Sesquiterpenes

SESQUITERPENOID LACTONES

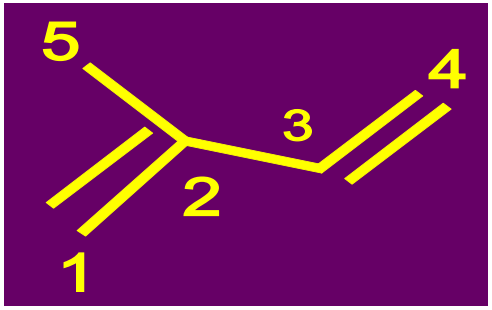
Prof. Dr. Ali H. Meriçli

Sesquiterpenoid lactones form a group of substances important by its size- approxymately 3.000 known structures- which was described in the older texts of Materia Medica, under the evocative names “bitter principles”. Sesquiterpenoid lactones have a rather scattered botanical distribution, bu they can be found mostly in the Apiaceae and especially in Asteraceae.

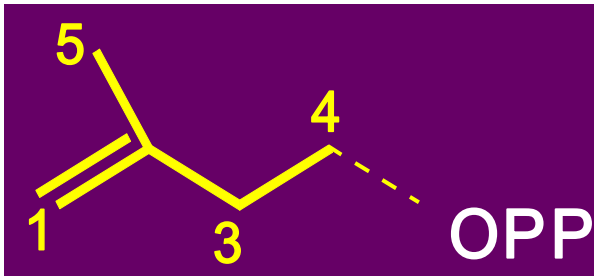
STRUCTURE

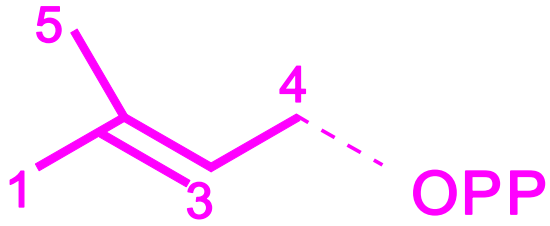
The skleta of sesquiterpenoid lactones vary, bu they all arise from the cyclodecadiene-type product of the cyclization 2*E*,6*E*-farnesyl pyrophosphate.

Sesquiterpenes are C-15 constituents occuring from 3 isopren units



isopren



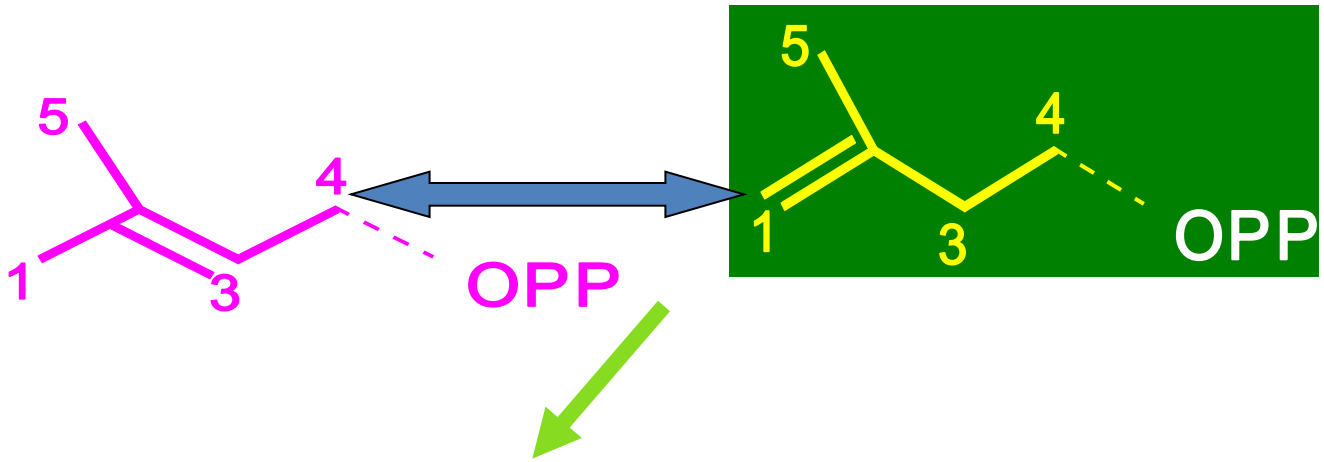


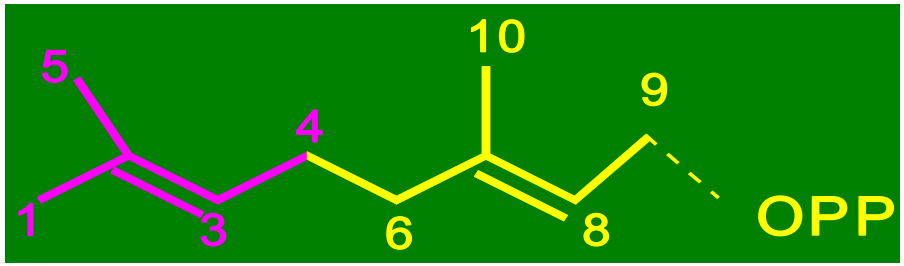
ISOPENTENYL PYROPHOSPHATE

(IPP)

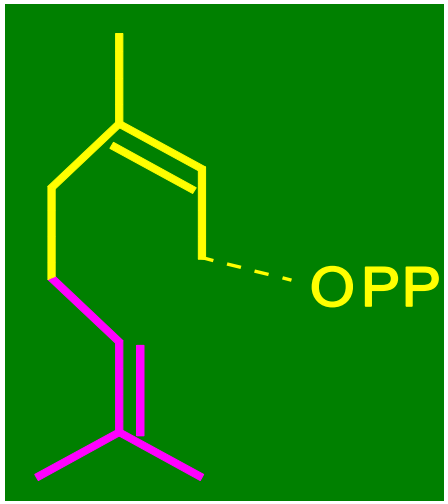
DIMETHYLALLYL PYROPHOSPHATE

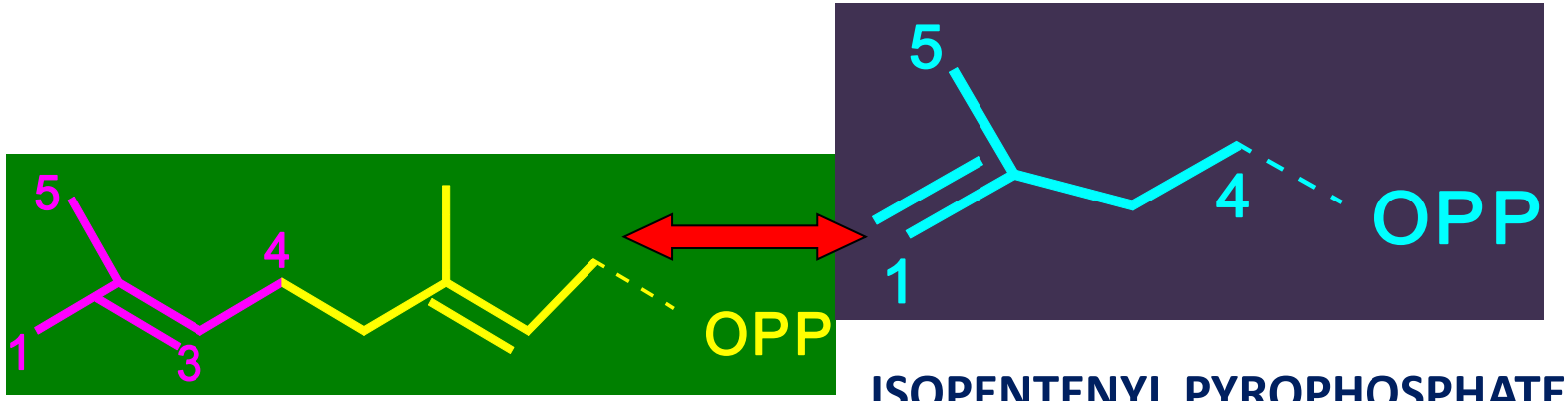
(DMAPP)





Geranyl pyrophosphate (GPP)



