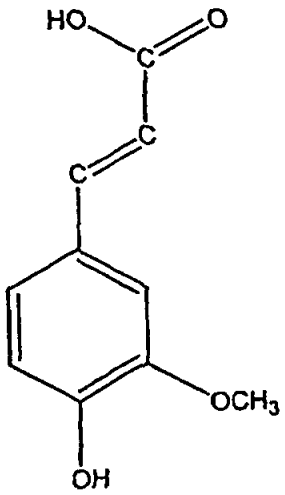


Gallic Acid

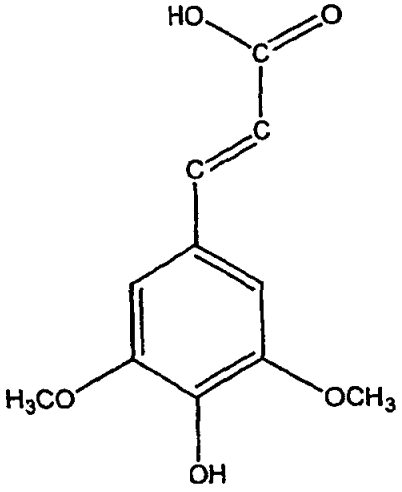
3,4,5-TriHydroxyBenzoic Acid



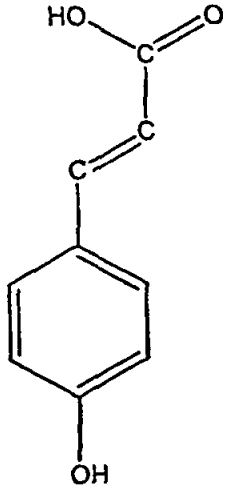
Caffeic Acid



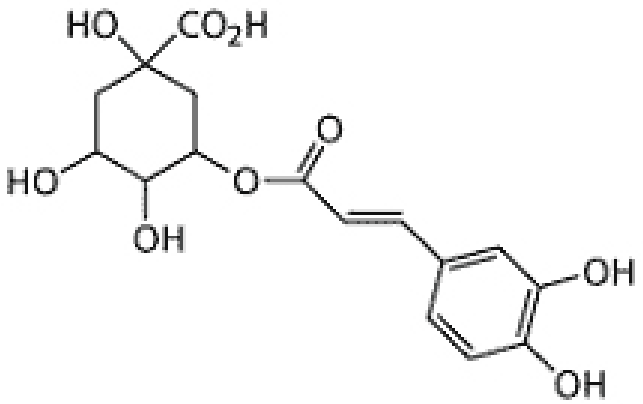
Ferulic Acid



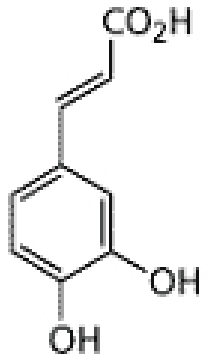
Sinapic Acid



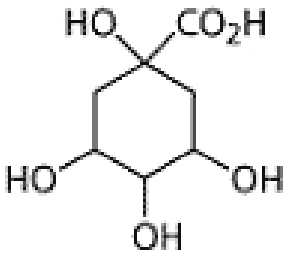
p-Coumaric Acid



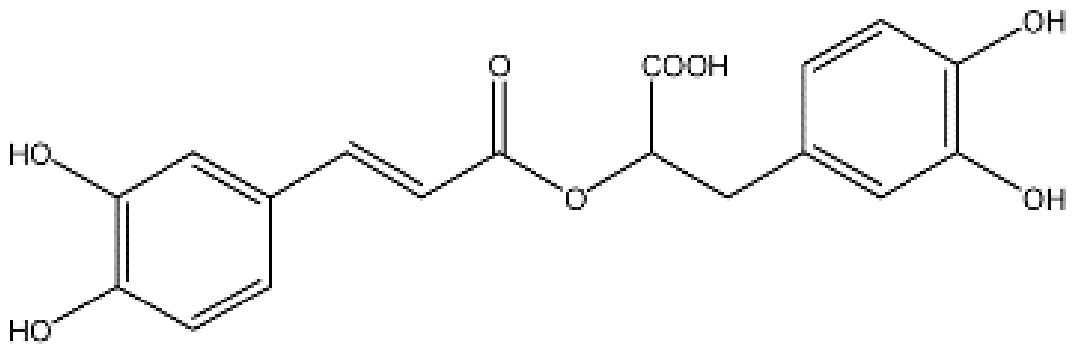
Chlorogenic acid



Caffeic acid



Quinic acid



Rosmarinic acid

PHYSICO-CHEMICAL PROPERTIES, CHARACTERIZATION, AND EXTRACTION

In general, phenols are soluble in polar organic solvents; they are soluble in sodium hydroxid and carbonate solutions. Phenolic acids are solubilized in bicarbonates; they can be extracted with organic solvents in slightly acidic conditions.The glycosides of these phenolic compounds are, clasically soluble in water. All of these compounds are unstable. All phenols are readily oxidized, especially in alkaline conditions.

These compounds are generally extracted preferably from fresh plant material,with alcohol, or alternatively, to extract less lipophilic substances and avoid partial esterification of the phenolic acids, with an alcohol and water mixture. Separation of the constituents of mixtures can be achieved by classic chromatographic techniques especially on poliamide, cellulose and silica gel.

PHARMACOLOGICAL APPLICATIONS AND USES

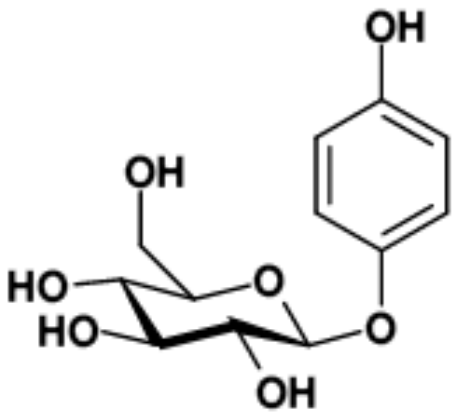
Some simple phenol-containing drugs have urinary, antiseptic, and anti-inflammatory properties. The properties that tradition attributes to drugs such as rosemary or artichoke, are said to be due, in part, to esters of cinnamic derivatives.

Glycosidic phenylpropanoid esters have interesting pharmacological potential. Some are enzym inhibitors. Several compounds in this series have antibacterial and antifungal properties, particularly against phytopathogenic organisms.

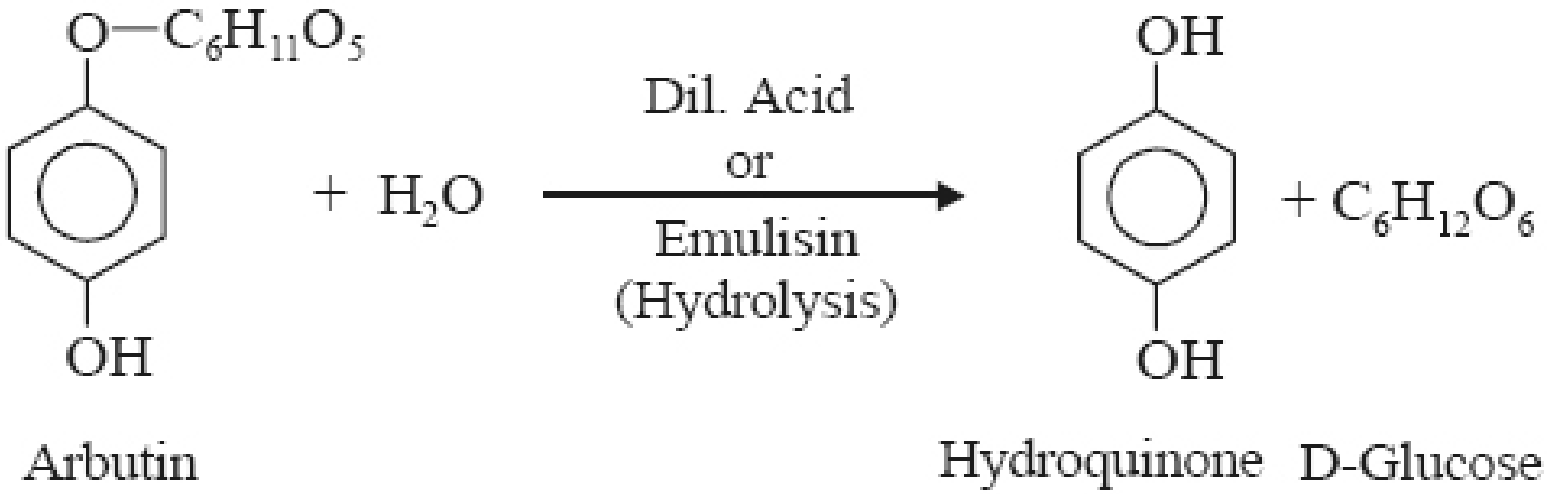
Uvae-ursi folium **bearberry** **ayı üzümü yaprağı**

Arctostaphylos uva-ursi **Ericaceae**

The active principles are phenolic glycosides, represented by arbutin (6-10%) and methyl arbutin. Upon hydrolysis, arbutin releases a diphenol which is oxidized to hydroquinone. Gallotannins, flavonoids and iridoids are the other compounds.



Arbutin



Arbutin Hydroquinone D-Glucose

The drug can be used as adjunctive therapy in the diuretic treatment of benign urinary disorders, and to enhance the renal excretion of water (oral route). Phytotherapy normally uses the infusion, although some authors prefer cold maceration which produces a preparation less rich in tannins.

The German Commission E monograph lists indications of the same type (inflammation of the urinary tract) and specifies that Uvae-ursi folium can cause nausea and vomiting in persons with a delicate stomach. The drug is contraindicated in pregnant and breast-feeding women. It must not be used in children under 12 years of age. Bearberry-based preparations must not be taken at the same time as substances that can potentially acidify the urine.

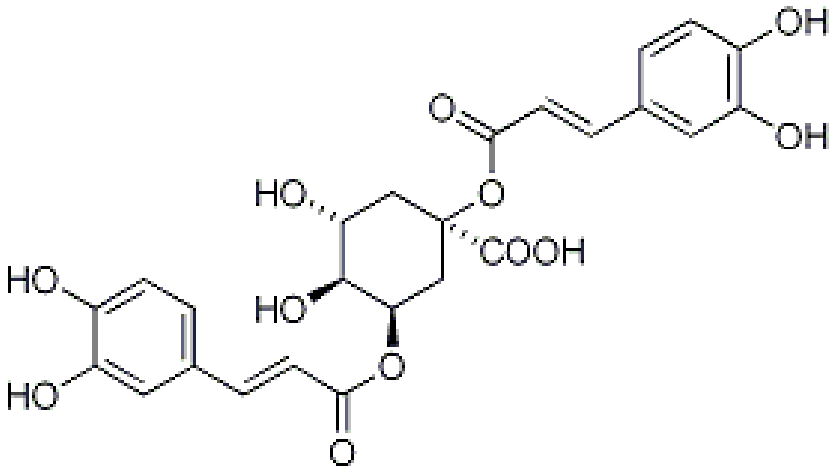
Caffeic acid Derivative-containing Drugs

Cynarae folium **artichoke** **enginar yaprağı**

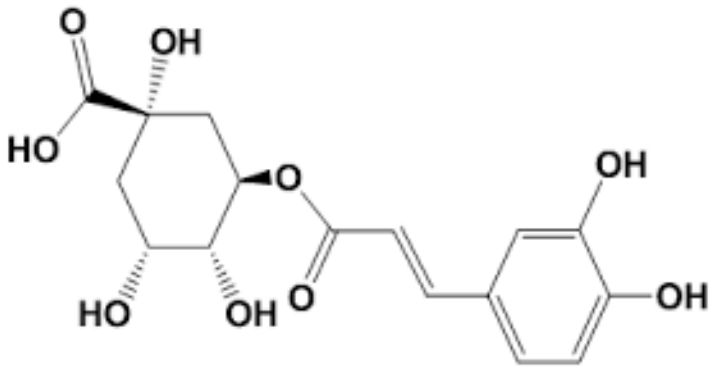
Cynara scolymus **Asteraceae**

This species is an improved cardoon unknown in the wild and only cultivated. To fulfill pharmaceutical needs, the first-year rosette of leaves is preferred and is harvested from plants produced especially for this purpose.