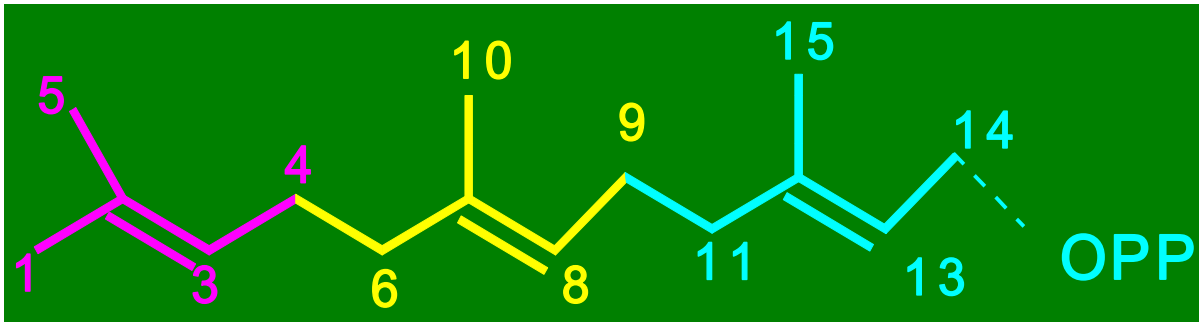


ISOPENTENYL PYROPHOSPHATE

IPP

Geranyl pyrophosphate

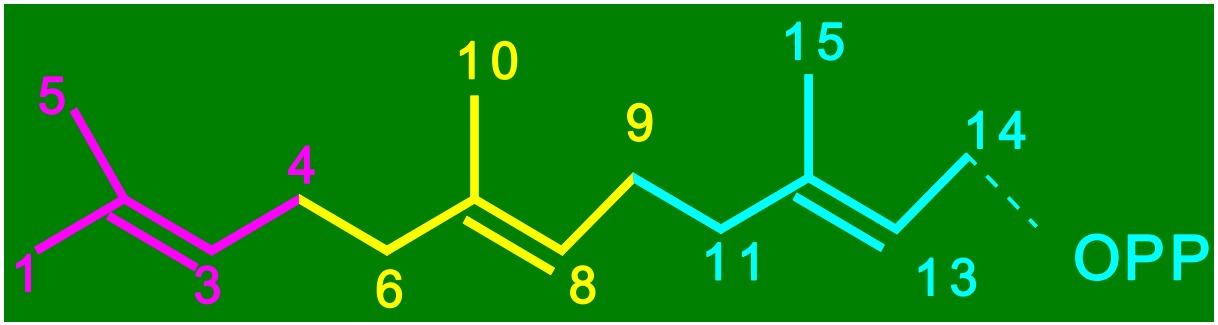
GPP



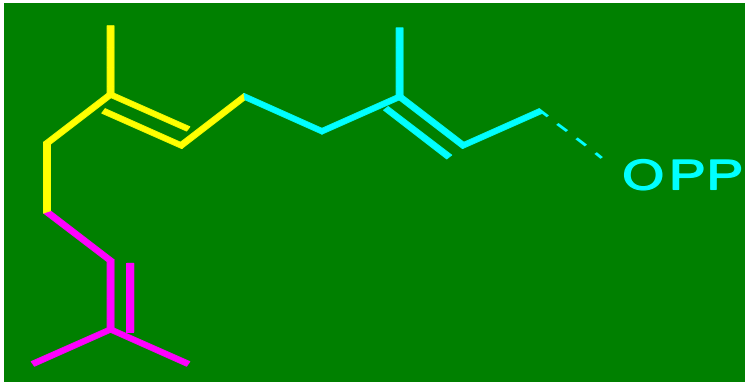
FARNESYL PYROPHOSPHATE (FPP)

15-C

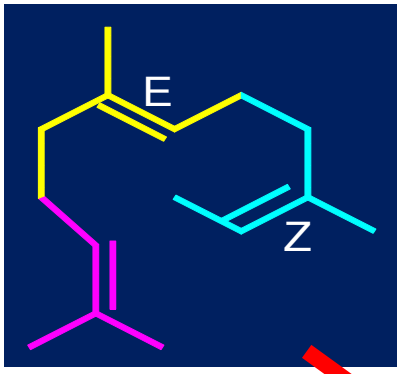
SESQUITERPENE

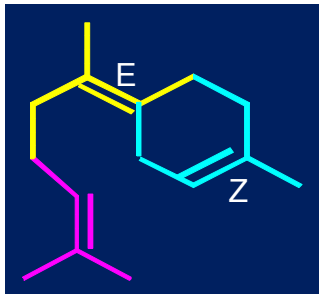


FARNESYL PYROPHOSPHATE
(FPP)