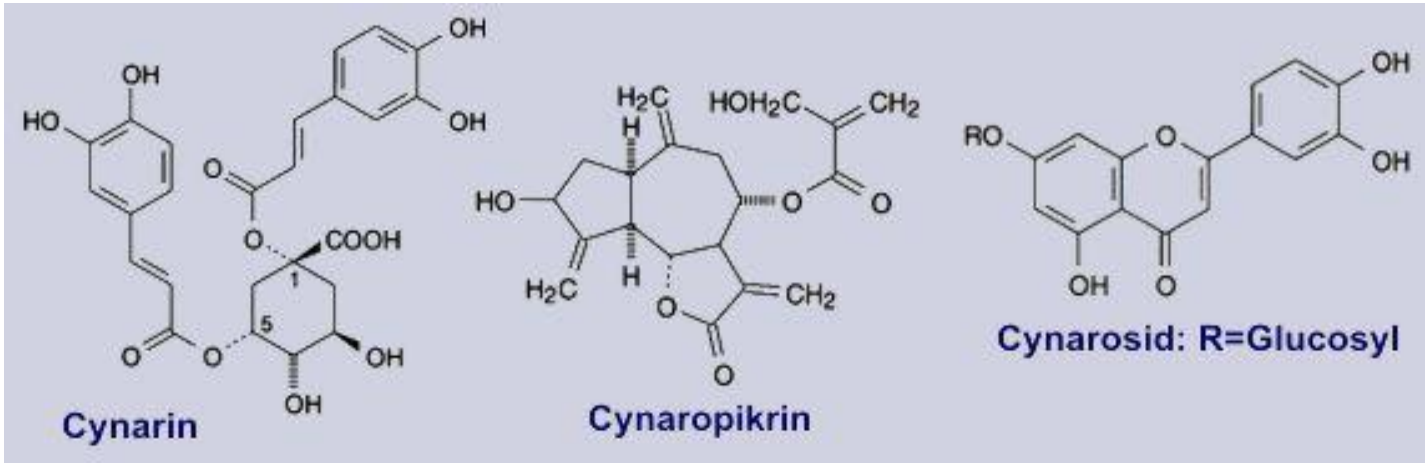
Chemical Composition : The active consituents are said to be phenolic acids and phenolic alcohols. The former are esters of caffeic acid (1%): 5-caffeoylquinic acid (or chlorogenic acid) and 1,5-dicaffeoylquinic acid (=**cynarin**). The drug also contains sesquiterpenoid lactones (cynaropicrin) responsible for its strong bitterness and up to 1% flavonoids which are glycosides of luteolin and apigenin (luteolin 7-glucoside = cynaroside).



cynarin



Chlorogenic Acid



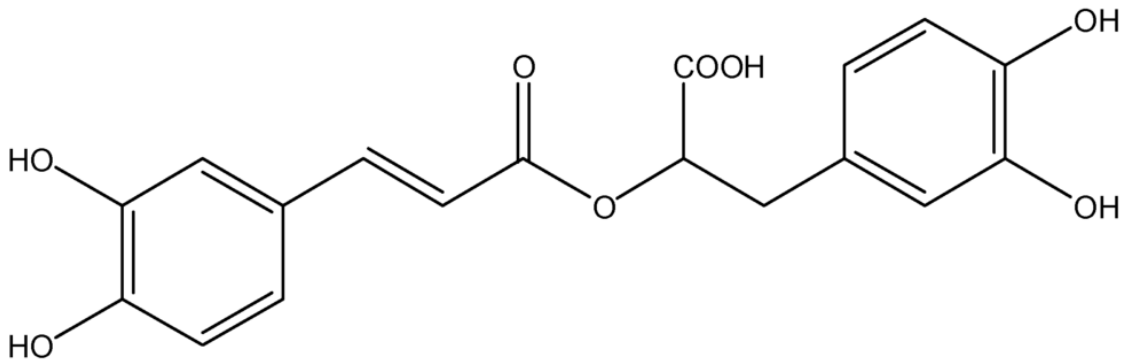
Pharmacological Activity and Uses : Cynarae folium (Artichoke leaf) is a drug known since remote times as choleretic. Experimentally cynarin displays a clear activity on the biliary flow rate. The antioxidant effect of the aquaeous extract has been shown. In human: marked decreases in blood cholesterol and triglycerides upon administration of *Cynara* extracts. The tincture, fluid extracts, nebulisates, and other forms are used in proprietary drugs for their choleretic activity. They are traditionally used to enhence urinary and digestive elimination functions, as a **choleretic** or **cholagogue**, **hepatoprotective**, and to enhence of the renal elimination of water (orally).

Rosmarini folium **Rosemary** **biberiye yaprağı**

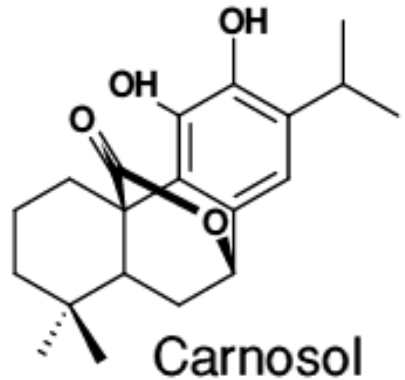
Rosmarinus officinalis **Lamiacae**

The drug has choleretic and diuretic activities.

Rosemary is very common in all of the Mediterranean basin. Used for the production of essential oil and used in phytotherapy, it is also of interest to food technology because its diterpenes are antioxidants. The drug contains an essential oil, in which the chief constituents are camphor, cineole, α-pinene, borneol, and camphene. Phenolic compounds are represented by flavonoids, and by the phenolic acids, particularly by derivatives: caffeic, chlorogenic, and rosmarinic acids. The drug also contains diterpenes (carnosol).



Rosmarinic acid

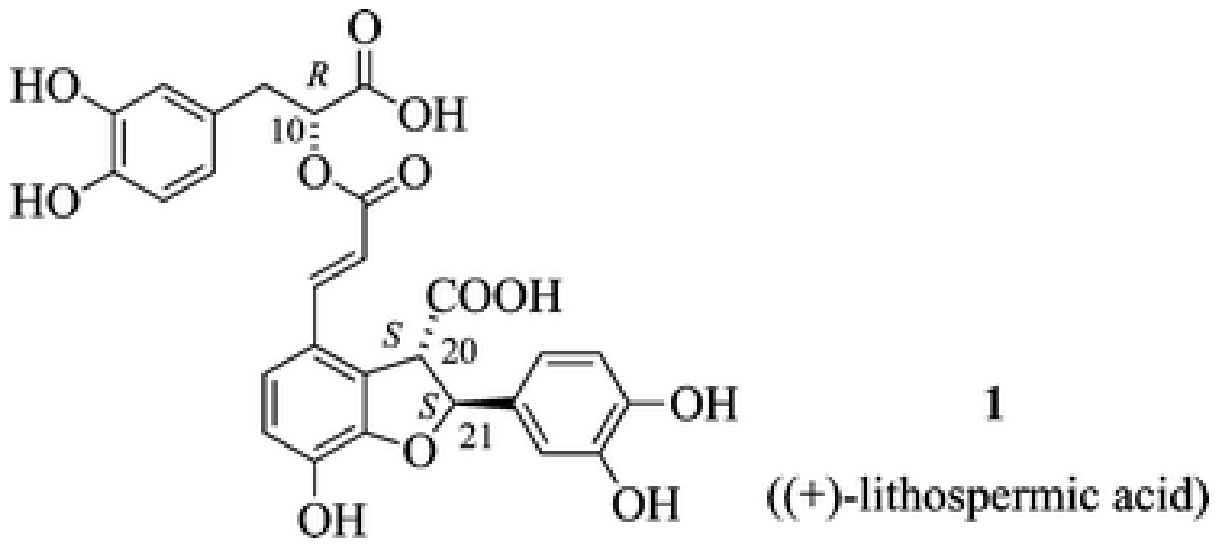


Carnosol

Orthosiphonis folium Orthosiphon = Java Tea Java çayı

Orthosiphon aristatus = Orthosiphon spicatus **Lamiaceae**

The drug containes diterpenes, an essential oil rich in sesquiterpenoid hydrocarbons, and phenolic compounds (flavonoids, caffeic acid- and lithospermic acid derivatives).



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((+)-lithospermic acid)

In Germany, the drug ,is reputed to be a diuretic and weak spasmolytic. It is used, with suitable fluid intake, for inflammation, urinary tract infection, and renal lithiasis.

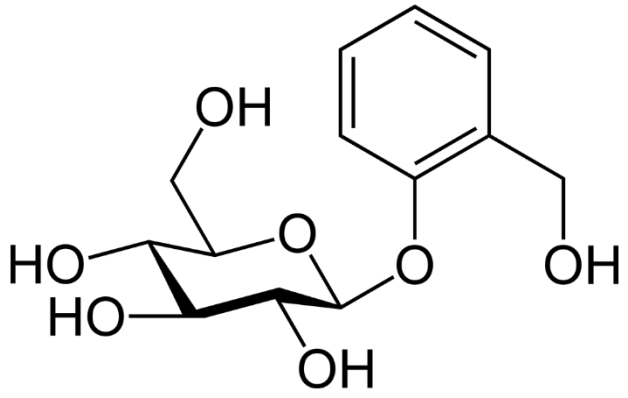
Salisylic acid Derivative-containing Drugs

Salicis cortex **Willow** **söğüt ağacı kabuğu**

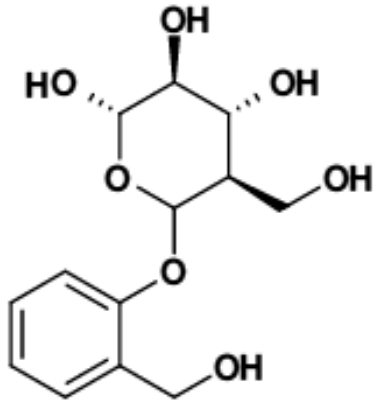
Salix alba **Saliceae**

Willows are exploited for their bark, which is rich in phenolic compounds : proanthocyanidins, flavonoids, and glycosides of phenols and phenolic acids (from 1 to 11% depending on the species, the source, and the age of the tree). Salicin (glycoside of salicyl alcohol) occurs alongside salicortin and their benzoyl derivatives (tremulacin, populin), as well as glycosides with a C_6-C_3 aglicone (triandrin, vimalin). The salicortin-type derivatives are thermolabile and are partially converted to salicin if the drug is dried at high temperature. Practically all authors agree to link the anti-inflammatory properties traditionally attributed to the drug to salicylic acid, which arises by oxidation of salicyl alcohol, formed upon intestinal hydrolysis of salicin, itself either native or produced by the slow degradation of salicortin.

This slow degradation may explain why the drug activity is more prolonged than that of pure salicylic acid. Willow bark is traditionally used orally for fever and flu-like symptoms, and as an antalgic (headaches, toothaches); it is used orally and topically for the symptomatic treatment of minor pains in the joints. The German Commission E monograph specifies that the drug is used for fever, rheumatic disorders, and headaches.



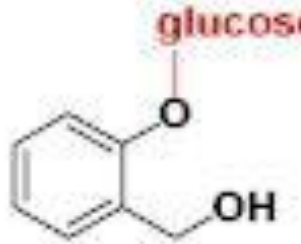
Salicin



Salicin

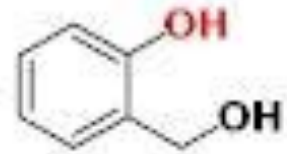
isolation

(1827)



salicin

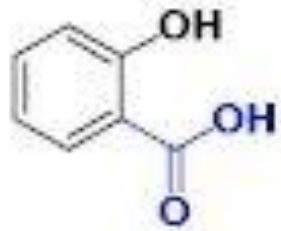
hydrolysis



salicyl alcohol
(saligenin)

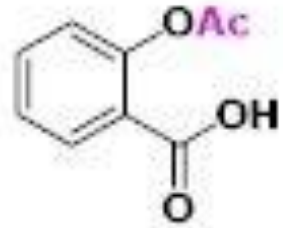
oxidation

(1938)



salicylic acid

acetylation



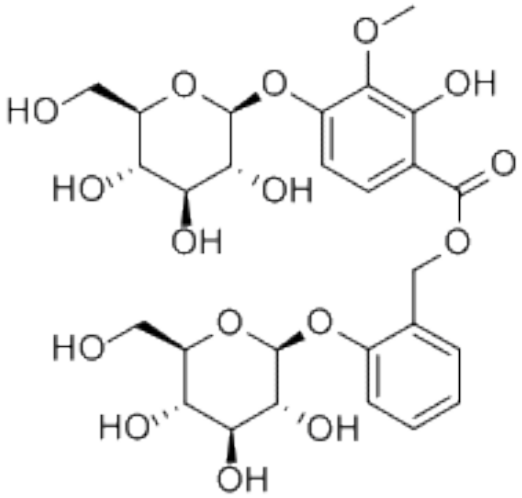
aspirin

Other Phenolic Acid-containing Drugs

Virgaureae herba — **European goldenrod**

Solidago virgaurea — **Asteraceae**

The drug contains tannins, essential oil, diterpenes, flavonoids, saponins, and phenolic acids. The latter are on the one hand caffeic asters, and on the other hand, specific compounds, namely virgaureoside A and leiocarposide.
Leiocarposide is a diuretic, and anti-inflammatory. The drug is traditionally used, by the oral route, to enhence urinary and digestive elimination structures, and to enhence the renal excretion of water.