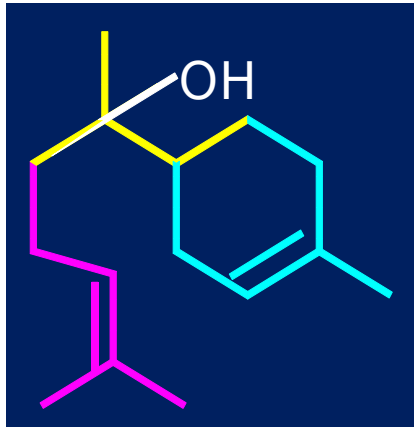


farnesene

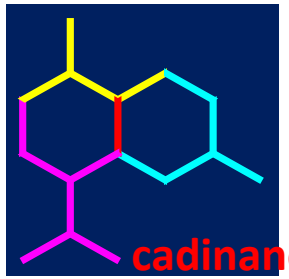




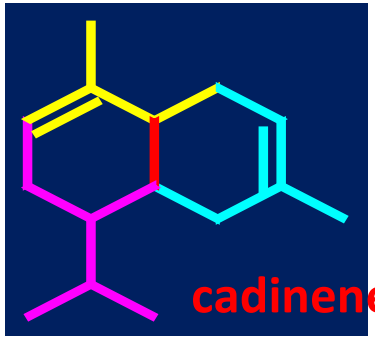
bisabolene



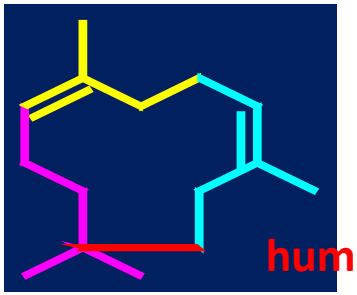
bisabolol



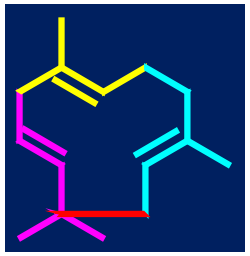
cadinane

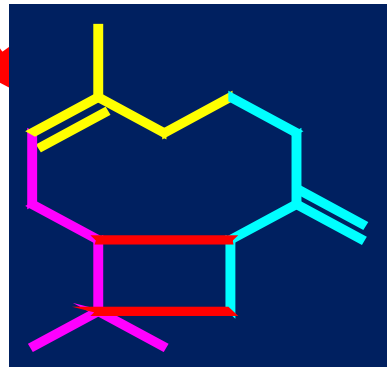


cadinene

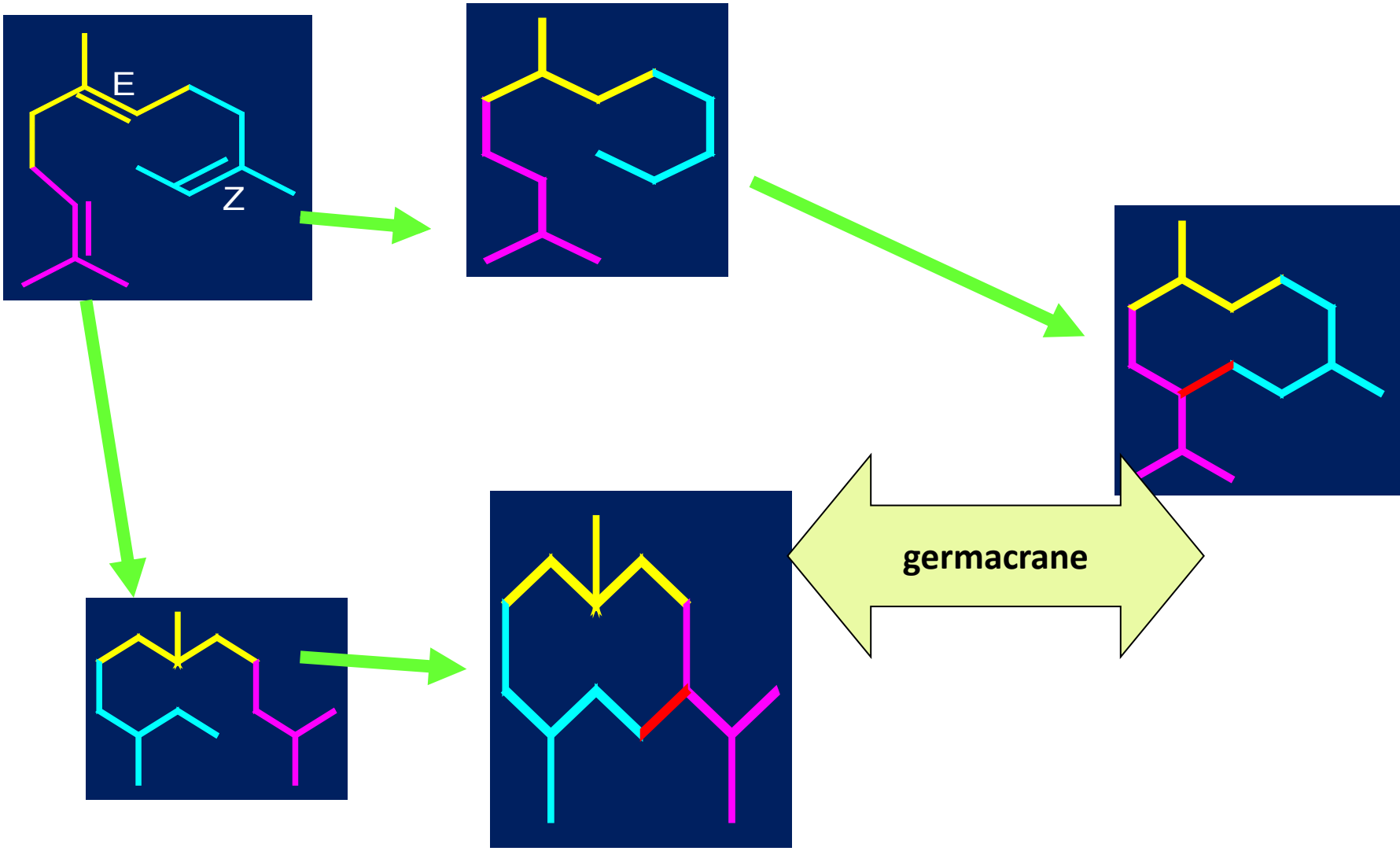


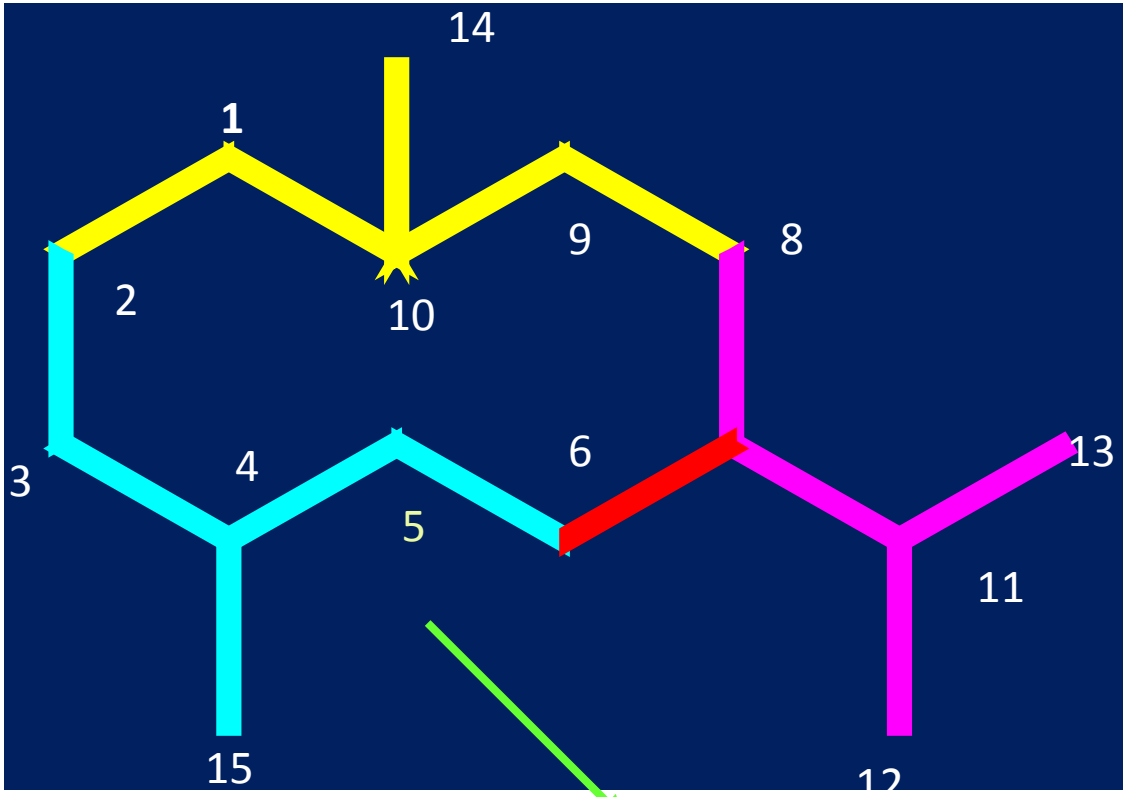
humulene



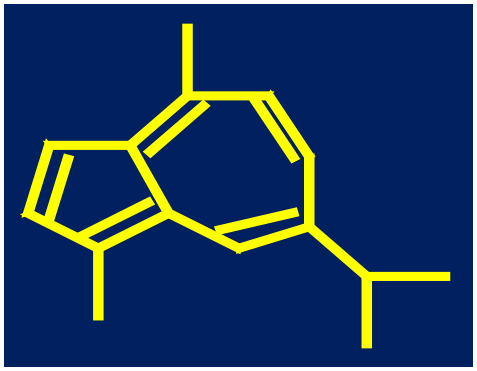


caryophyllene


E
Z
germacrane

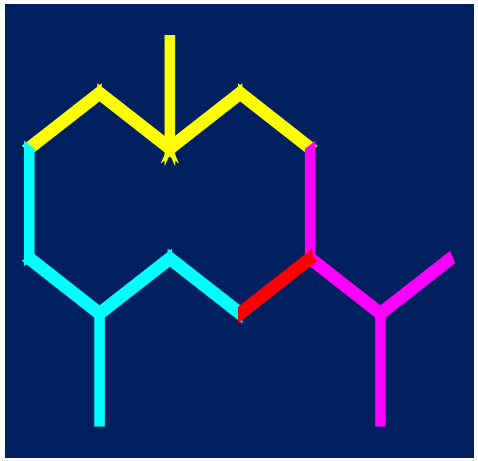


Guaiane ring

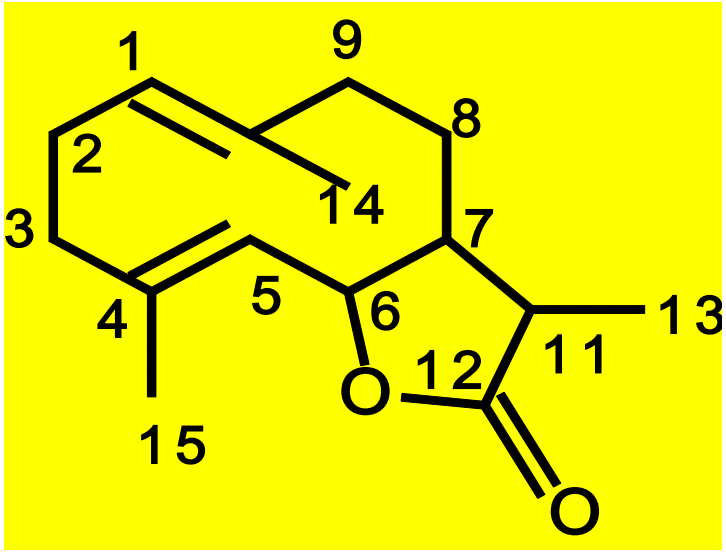


chamazulene

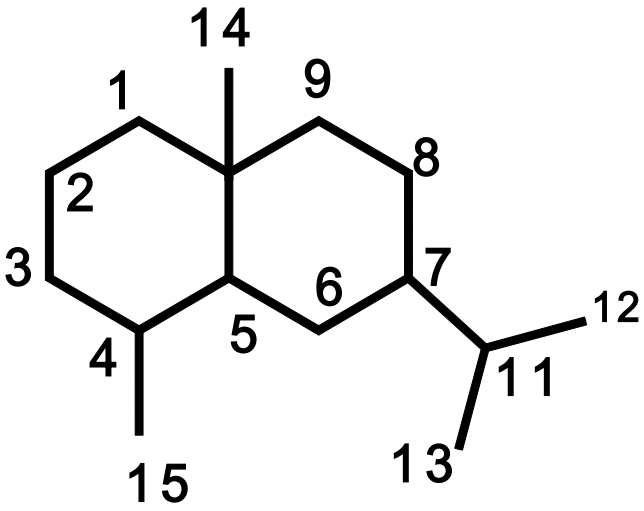
The main sesquiterpenoid lactone groups are : Germacranolides, Guaianolides, Pseudoguaianolides, Eudesmanolides, Elemanolides and Eremophilanolides.



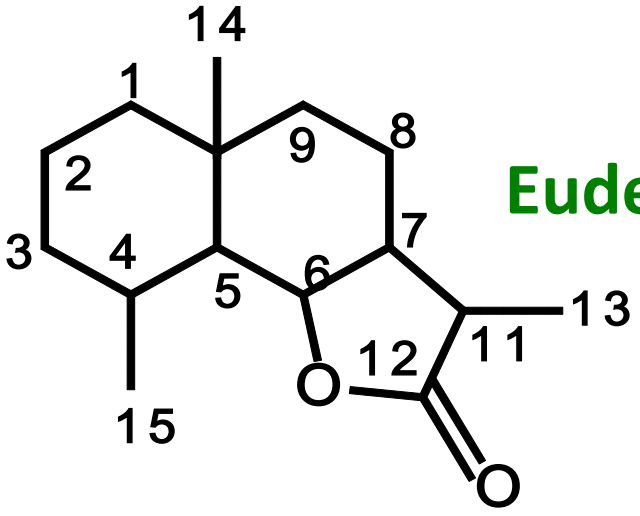
Germacrane



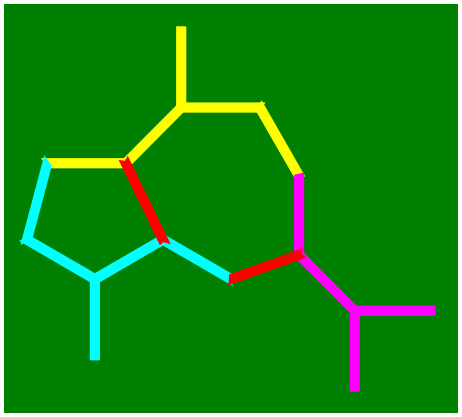
Germacranolide



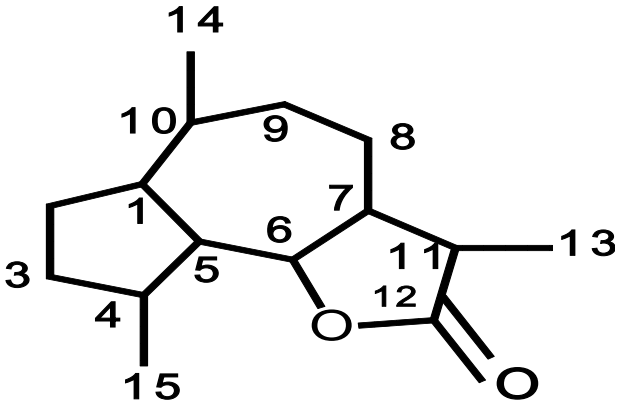
Eudesmane



Eudesmanolide



Guaiane

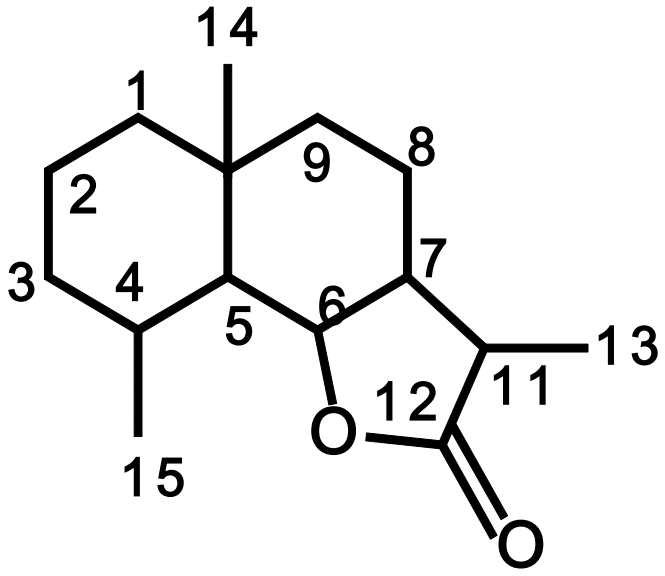


Guaianolide

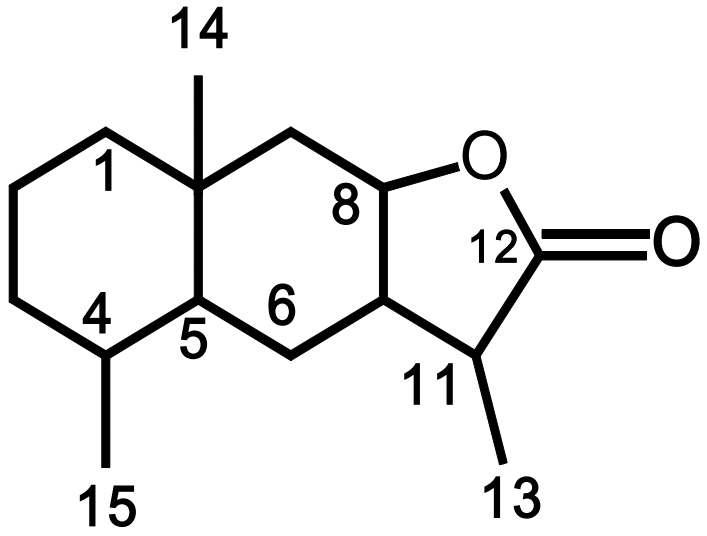
There are many secondary structural variations which affect :
The lactone,which can be *cis*-6,7, *cis*-7,8, *trans*-6,7 or in most cases *trans*-7,8.

The methyl groups, which are often functionalized (alcohols, carboxylic acids)

The unsaturations, which may be reduced or oxidized (epoxydes, hydroxyl groups, when hydroxyl groups are present, they are frequently esterified.



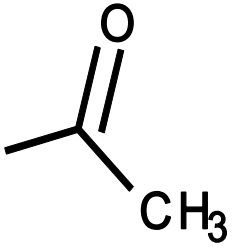
6,7-lactones

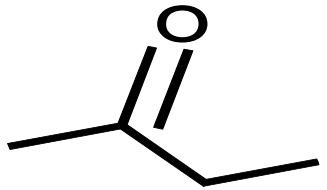


7,8-lactones

Sesquiterpenoid lactones can have many substituents

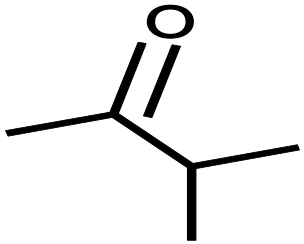
Acetate



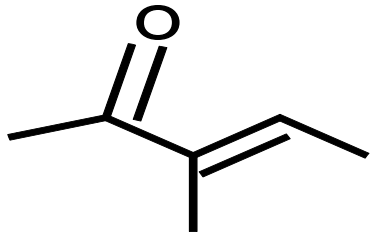


Propionate

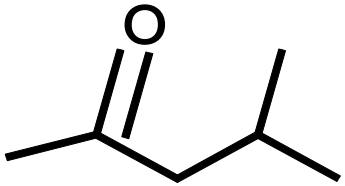
Isobutyrate



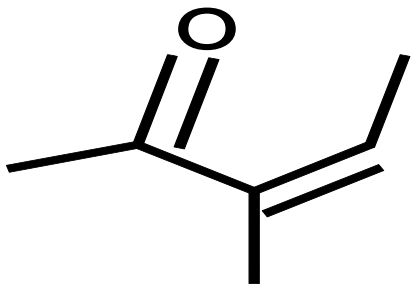
Tiglate



Isovaleriate



Angelate



There is no extraction method spesific to sesquiterpenoid lactones. They can be extracted with dichloromethane, or with a mixture of diethyl ether, petroleum ether, and methanol (1:1:1), and the extract can be fractionated by approciate chromatographic technique. Various reagents are avelaible to visualize the TLC spots, including iodine vapors, a dilute solution of $KMnO_4$, vanillin in the presence of hydrochloric acid, and cobalt chloride in an aqueous sulfuric acid solution.

DRUGS CONTAINING SESQUITERPENOID LACTONES

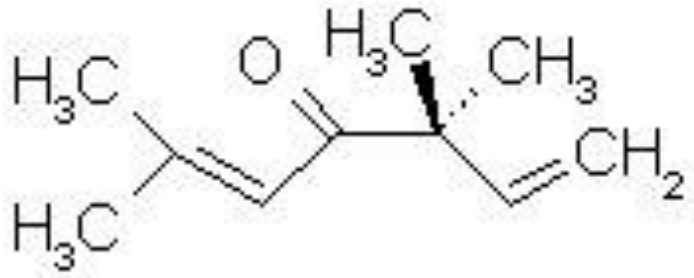
SWEET WORMWOOD (pelin)
ARTEMISIAE ANNUAE HERBA

Artemisia annua **Asteraceae**

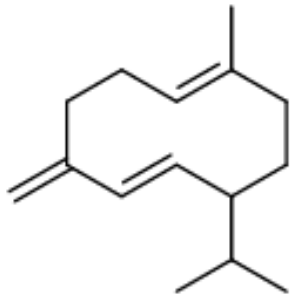
In the early 1970's the discovery of the antimalarial properties of extracts of this drug led to the isolation of the active principle, artemisinin=qinghaosu, as well as to a number of chemical, pharmacological, and clinical studies. The leafy stems are now used to obtain artemisinin, part of which is converted into dihydrogenated ethers and esters.

In Chinese medicine this drug (=Qinghao) is traditionally used to treat fevers and malaria. This wormwood, originally indigenous to Asia also grows wild in central and southern Europe and also in Turkey.

Chemical Composition : The concentration and the composition of the essential oil vary depending on the source of the drug : the Chinese chemotype is very rich in oil (40 ml/kg) and characterized by irregular monoterpenes (artemisia ketone, 64%), and also camphor and germacrene D.