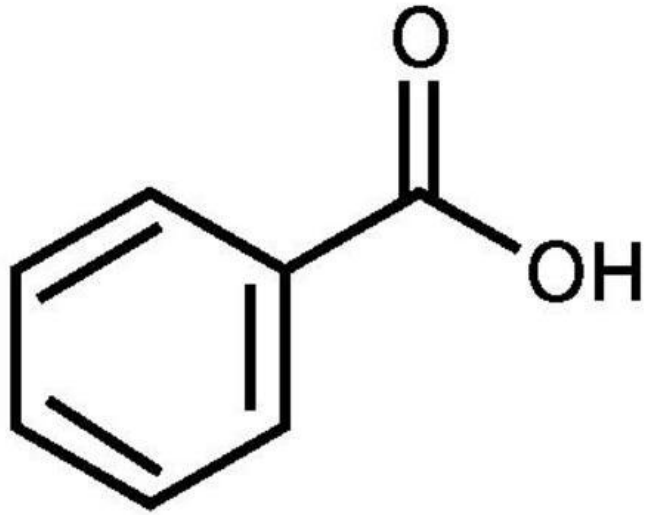
leiocarposide

BENZOIC AND CINNAMIC ESTER-CONTAINING DRUGS
BALSAMS AND BENZOINS

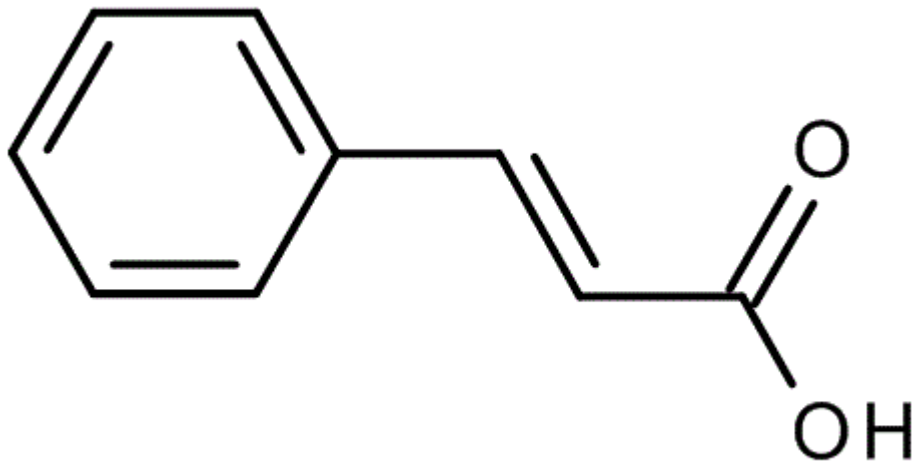
Balsams are defined as oleoresins containing substantial proportions of benzoic acid, cinnamic acid and their esters.

Balsamum peruvianum Peruvian balsam Peru balsamı
***Myroxylon balsamum* Fabaceae**

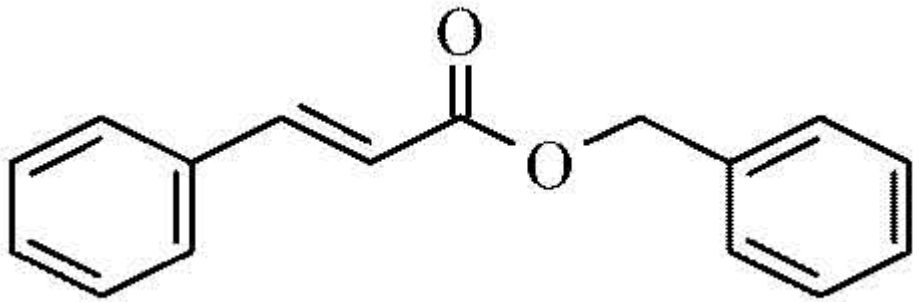
Peruvian balsam is the product obtained from the (tree) trunk scarified at high temperature. When the trunk is beaten, stripped, and in a subsequent step, storched with a torch, it secretes a pathological exudate which is the balsam. Peruvian balsam contains approximately 6-8% benzoic and cinnamic acids in the free state and 50-60% «cinnamein» (a mixture of benzyl benzoate, benzyl cinnamate and cinnamyl cinnamate). The drug has wound healing and antiseptic effects. It is irritating when taken orally, and therefore only used externally.



Benzoic acid



Cinnamic acid



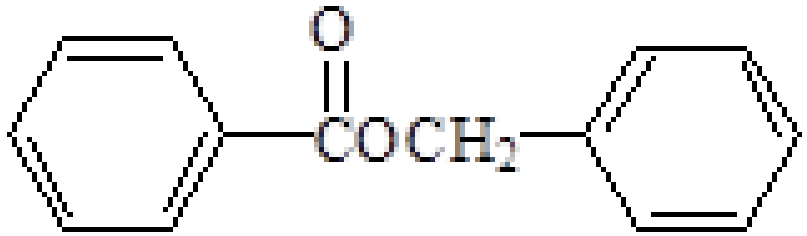
Benzyl cinnamate

Balsamum tolutanum **Tolu balsam** **Tolu balsamı**

Myroxylon toluiferum **Fabaceae**

The balsam is obtained by deep incision of the tree trunk. It is a greyish and soft semi-solid when fresh, then it slowly dries becomes hard and reddish-brown. Tolu balsam is a mixture of free acids (benzoic acid 6-8%, and more cinnamic acid 10-15%), and benzyl benzoate which is slightly volatile.

Tolu balsam is considered as an antiseptic and expectorant, and is used internally. In perfumery, it is a fixative for volatile products.



Benzyl benzoate

Other balsams:

Benzoe	**Siam benzoin**	***Styrax tonkiensis***	**Styracaceae**
Styrax	**Sumatra benzoin**	***Styrax paralleloneurus***	**Styracaceae**

Styrax liquidus **levant storax** **sığala yağı**

Liquidambar orientalis **Hamamelidaceae**

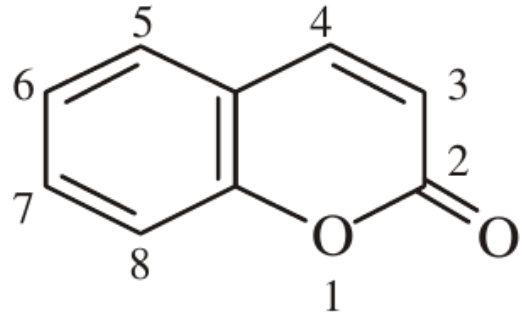
Styrax liquidus is a balsam which flows after incision of the trunk of *Liquidambar orientalis*, an endemic tree to Turkey, growing on the west coast of Anatolia (especially Muğla-Marmaris). The drug contains a large amount of free and combined cinnamic acid, styrene and an ill-defined resinous fraction. The drug is healing and antiseptic. The plant material has been used for the treatment of peptic ulcer symptoms in Turkish folk medicine since centuries.

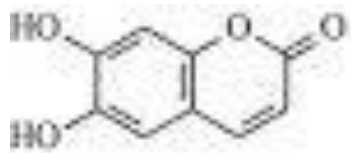
Coumarins

Coumarins are 2H-1-benzopyran-2-ones which may be considered, on first approximation, to be the lactones of the 2-hydroxy-Z-cinnamic acids. Over one thousand coumarins have been described, and the simplest among them are widely distributed in all of the vegetale kingdom. Fabaceae, Asteraceae, and especially Apiaceae, and Rutaceae are rich in coumarins.

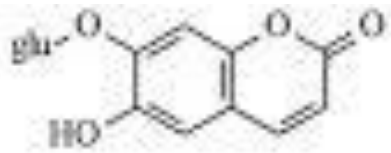
CHEMICAL STRUCTURE AND CLASSIFICATION

Except for a few rare cases, including coumarin per se, all coumarins are substituted by a hydroxyl group in position 7.

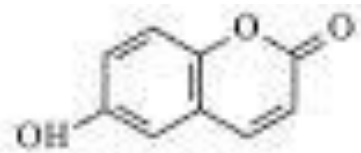




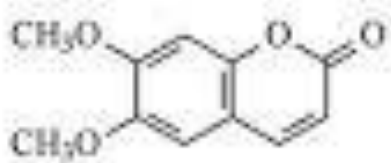
Aesculetin



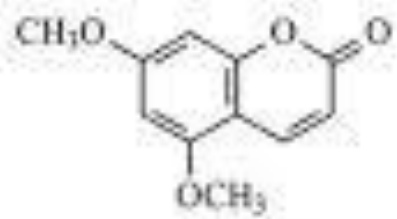
Aesculin



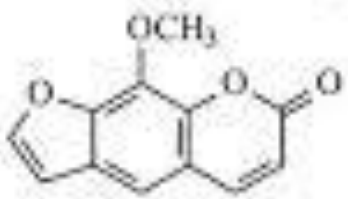
Umbelliferone



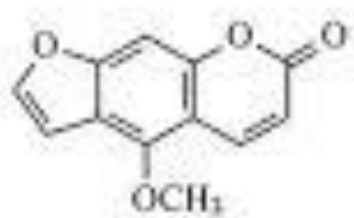
Scoparone



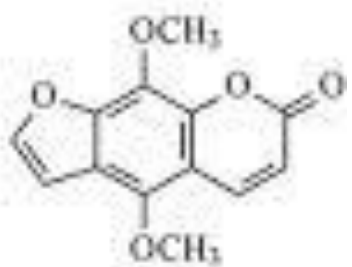
Limettin



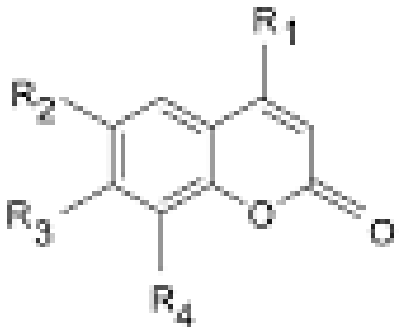
Xantotoxine



Bergapten



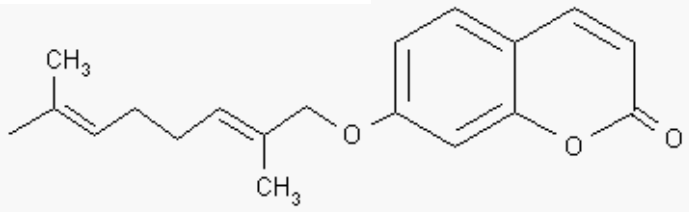
Isopimpinelin



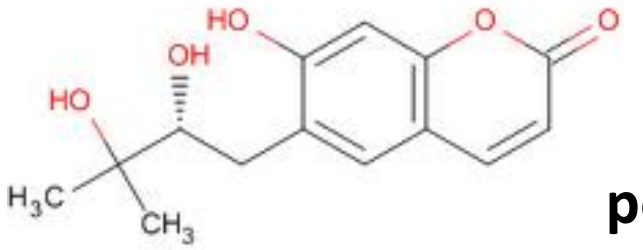
	R_1	R_2	R_3	R_4
Esculin	H	Glu	OH	H
Daphnetin	H	H	OH	OH
Fraxetin	H	CH_3O	OH	OH
Umbelliferone	H	H	OH	H
4-methylumbelliferone	CH_3	H	OH	H
4-hydroxycoumarin	OH	H	H	H
Scoparone	H	CH_3O	CH_3O	H
Coumarin	H	H	H	H
Herniarin	H	H	CH_3O	H

Cinnamyl alcohol

aurapten



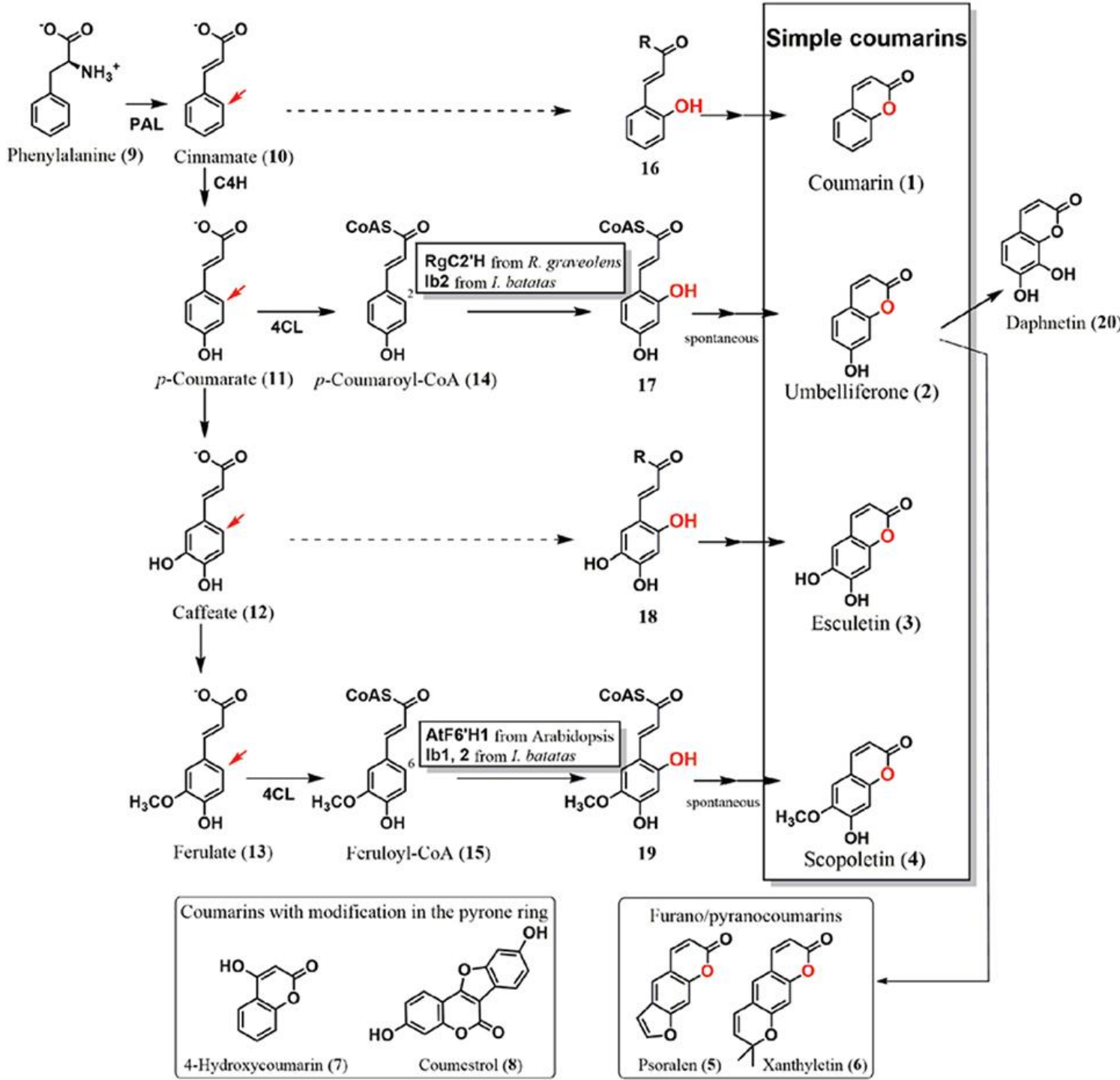
$C_{19}H_{23}O_3$



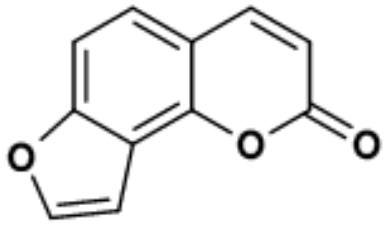
peucedanol

BIOSYNTHESIS

Like other phenylpropanoids, coumarins arise from the metabolism of phenylalanine via a cinnamic acid, p-coumaric acid.

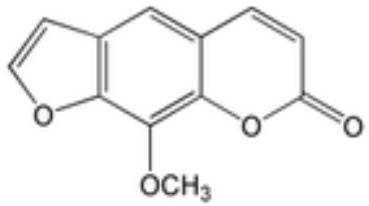

Simple coumarins
Phenylalanine (9)
PAL
Cinnamate (10)
C4H
16
Coumarin (1)
p-Coumarate (11)
4CL
p-Coumaroyl-CoA (14)
RgC2'H from R. graveolens
Ib2 from I. batatas
17
spontaneous
Umbelliferone (2)
Daphnetin (20)
Caffeate (12)
18
Esculetin (3)
Ferulate (13)
4CL
Feruloyl-CoA (15)
AtF6'H1 from Arabidopsis
Ib1, 2 from I. batatas
19
spontaneous
Scopoletin (4)
Coumarins with modification in the pyrone ring
4-Hydroxycoumarin (7)
Coumestrol (8)
Furano/pyranocoumarins
Psoralen (5)
Xanthyletin (6)

Furano- and Pyranocoumarins

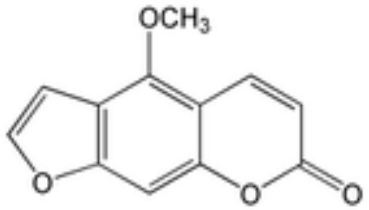


Angelicin
[A furanocoumarin]

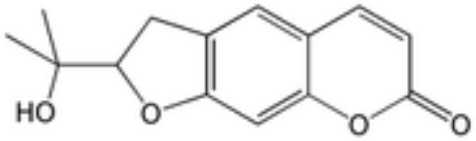
Angelicin



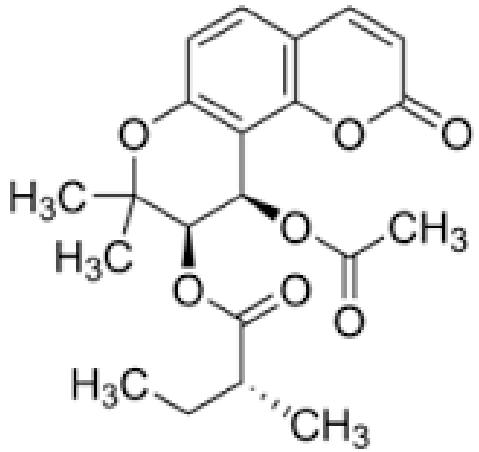
Xanthotoxin



Bergapten

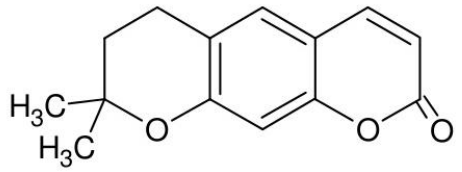


Nodakenetin



visnadin

PYRANOCOUMARIN(linear)



xanthyletin

PROPERTIES, EXTRACTION, AND 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. For purification, it is possible to take advantage of the propertie specific to the lactone: opening and solubilization in alkaline conditions, closing in acidic medium.

Coumarins have a characteristic UV spectrum which is heavily influenced by the nature and the position of substituents, and by alkalinization (KOH, $NaOCH_3$), colors which are enhanced in the presence of ammonia, and range from blue to yellow and purple.

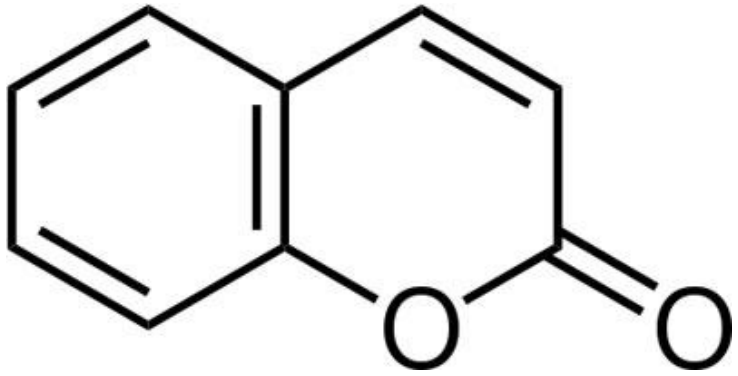
PHARMACEUTICAL PROPERTIES AND USES

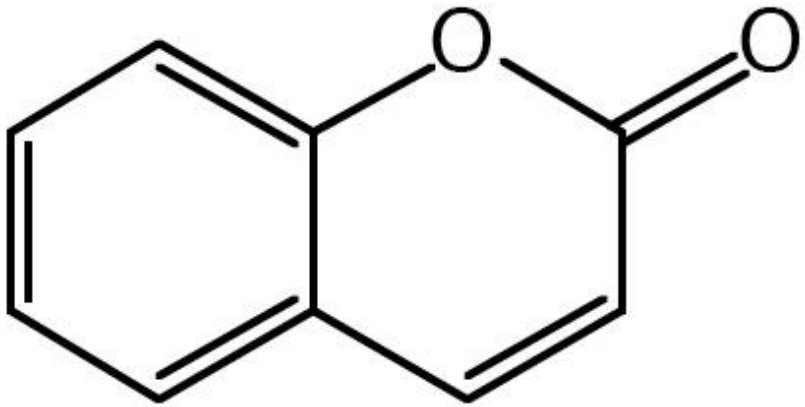
The pharmacological interest of coumarin-containing drugs is limited. Aesculin is said to be a venous tonic and a vascular protective agent. *Melilotus officinalis* (sweet clover) extract is used for the symptomatic treatment of venous and lymphatic vessel insuffiency. Some furanocoumarins are photosensitizers, therefore they are indicated for the therapy of psoriasis and vitiligo. Visnadin, a pyranocoumarin isolated from *Ammi visnaga* (khella), has been extracted and marketed for its coronary vasodilator effect and promoted as having a favorable action on senile cerebral insuffiency. Coumarin is known for its antiedema properties and has undergone clinical trials in patients with advanced cancer: it is an immunostimulant with a cytotoxic activity.

CHIEF COUMARIN-CONTAINING DRUGS

COUMARIN

Coumarin itself was marketed in France. It was indicated to treat the lymphedema of the arm subsequent to breast cancer radiotherapy and surgery. The large number of hepatitis cases attributed to coumarin, led to removal from the market of coumarin-containing pharmaceuticals.



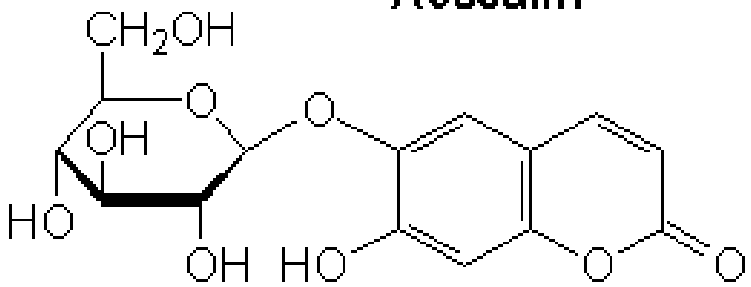


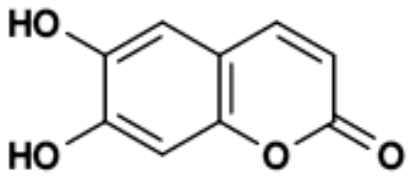
Hippocastani cortex **Common horse chestnut** **at kestanesi gövde kabuğu**

Aesculus hippocastanum **Hippocastanaceae**

Aesculin is found in the bark of the tree. Considered a vascular protective agent, this glycoside, as well as aesculetin and its methylated derivative (synthetic), are ingredients of proprietary drugs which depending on their formulation (combination with flavonoids, ruscus extracts, local anesthetics, ascorbic acid) are promoted as a treatment for the symptoms of venous and lymphatic vessel insuffiency. Phytotherapeutic products containing the drug are traditionally used, orally and topically, to treat the functional symptoms of cutaneous capillary fragility (ecchymosis, petechiae), for the subjective symptoms of venous insuffiency.