Artemisia ketone

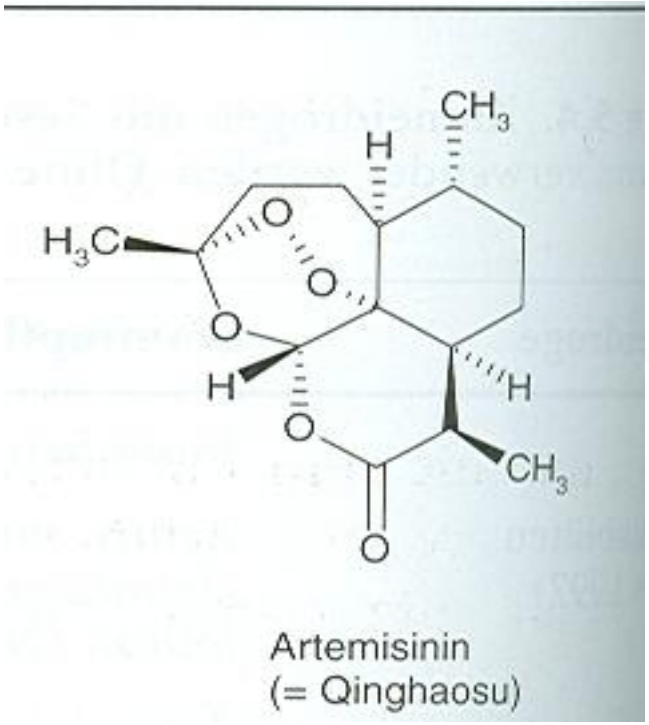


Germacrene D

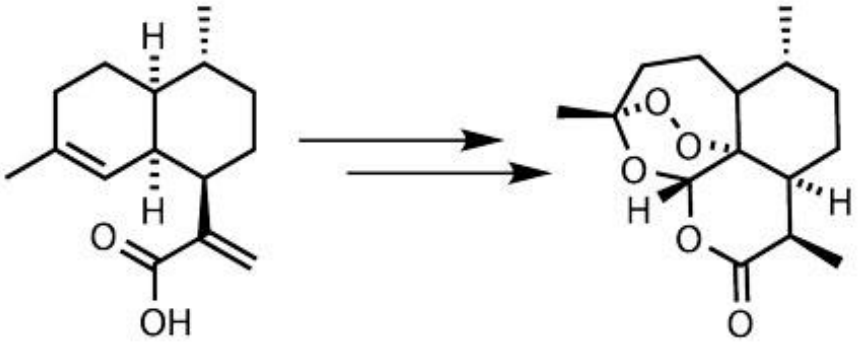
Also found are flavonoids, polyalkines, coumarins, and many sesquiterpenoid lactones with a cadinane skleton arising from the rearrangement of a cadinane nucleus : artemisin, artemisinic acid (arteannuic acid), arteannuin B, and more.

The active principle is artemisinin or qinghaosu. Its concentration in the dried aerial parts varies (0.01-0.08% China; up to 0.86% Vietnam, wild plants). According to the some authors, the concentration could exceed 12% in some Chines clones.

Artemisinin is an endoperoxide, probably formed from artemisinic acid (arteannuic acid) via arteannuin B.

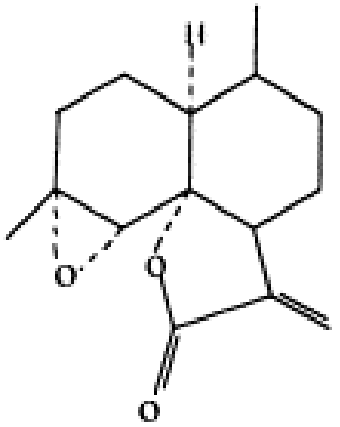


Artemisinin
(= Qinghaosu)