Aesculin



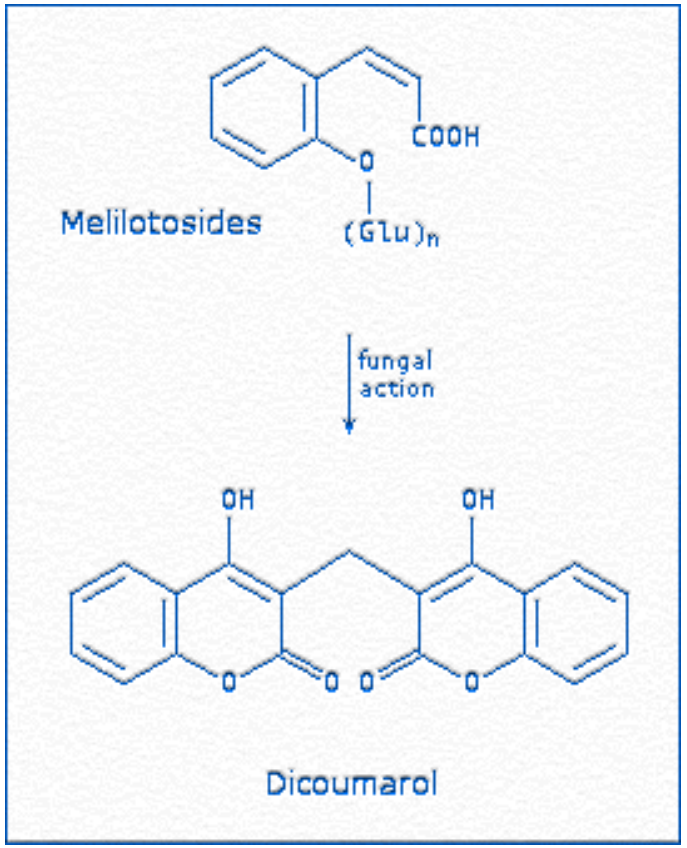


Aesculetin

Meliloti herba **sweet clover** **kokulu yonca**

Melilotus officinalis **Fabaceae**

The drug contains saponins, flavonoids, phenolic acids, and especially in the young leaves, melilotoside, the glucoside of 2-hydroxycinnamic acid, which following facile hydrolysis, lactonizes to coumarin, in the event of fungal contamination, 2-hydroxycinnamic acid may be metabolized to form an anticoagulant dicoumarol.



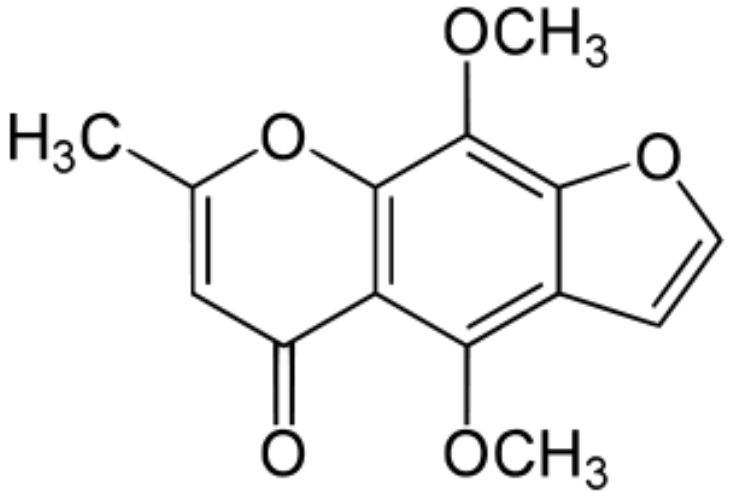
Animal experiments have shown the antiedemic properties of the drug, which also increases venous and lymphatic flow rates, and decreases capillary permeability. Coumarin, which is not an anticoagulant, stimulates, the reticulo-endothelial system.
The German Commission E monograph lists internal uses by the activity on venous and lymphatic vessels, including itching, fullness in the legs cramps, edema, and hemorrhoids. The drug and its preperations are also used topically for contusions, sprains, or superficial bleedings. Recall the coumarin-type anticoagulants currently synthesized were designated with dicoumarol as a model, an anticoagulant arising upon fungal contamination of *Melilotus officinalis*. Dicoumarol is responsible for cattle intoxications.

Ammeos visnagae fructus
Ammi visnaga

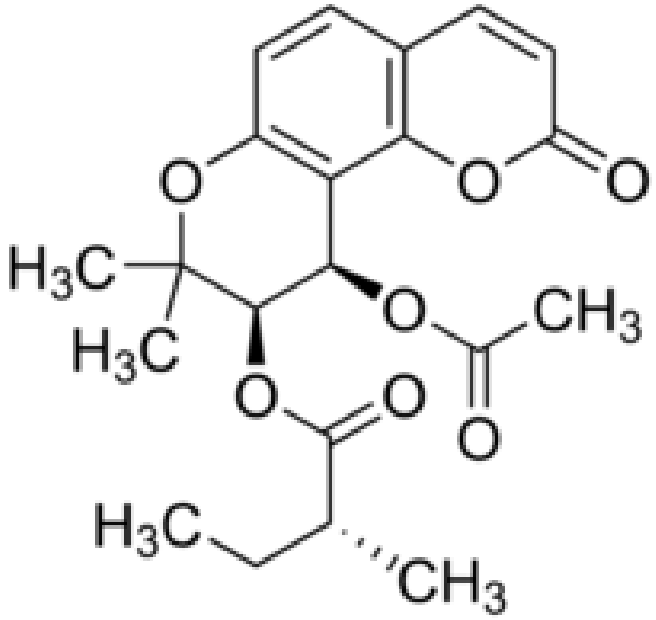
khella
Apiaceae

diş otu meyvesi

The chief constituents of the drug are furanochromones (2-4%), including khellin (0.3-1.2%), visnagin (0.05-0.3%), khellol, and khellinol, and angular pyrano-coumarins (0.2-0.5%), including visnadin, samidin, and dihydrosamidin.The drug also contains lipids, flavonoids, and essential oil.



Khellin (furanochromon)



Visnadin (pyranocoumarin)

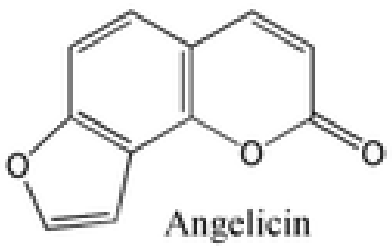
Khellin is a spasmolytic agent. Visnadin is a coronary vasodilator and a positive inotropic, radycardic, and spasmolytic, probably as a result of its calcium blocking activity. Khellin has been used in the preventive therapy of angina pectoris.

Angelicae radix angelica melek otu kökü

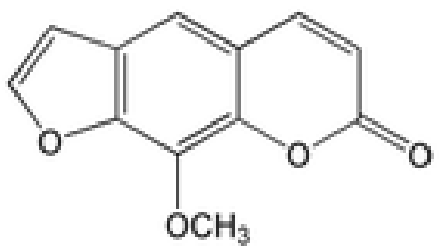
Angelica archangelica Apiaceae

The drug contains up to 6 ml/kg essential oil, macrocyclic lactones and coumarins (bergapten, xanthotoxin, angelicin, archangelicin). Lateral roots are 2.5 times richer than the main root. The essential oil has a spasmolytic effect. The root can be used for gastrointestinal distress , and lack of appetite. Patients are advised to avoid prolonged exposure to sunlight or to UV irradiation during the treatment (furanocoumarins can induce photodermatitis).

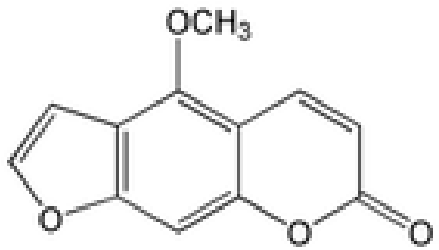
Angelicas are widely used in Asia. In China, the dried root of *Angelica dahurica* is reputed to be antipyretic and analgesic (headaches, toothaches).



Angelicin



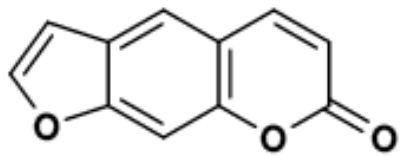
Xanthotoxin



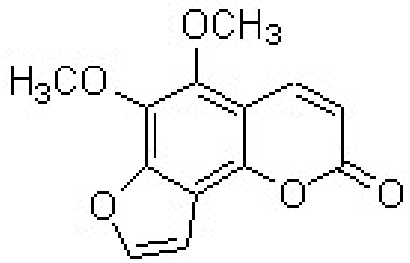
Bergapten

FURANOCOUMARINS AND PHOTOTOXICITY

It has long been known that various plant species from different parts of the world are capable of causing a transient cutaneous hyperpigmentation. These cutaneous accidents reflect phototoxicity : they always occur after contact with the plant. The phototoxic constituents, common to all these species are linear furanocoumarins (psoralen, bergapten, xanthotoxin), angular furanocoumarins are only weakly toxic (angelicin, bergapten).



Psoralen
[A furanocoumarin]



pimpinellin

Other toxic coumarins

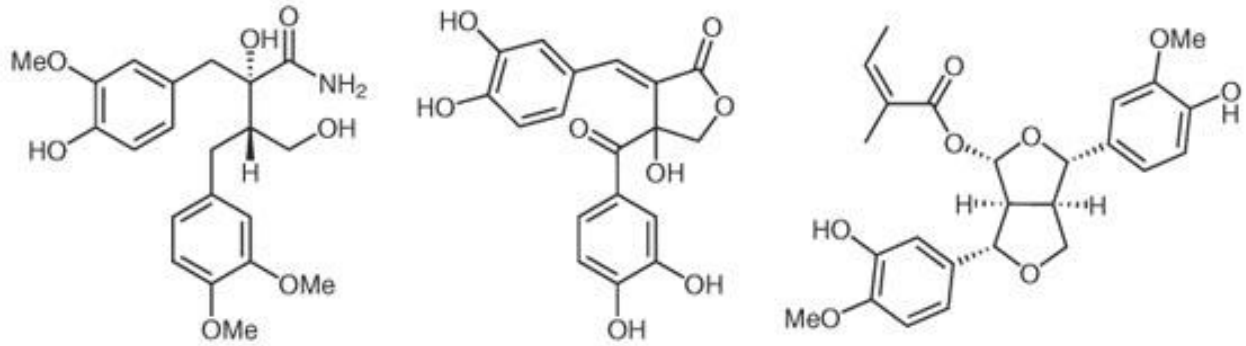
Some coumarins synthesized by lower fungi are toxic, for example aflatoxins are carcinogenic. Their absence must be carefully verified in animal feed (cattle cake) and human food (oil, milk, butter).

FURANOCOUMARIN APPLICATIONS

The photodynamic sensitizing properties of bergapten and methoxypsoralen are applied during PUVA treatment, or photochemotherapy of psoriasis and other dermatological disorders. The therapy is not without risks : gastrointestinal disorders, dry skin photosensitilization…This treatment is contraindicated for pregnant women, and children. Long term PUVA treatment increases the risk of cancer (carcinoma, melanoma). **PUVA: PUVA stands for psoralen (P) and ultraviolet A (UVA) therapy in which the patient is exposed first to psoralens (drugs containing chemicals that react with ultraviolet light) and then to UVA light.**

Lignans, Neolignans, and related Compounds

The term lignan commonly designates compounds whose skleton results from bonding between the β carbons of the side chains of two units derived from 1-phenylpropane (8-8’ bond).



Trachelogenin amide (**1**)
(dibenzylbutane lignan)

Actaelactone (**2**)
(dibenzylbutyrolactone lignan)

9α-Angloyloxypinoresinol (**3**)
(furofuran lignan)

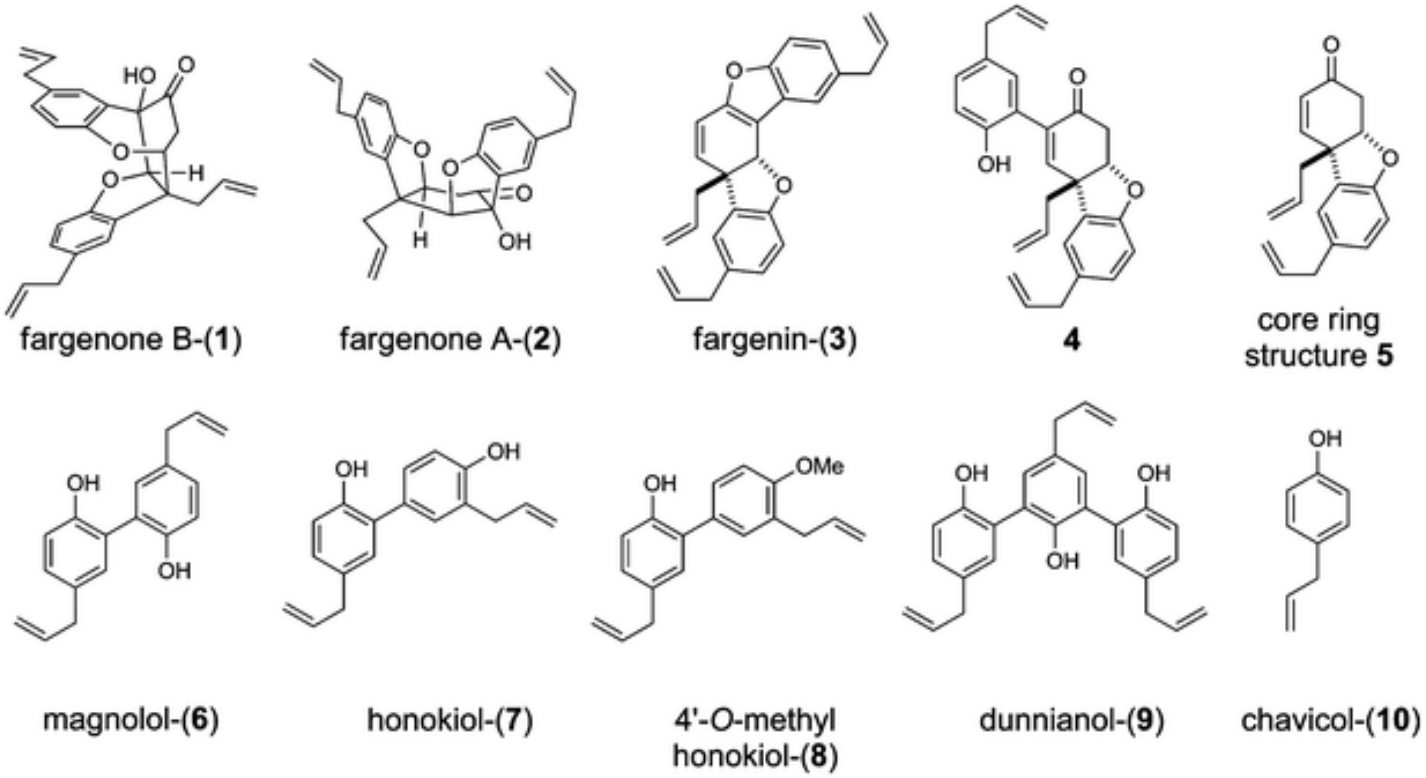
Kadsuralignan J (**4**)
(dibenzocyclooctadiene lignan)

Beilschmin A (**5**)
(substituted tetrahydrofuran lignan)

Podophillotoxin (**6**)
(aryltetralin lignan)

Types and examples of biological active lignans.

Neolignans are also condensation products of phenylpropanoid units, but the actual bond varies and involves no more than one β carbon.



Chemotaxonomically, lignans are widely distributed. In Gymnosperms they occur mainly in wood, whereas in Angiosperms they have been identified in all tissues. Neolignans appear to have a narrower distribution; they are especially common in Magnoliales and Piperales.

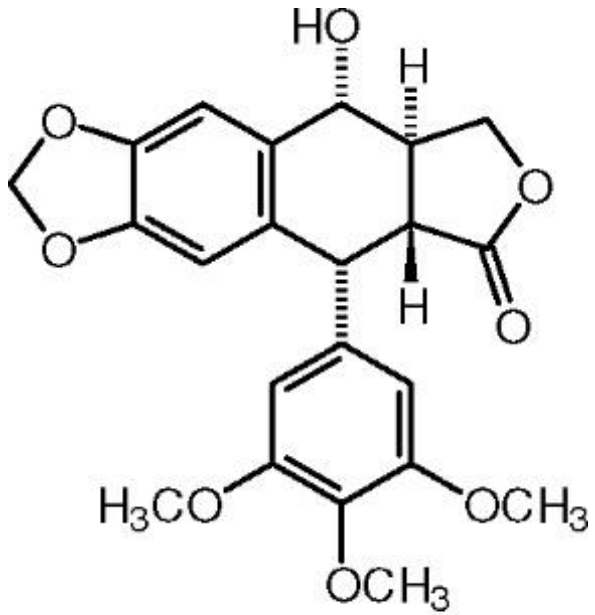
BIOLOGICAL INTEREST IN LIGNANS

In plants, lignans and neolignans probably play an important defense role: antibacterial, antifungal, and antifeedant properties have been described for many compounds in this group. Some of them are enzym inhibitors. Other activities : anti-platelet aggregation, calcium blocking activity, antihypertensive action, antiviral activity.

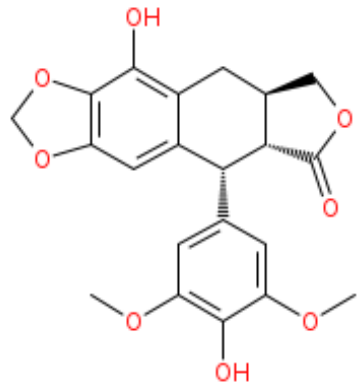
Podophylli peltati rhizome **may apple, mandrake**

Podophyllum peltatum **Berberidaceae**

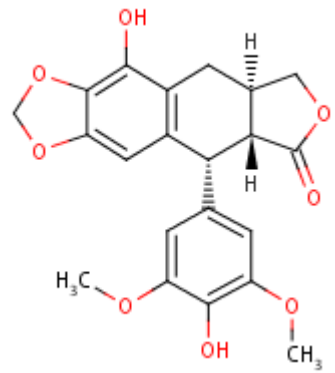
The resin of the podophyllum rhizome, traditionally used as a contact cathartic, is a source of **podophyllotoxin**. This antimitotic lignan is extracted from various sources to be transformed into the **semisynthetic antineoplastic derivatives teniposide and etoposide**. The drug contains 3 to 6% resin. Known in the past as podophyllin, this resin can be obtained by diluting an alcoholic extract with water that is eventually acidified : it precipitates, is collected, then dried. The main constituents of the resin are 1-aryltetrahydronaphtalenes : podophyllotoxin (20%), α- and β-peltatins (5 and 10%),and some other lignans. Some of these compounds occur as glycosides.



podophyllotoxin



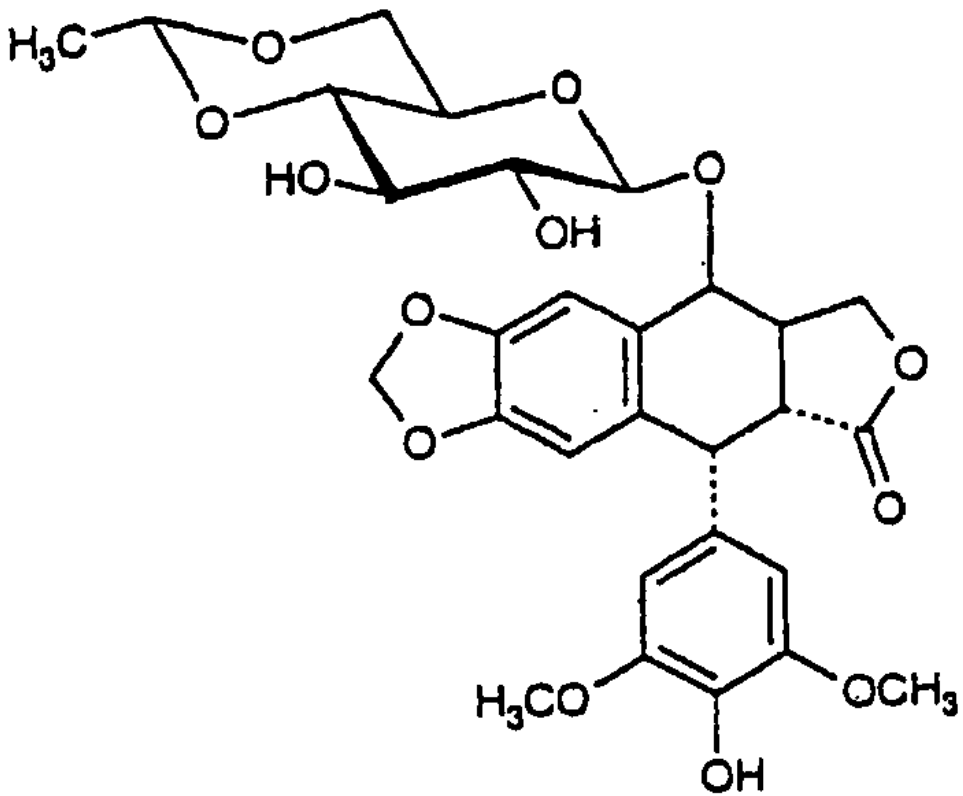
α-peltatin



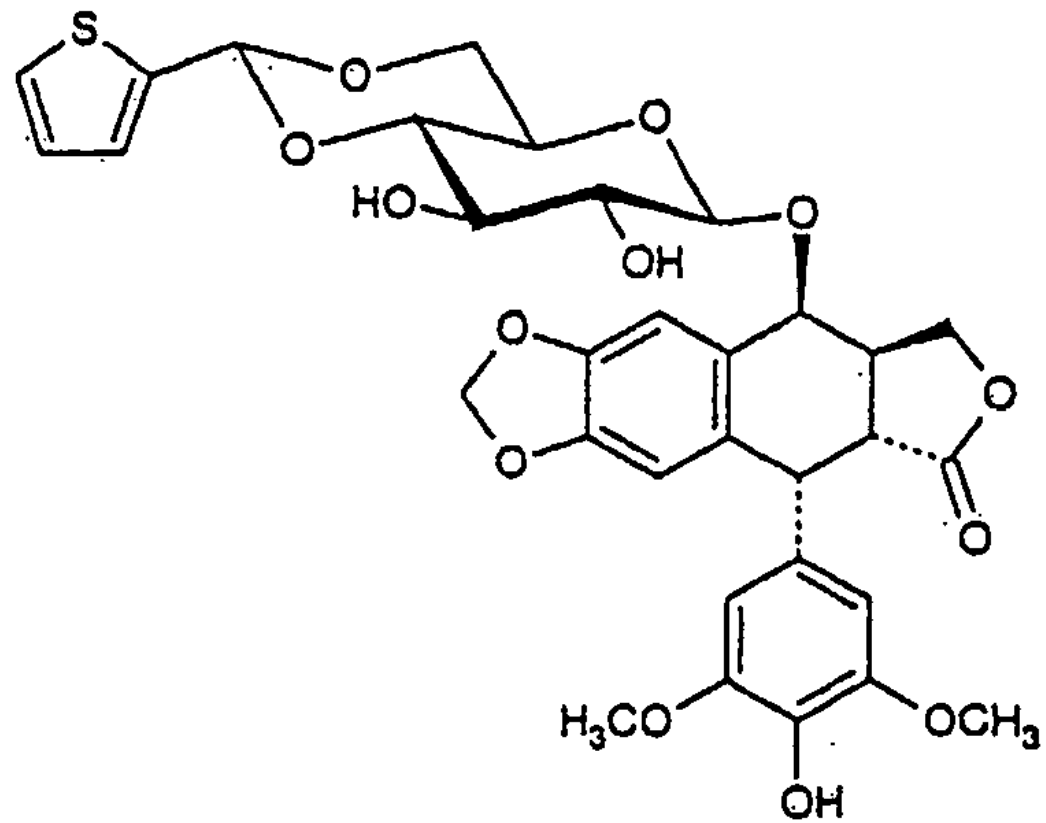
β-peltatin

Pharmacological Activity : Podophyllotoxin and peltatins inhibit the growth of experimental tumors induced in the mouse. Their action takes place at the level of the microtubules. The competitive inhibition of colchicine binding to tubuline shows that the mechanism of action is similar.

Synthetic work and the study of structure-activity relationships have made possible the design of semisynthetic derivatives combining good activity and relatively limited side effects: tenioposide, etoposide.



Etoposide



Tenioposide

Toxicity : Podophyllotoxin is extremely toxic. Following ingestion (or skin contact), it causes gastrointestinal distress, and later on, encepholopathy and peripheral neuropathy.

Uses : The resin was long used as a laxative and cholagogue. **The resin is no longer used except for the extraction of podophyllotoxin, which is also commonly extracted from another species *Podophyllum hexandrum = Podophyllum emodi*. The latter, of Himalayan origin contains 6 to 12% resin, in which the concentration of podophyllotoxin is around 40%.**

Uses of **podophyllotoxin** :

• In the treatment of external condylomas. The antimitotic properties of this lignan make pregnancy and and breast-feeding absolute contraindications.