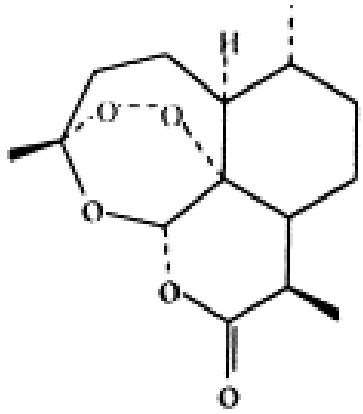
artemisinic acid

artemisinin

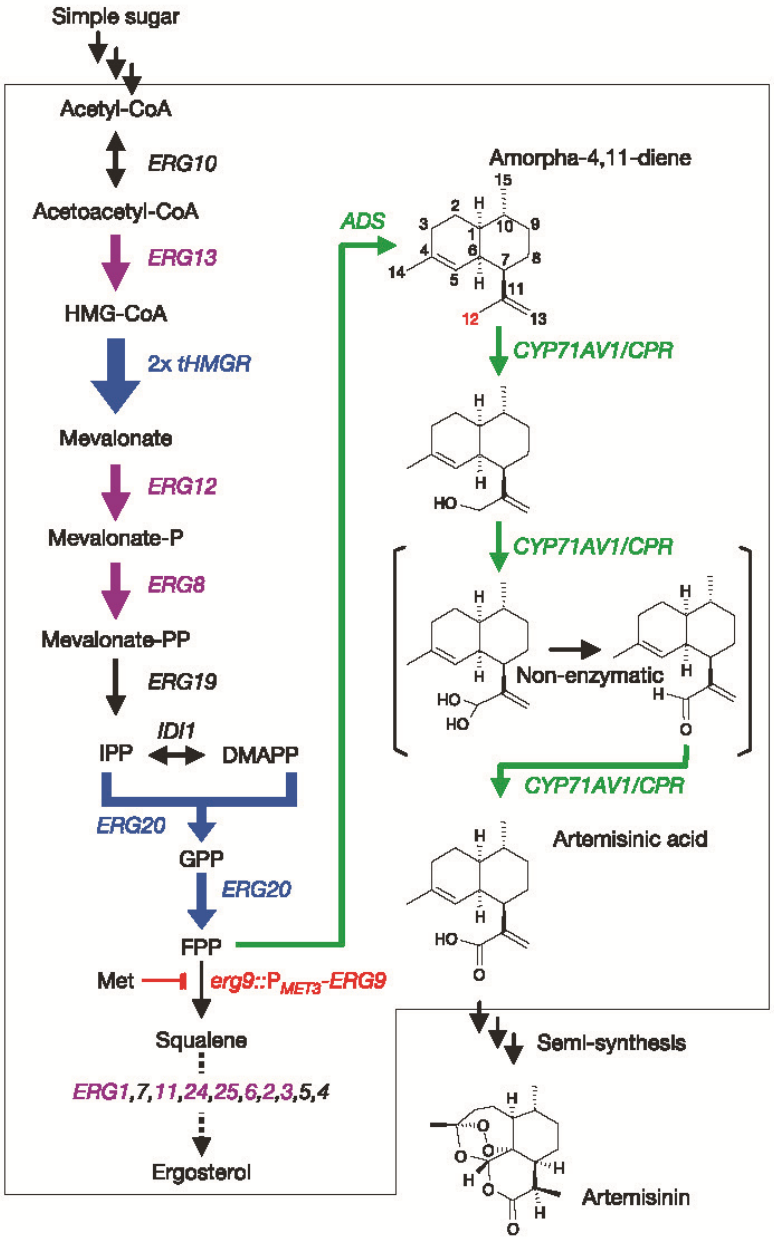


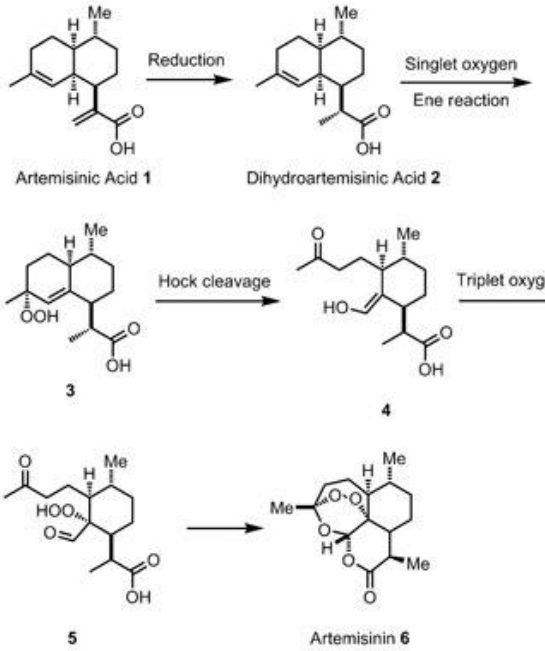
Arteannuin B

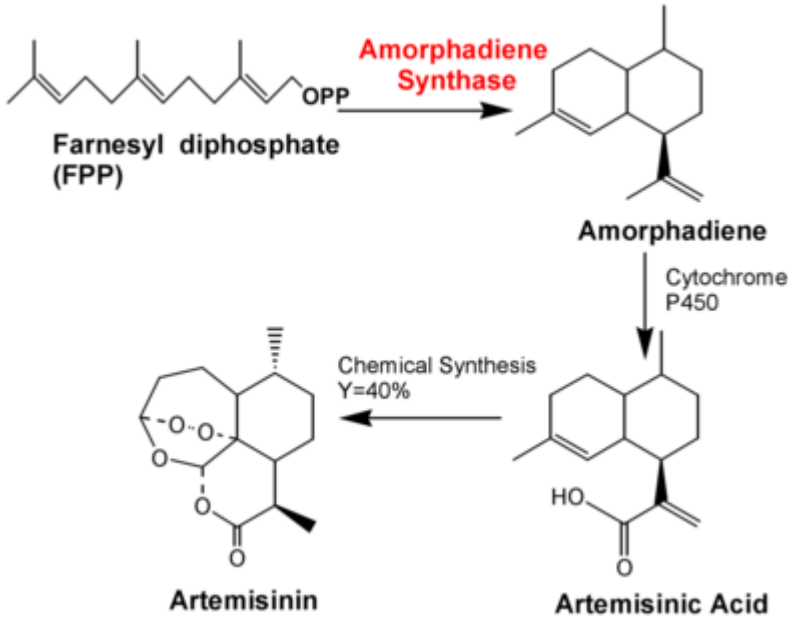
Leaf extract
ATP+Mg+Mn



Artemisinin

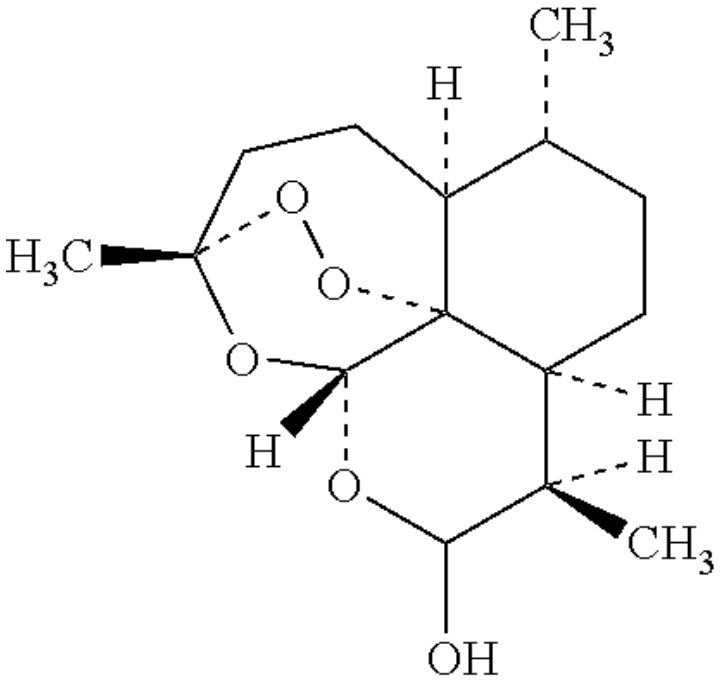

Simple sugar
Acetyl-CoA
ERG10
Acetoacetyl-CoA
ERG13
HMG-CoA
2x tHMGR
Mevalonate
ERG12
Mevalonate-P
ERG8
Mevalonate-PP
ERG19
IDI1
IPP
DMAPP
ERG20
GPP
ERG20
FPP
Met
erg9::P MET3 -ERG9
Squalene
ERG1,7,11,24,25,6,2,3,5,4
Ergosterol
ADS
Amorpha-4,11-diene
CYP71AV1/CPR
CYP71AV1/CPR
Non-enzymatic
CYP71AV1/CPR
Artemisinic acid
Semi-synthesis
Artemisinin


Reduction
Singlet oxygen
Ene reaction
Artemisinic Acid 1
Dihydroartemisinic Acid 2
Hock cleavage
Triplet oxygen
3
4
5
Artemisinin 6


OPP
Amorphadiene Synthase
Farnesyl diphosphate (FPP)
Amorphadiene
Cytochrome P450
Chemical Synthesis Y=40%
Artemisinin
Artemisinic Acid

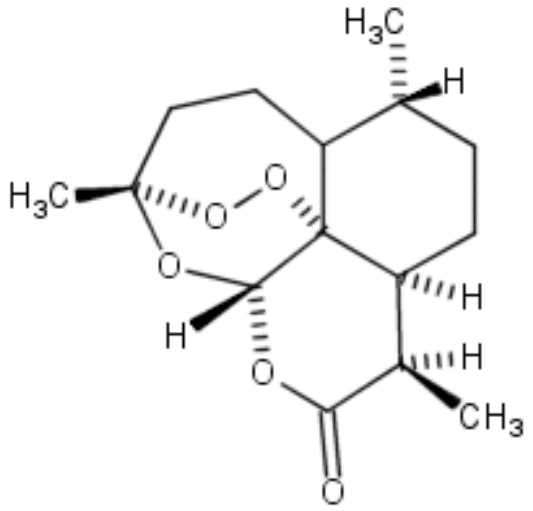
Pharmacological Properties : Artemisinin is an antimalarial agent. It is selectively toxic to various species of *Plasmodium* (*P. falciparum, P. vivax, P. ovale*) *in vitro* and *in vivo*, including at nanomolar concentrations against chloroquine-resistant strains. Artemisinin is effective against blood-stage parasites ; the activity is maximum on the ring-stage parasite and the trophozoites during the growth stage.

Synthetic efforts aimed at improving bioavailibity and efficacy have yielded active derivatives, including α- and β-artemethers, arteether, and sodium artesunate. In the body, all of these derivatives release dihydroartemisinin, which is thought to be active form.

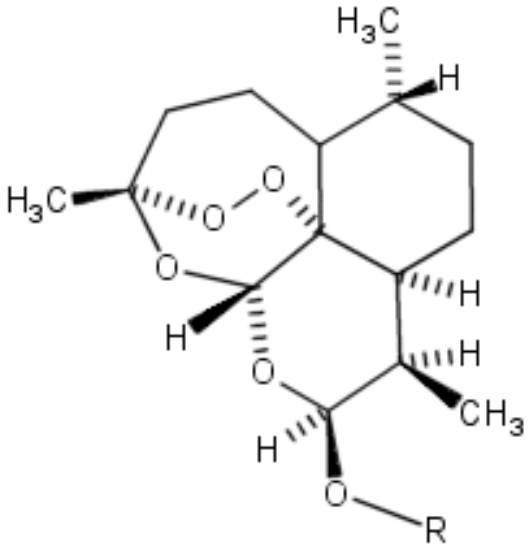


Dihydroartemisinin

Artemisinin and Several of its Semisynthetic Derivatives



Artemisinin



Derivative	R
Artemether	methyl
Arteether	ethyl
Artesunate	-O-CO-CH$_2$CH$_2$-COO$^-$
Artelinic Acid	-O-CH$_2$-(p-phenyl)-COOH

Tests : Sweet wormwood sesquiterpenes can be extracted with petroleum ether and analyzed by TLC (visualization by vanillin and anisaldehyde in the peresence of sulfuric acid or by iodine vapors).

Uses : Sparingly soluble in water and in lipidic phases, artemisinin may be administered in aqueous or oily suspension (IM), or in tablets or suppositories. Since 1993; the WHO has recommended against the use of artemisinin and its derivatives (especially β-artemether and artesunate) for prophylaxis, by prescription, especially IM injection.

SANTONICA FLOWERS
WORMSEED

CINAE FLOS
SEMEN CONTRA

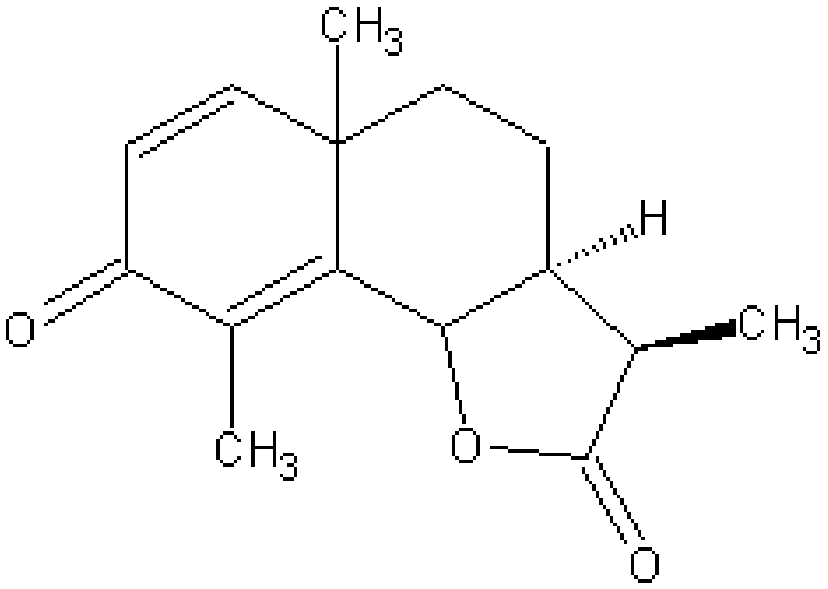
Artemisia cina,

Asteraceae

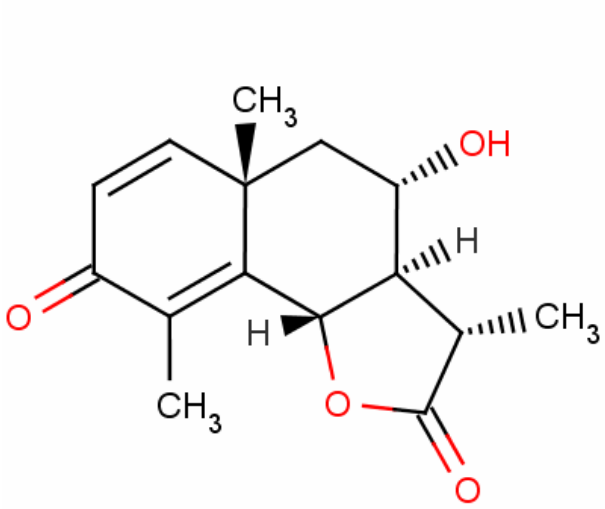
Wormseed consists of the dried unexpanded flower-heads of *Artemisia cina* and other santonin-containing species of *Artemisia* (Asteraceae). *A. cina* is a small plant abundant in Turkestan where a factory for the extraction of santonin exists at Chimkent. Santonin is now being prepared from *Artemisia* species found wild in the Kurran valley in Pakistan and cultivation in this area has been successfully commended.