•To obtain semisynthetic derivatives prescribed in the hospital and under strict medical observation :

- **Etoposide** : is active when used alone in chemotherapy for following indications : embryonic carcinoma of the testicles, small cell bronchogenic carcinoma, placental choriocarcinoma, previously treated breast cancer, malignant lymphoma (Hodgkin's disease), and acute leukemia.

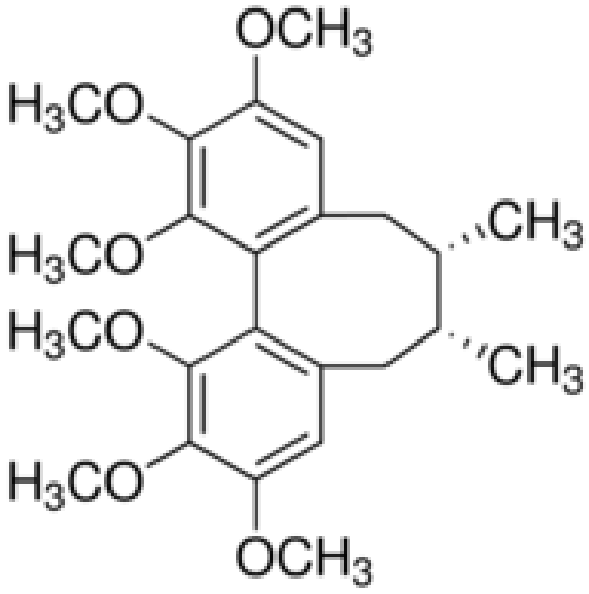
- Common indications of **tenioposide** are the treatment of Hodgkin's disease, non Hodgkin's lymphomas, and brain and bladder tumors.

- The pharmaceutical industry recently made avelaible a prodrug, etoposide phosphate. In contrast to etoposide, the phosphate is water soluble (injectable lyophilisate). Etoposide phosphate is rapidly hydrolyzed to etoposide by serum phosphatases.

Schisandrae fructus **schizandra**

Schisandra chinensis **Schisandraceae**

Traditional Chinese medicine attributes to the fruits of this creeping plant of northern China tonic, antitussive, and CNS stimulating properties. The seeds contain about 30 lignoid-type compounds, schisandrines, gomisines, deoxyschisandrin and more.



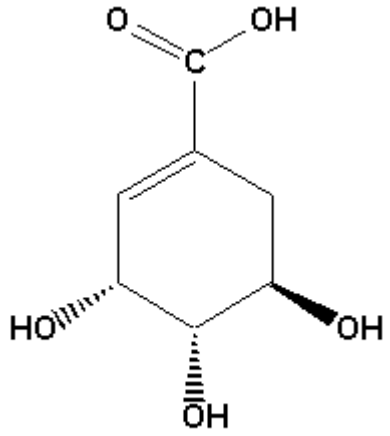
Schisandrin A

SHIKIMATES

Shikimates are phenylpropane Chain Elongation Derivatives

They are

Diarylheptanoids and Arylalkanones
Stilbenoids
Xanthones
Strylpyrones
Flavonoids
Isoflavonoids
Neoflavonoids



Shikimic Acid

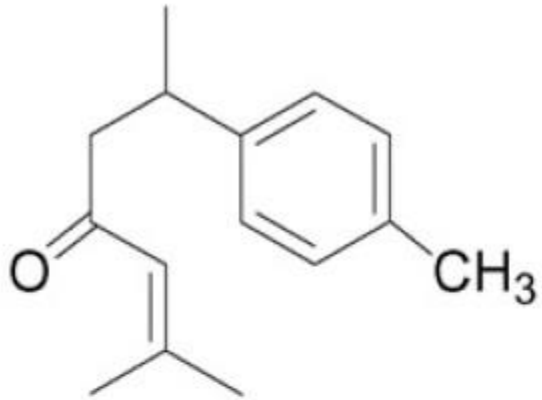
Diarylheptanoids and Arylalkanones

These compounds, including curcuminoids, gingerols, and their derivatives, are specific to several genera of the family Zingiberaceae. They are coloring substances of turmerics and the pungent principles of ginger. Over the lasy twenty years, multiple studies have shown that they are pharmacologically active.

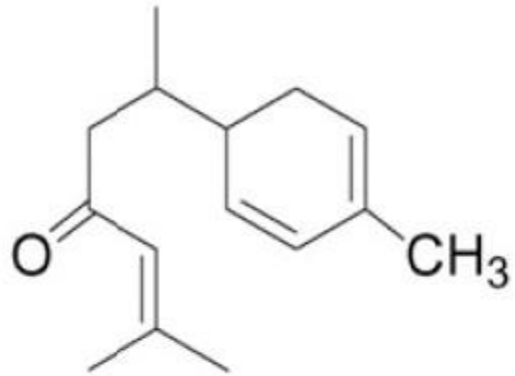
Curcumae rhizoma **turmeric** **zerdeçal**

Curcuma domestica **Zingiberaceae**

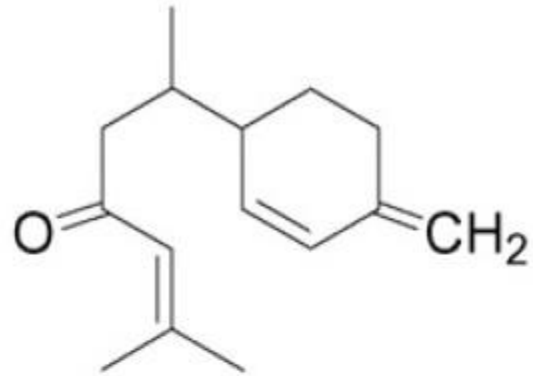
The rhizome of **turmeric** (= **curcuma**) is a main ingredient of **curry** powders, and has been the subject of many studies, mostly be scientists from India who have defined its pharmacological properties. The drug is rich in starch (45-55%), it also contains arabinogalactans (ukonans) and 2.5 to 6% of an essential oil with monocyclyc monoterpenes : hydrocarbons (zingiberene, β- and δ-curcumene) and mostly oxygenated derivatives (turmerone, S-(+)-ar-turmerone, curlone, α- and ϒ-atlantone). Note, in addition, the presence of monoterpenes. Sesquiterpenes (bisabolanes and germacranes) are also found in the oleoresin and the various extracts, which generally contain more ar-turmerone than the essential oil (steam distillation is thought to induce aromatization).



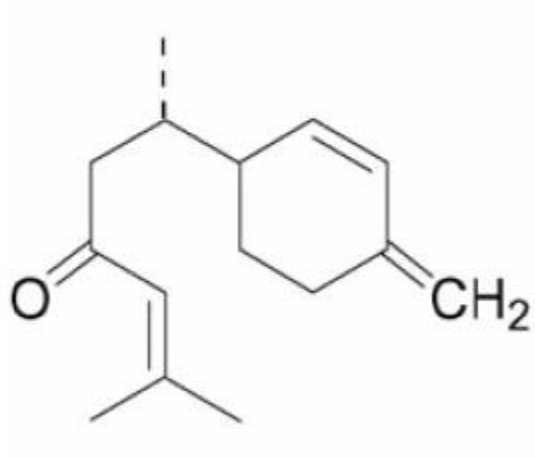
ar-turmerone



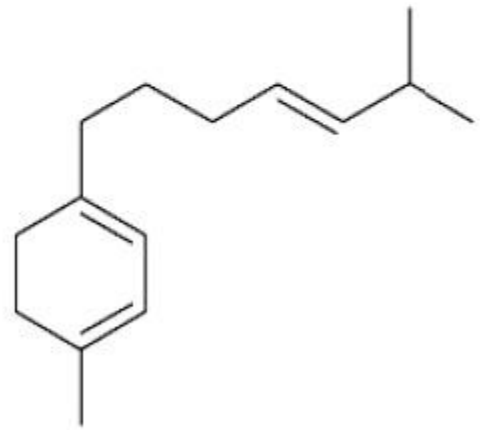
α-turmerone



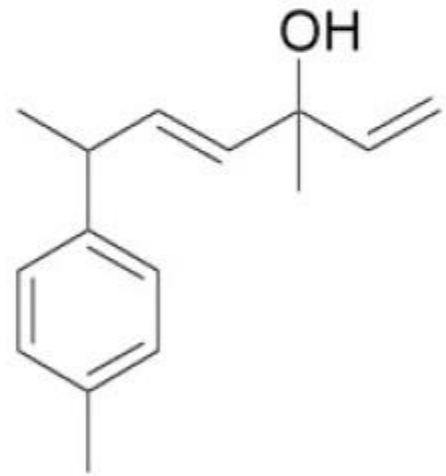
β-turmerone



Curlone

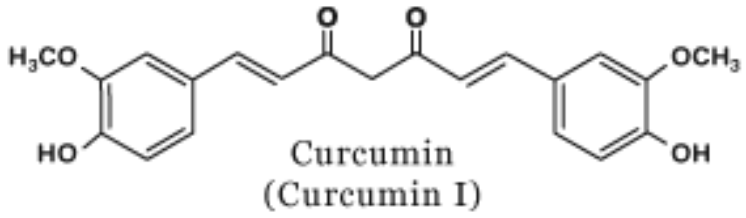


Zingiberene

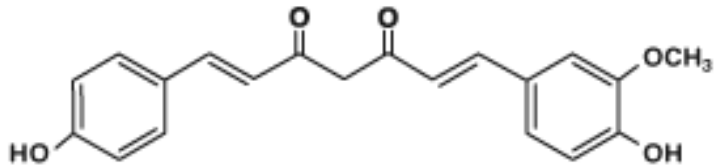


Curcumene

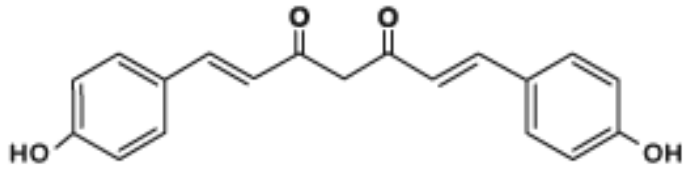
The coloring principles in the drug are **curcuminoids**. These molecules, structurally related to a diarylheptane, occur at a concentration that varies greatly with the cultivar and can reach 8%. The chief component (50-60%) is curcumin, it occurs together with related components.



Curcumin
(Curcumin I)



Demethoxycurcumin
(Curcumin II)



Bis-demethoxy
(Curcumi

Pharmacological Properties : The anti-inflammatory activity of curcumin has been demonstrated on acute inflammation. The drug has a definite action on the hepatic parenchima. Note also some activity on the stomach.

Uses : Pharmacy uses turmeric rhizomes as a constituent of pharmaceuticals with the following indications : traditionally used

1. as a choleretic and cholagogue, 2. functional dyspepsia attributed to hepatic origin, 3. as an appetite stimulant. The German Commission E mongraph recognizes uses of the same type, but specifies that biliary tract obstruction is a contraindication.