The chief anthelminthic constituent of the drug is the sesquiterpenoid lactone santonin. Wormseed also contains a little volatile oil and a second crystalline sesquiterpenoid lactone artemisin closely related to santonin. The amount of santonin present varies considerably not only in the different species and hybrids, but also at different seasons of the year; Russian workers have reported diurnal variations.

In use wormseed has been replaced by santonin, which is very efficient in its action on roundworms. It has less effect on thread worms and none whatever on *Taenia.*



α-Santonin



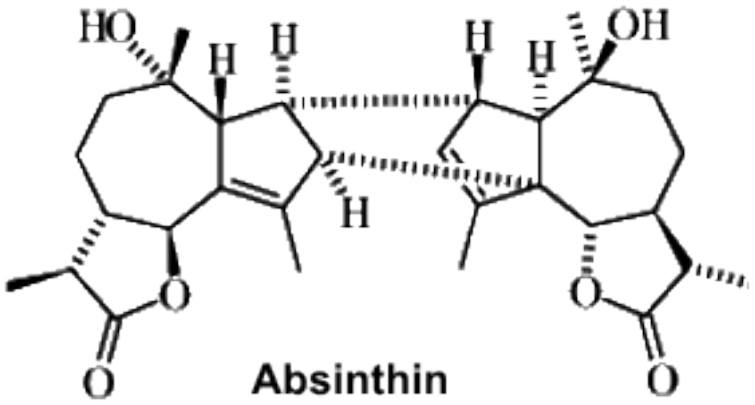
artemisin

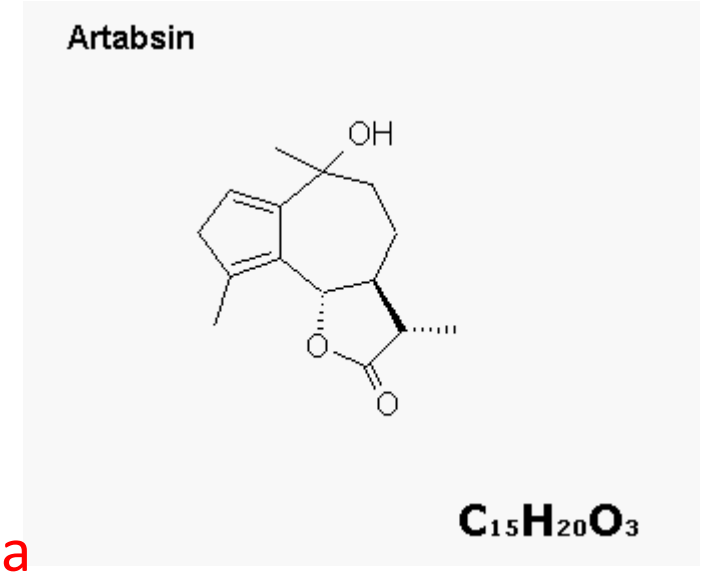
Preparation The British Pharmacopoeia (1885) gives detailed directions for santonin preparation, which consists in boiling the bruised santonica seeds in water with addition of slaked lime, concentrating the solution of calcium santonate, adding hydrochloric acid, and allowing it to stand for 5 days. Wash the precipitated santonin (santonic anhydride) with water and ammonia water, which removes resin, and recrystallize from alcohol after treating the solution with animal charcoal. Another method consists in boiling out a mixture of santonica seeds and slaked lime with alcohol of 60 per cent (by volume), and decomposing the calcium santonate with carbonic acid.

REMEMBER **WORMWOOD** ***Artemisia absinthium***

Absinthii herba

The plant also contains polyalkynes, flavonoids, and sesquiterpenoid lactones : absinthin (dimer), artabsin, matricin, and closely related derivatives.



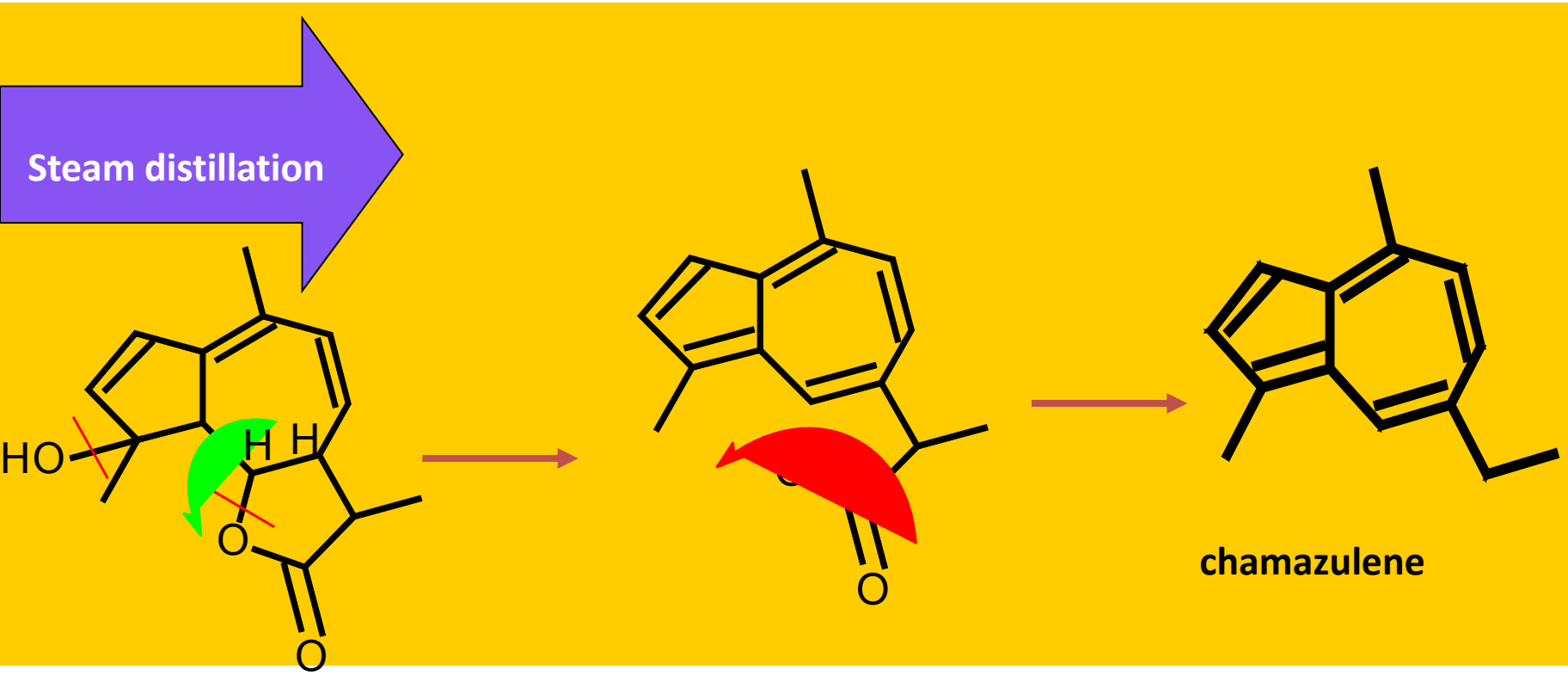


Wormwood (*Artemisia absynthium*), a **bitter drug**, because of its sesquiterpene lactones (absinthin, artabsin), is used to stimulate the appetite and for dyspepsia.