GINGER **ZINGIBERIS RHIZOMA** **Zingiberaceae**

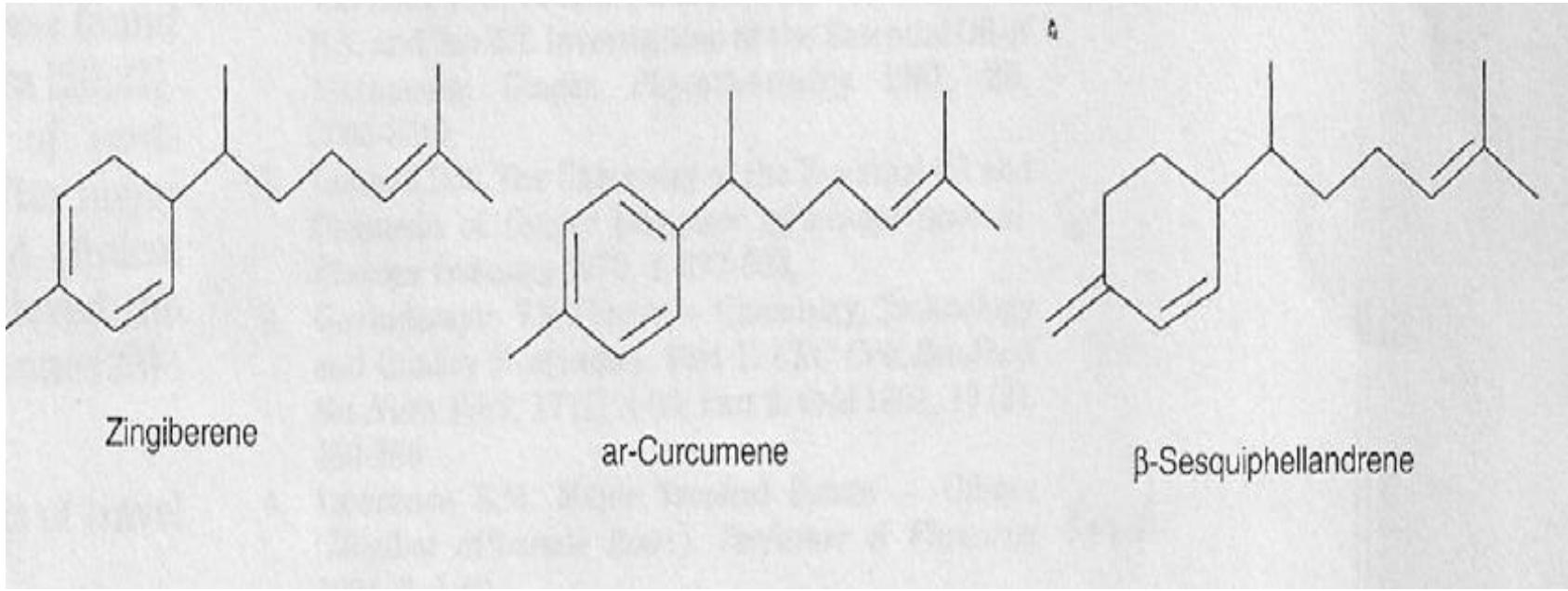
Zingiber officinale **Zencefil**

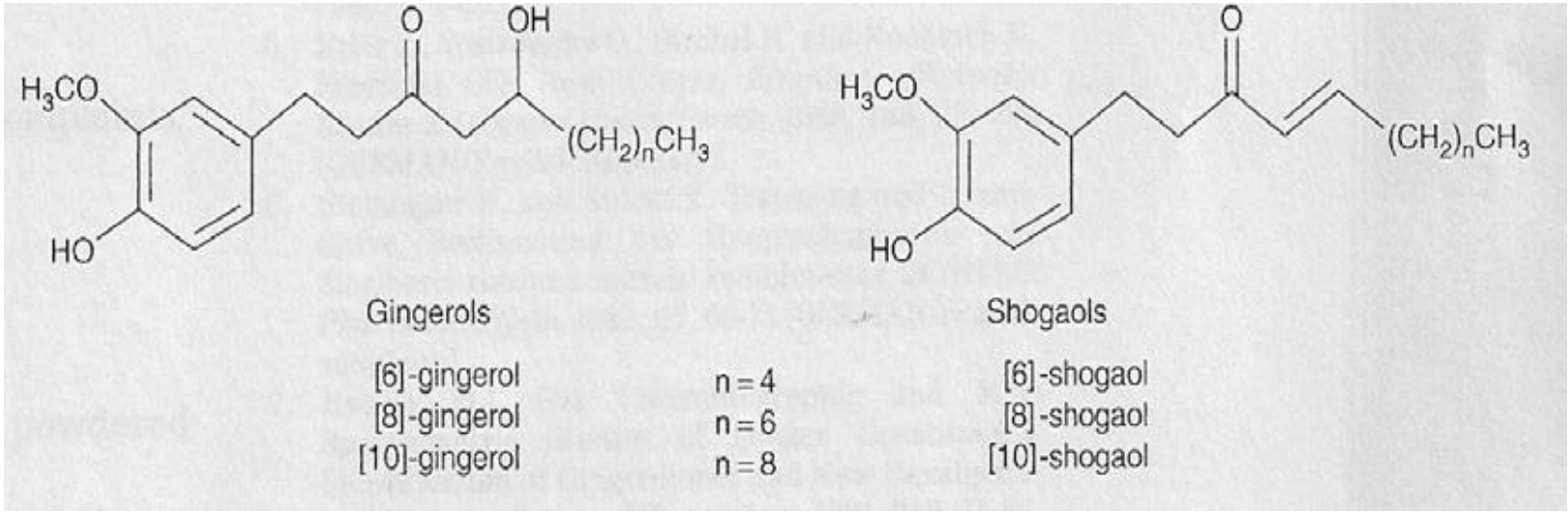
Ginger (Zingiber) is the scraped or unscraped rhizome of *Zingiber officinale* (Zingiberaceae), it is another ingredient of **curry** powders, . *Z. officinale*, a reed-like plant, is grown in many parts of the world, including Jamaica, China, India and Africa (Nigeria). Jamaican ginger, once the traditional pharmaceutical ginger, has been largely replaced by other sources.

History : Ginger has been cultivated in India from the earliest times; the plant is unknown in the wild state. The spice was used by the Greeks and Romans, and was a common article of European commerce in the Middle Ages. It was well known in England in the eleventh century.

Chemical Constituents : Volatile oil 1-4 % . More than 100 compounds are identified, most of them terpenoids mainly sesquiterpenoids (α-zingiberene, β-sesquiphellandrene, β-bisabolene, α- farnesene, ar-curcumene (zingiberol) and smaller amounts of monoterpenoids (camphene, β- phellandrene, cineole, geraniol, curcumene, citral, terpineol, borneol). The composition of the oil depends on the origin of the material.

The pungent principles, the gingerols (4-7.5 %) are a homologous series of phenols. The principal one of these is 6-gingerol. Gingerols with other chain-lengths, e.g., 8-gingerol and 10-gingerol, are present in smaller amounts. During drying and storage, gingerols are partly dehydrated to the corresponding shogaols which may undergo further reduction to form paradols, also present in stored ginger.


Zingiberene
ar-Curcumene
β-Sesquiphellandrene


O
OH
H3CO
HO
(CH2)nCH3
Gingerols
[6]-gingerol
[8]-gingerol
[10]-gingerol
n = 4
n = 6
n = 8
O
H3CO
HO
(CH2)nCH3
Shogaols
[6]-shogaol
[8]-shogaol
[10]-shogaol

Medicinal Uses : Traditional ayruvedic medicine

Ginger plays an important role in traditional Indian Ayurvedic medicine. It is also used as an ingredient in traditional Indian drinks. Fresh ginger is one of the main spices used for making dishes, both vegetarian and non vegetarian based foods. Indian traditional medicinal remedies especially for cough and asthma consists of juice of fresh ginger with a little juice of fresh garlic mixed with honey. It is also suggests 1-2 tea spoons of ginger juice with honey is a potent cough suppressant. Besides these ginger is very often used to cure many illness such as indigestion, tastelessness, loss of appetite, flatulence, intestinal, nausea, vomiting, allergic reactions, acute and chronic cough, common cold, fever, allergic rhinitis, sinusitis, acute chronic bronchitis, respiratory troubles, pain, headache, backache or any kind of muscular catch, painful tooth and swelled gum.

Gastrointestinal relief : Modern scientific research has revealed that ginger possesses numerous therapeutic properties including antioxidant effects, an ability to inhibit the formation of inflammatory compounds, and direct antiinflammatory effects. Ginger is very effective in preventing the symptoms of motion sickness, especially seasickness. Ginger reduces all symptoms associated with motion sickness including dizziness, nausea, vomiting, and cold sweating [18]. Some active components of ginger are reported to stimulate digestion, absorption, relieve constipation and flatulence by increasing muscular activity in the digestive tract.

Anti-Inflammatory Effects : Ginger contains potent anti-inflammatory compounds called gingerols. These substances are believed to explain why so many people with osteoarthritis or rheumatoid arthritis experience reductions in their pain levels and improvements in their mobility when they consume ginger regularly. One of the mechanisms by which ginger exerts its ameliorative effects could be related to inhibition of prostaglandin and leukotriene biosynthesis.

Possible Interactions : Ginger may interact with prescription and nonprescription medications. If you take any of the following medications, you should not use ginger without first talking to your health care provider.

Blood-thinning medications -- Ginger may increase the risk of bleeding. Talk to your doctor before taking ginger if you take blood-thinners such as warfarin (Coumadin), clopidogrel (Plavix), or aspirin.

Diabetes medications -- Ginger may lower blood sugar. That can raise the risk of developing hypoglycemia or low blood sugar.

High blood pressure medications -- Ginger may lower blood pressure, raising the risk of low blood pressure or irregular heartbeat.

Stilbenoids

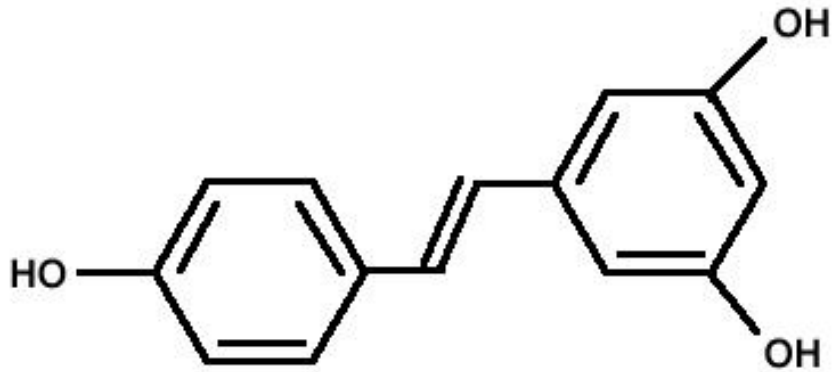
Resveratrol : **Resveratrol** (3,5,4'-trihydroxy-*trans*-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced naturally by several plants in response to injury or when the plant is under attack by pathogens such as bacteria or fungi. Food sources of resveratrol include the skin especially of **grapes**, and also blueberries, raspberries, and mulberries.

Benefits of Resveratrol

Resveratrol has gained a lot of attention for its reported antiaging and disease-combating benefits. Early research, mostly done in test tubes and in animals, suggests that resveratrol might help protect the body against a number of diseases, including:

Heart disease. Resveratrol helps reduce inflammation, prevents the oxidation of LDL "bad" cholesterol, and makes it more difficult for platelets to stick together and form the clots that can lead to a heart attack.

Cancer. Resveratrol is thought to limit the spread of cancer cells and trigger the process of cancer cell death (apoptosis).
Alzheimer's disease. Resveratrol may protect nerve cells from damage and the buildup of plaque that can lead to Alzheimer's.
Diabetes . Resveratrol helps prevent insulin resistance, a condition in which the body becomes less sensitive to the effects of the blood sugar-lowering hormone, insulin. Insulin resistance is a precursor to diabetes.
Rodent studies suggest that resveratrol might even help against some of the effects of an unhealthy lifestyle and lead to increased longevity. Resveratrol-treated mice fed a high-calorie diet lived longer than similarly fed mice not given resveratrol. Resveratrol protected mice fed a high-calorie diet from obesity-related health problems by mimicking the effects of caloric restriction.
Resveratrol has also been linked to prevention of age-related problems such as heart disease and insulin resistance. Researchers believe that resveratrol activates the SIRT1 gene, a biological mechanism that seems to protect the body against the harmful effects of obesity and the diseases of aging.



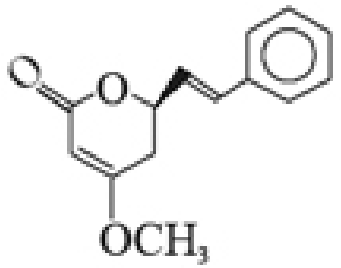
Resveratrol

Strylpyrones

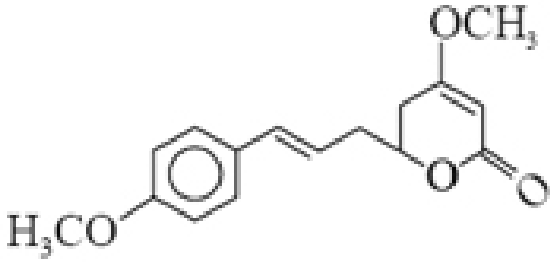
Kava rhizoma **Kava** **kawa-kawa**

Piper methysticum **Piperaceae**

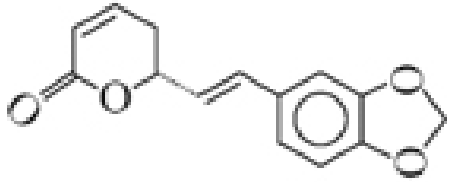
The active ingredients of kava are mono- or di-unsaturated α-pyrones. They include yangonin, (+)-methysticin, kawain, and minor products.



Kawain



Yangonin



Methysticin

Kava, its extracts, the fat soluble fraction have undergone much pharmacological research. The pyrones induce sleep in rodents (per os) and are sedatives in rodents, cats, and rabbits. They also cause muscle relaxation. Kava products were promoted as sleep disorder and axiety medicines especially in Germany. The use of the drug was abandoned after onset of their hepatotoxic effects.

Reference Books :

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