REMEMBER MATRICARIA

MATRICARIAE FLOS
MATRICARIAE AETHEROLEUM

***Matricaria chamomilla* = *Chamomilla recutita* = *Matricaria recutita* (mayıs papatyası)**


Steam distillation
HO
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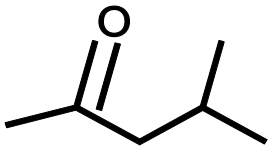
chamazulene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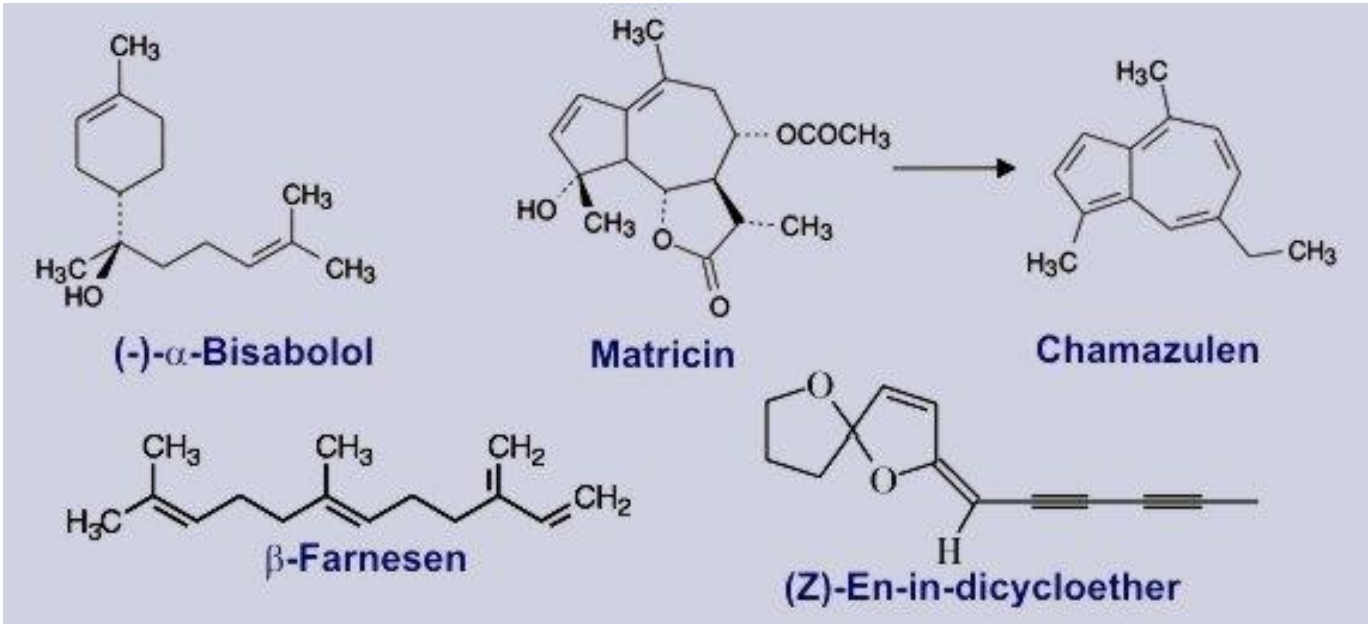
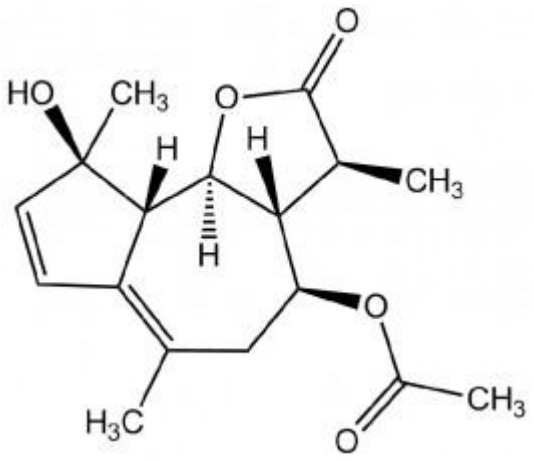


Chamazulene has strong anti-inflammatory (antiphlogistic) activity.



Matricin(e)

ARNICA

Arnica montana

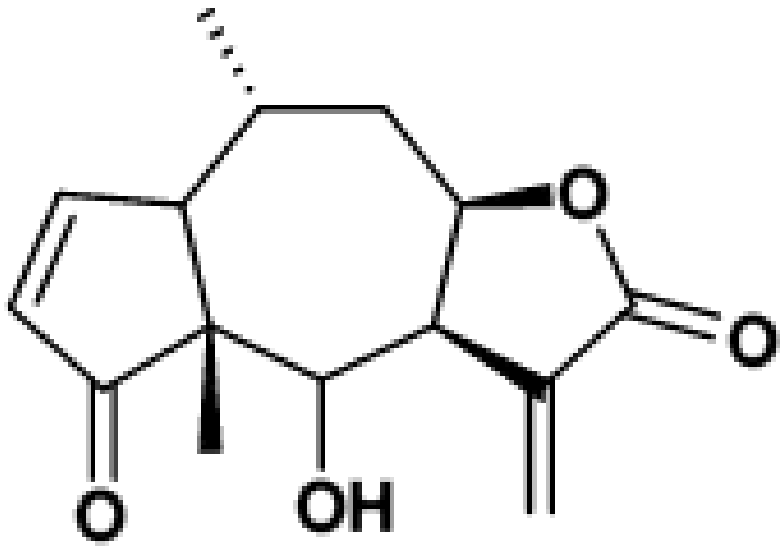
ARNICAE FLOS

Asteraceae

The drug consists of the dried capitulums. It is used externally for its "vulnerary" properties. Arnica is a species indigenous to mountain areas of Europe. It is not found in Turkey and Cyprus.

Chemical Composition : The color of arnica drug is due to carotinoids. Its odor is due to 5 ml/kg essential oil of pasty consistency because of a high concentration of fatty acids ; it contains, among others, terpenoid hydrocarbons, and thymol derivatives. The bitterness is due to sesquiterpenoid lactones (0.2-0.5% helenalin, dihydrohelenalin, and their esters.

The drug also contains triterpenoids, phytosterols, fatty acids, polysaccharides, phenolic acids, coumarins, polyalkines, and 0.2-0.3% flavonoids



Helenalin

Pharmacological Properties- Toxicity:

Anti-inflammatory, analgesic, and antiecchymotic properties (ecchymosis :The passage of blood from ruptured blood vessels into subcutaneous tissue, marked by a purple discoloration of the skin) are traditionally attributed to arnica. We cannot exclude that the sesquiterpenoid lactones are in part responsible for this activity : they are known to inhibit the migration of polymorphonuclear leucosytes and the rupture of lyosomal membranes. An inhibitory activity on platelet aggregation has also been reported.

All of the galenical forms of arnica cause allergic reactions, and in sensitive subjects, cross-reactions with Asteraceae and other lactone-containing species are frequently observed. The systemic toxicity of lactones are also known : vomiting, respiratory and cardiac difficulties, bloody sputum, cerebral problems, and even deaths following the administration of arnica preparations for the purpose of abortion.

Uses : Arnica and its preparations are reserved for external use, because when they are taken orally, they can cause headaches, abdominal pains, as well as vasomotor problems and breathing difficulties. Arnica and its preparations are also traditionally used for sunburns, superficial and limited burns, and diaper rashes. Arnica preparations should not be applied on open wounds or near the eyes or mouth.

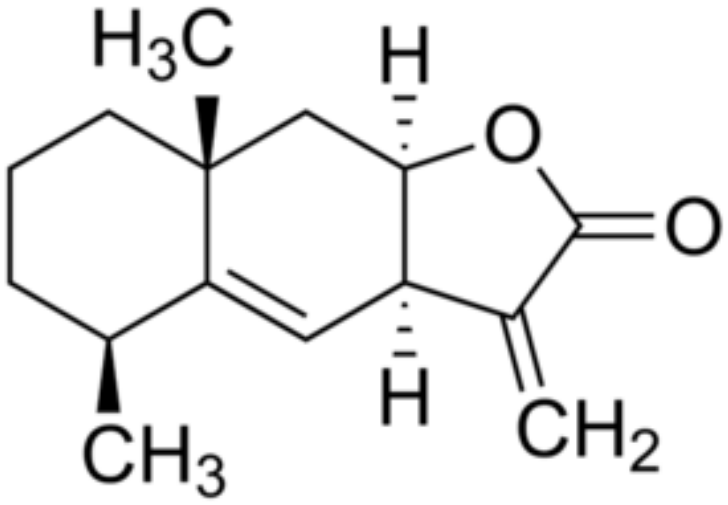
In homeopathy, arnica passes as an agent that promotes the resorption of extravasated blood and prevents hemorrhages.

ELFDOCK (andız otu) INULAE RADIX

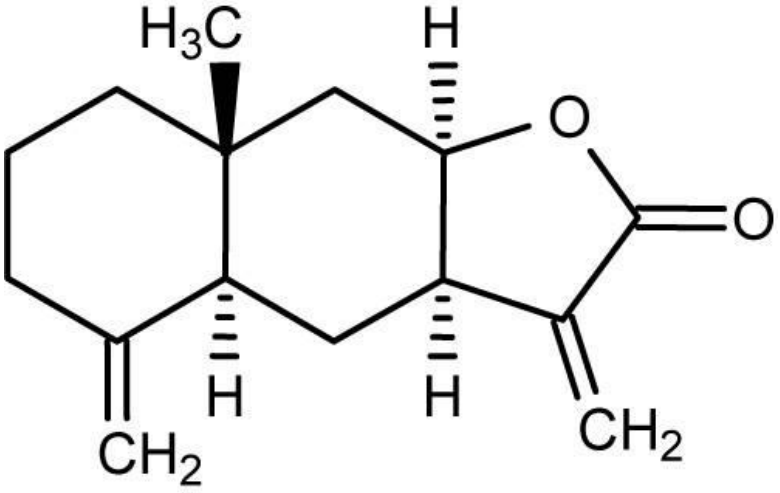
Inula helenium **Asteraceae**

The dried root and rhizome of the plant, which grows wildly in Europe and also in Turkey, are said to be diuretics, and anthelminthics.

The drug contains eudesmanolides (alantolactone, isoalantolactone), a germacranolide, triterpenes, sterols and depending on the season 20-45% inulin.



alantolactone



isoalantolactone

Alantolactone and isoalantolactone are cytotoxic and display antibacterial and antifungal properties. These lactones are also reputed to be anthelminthic and hypotensive.

The drug is traditionally used orally 1. to enhance urinary and digestive elimination functions and 2. to treat the symptoms of cough. The German Comission E monograph lists uses for respiratory, gastrointestinal, renal, and urinary disorders. After a reminder that lactones can cause allergic reactions (in high doses : vomiting, diarrhea).

DANDELION

TARAXACI RADIX CUM HERBA

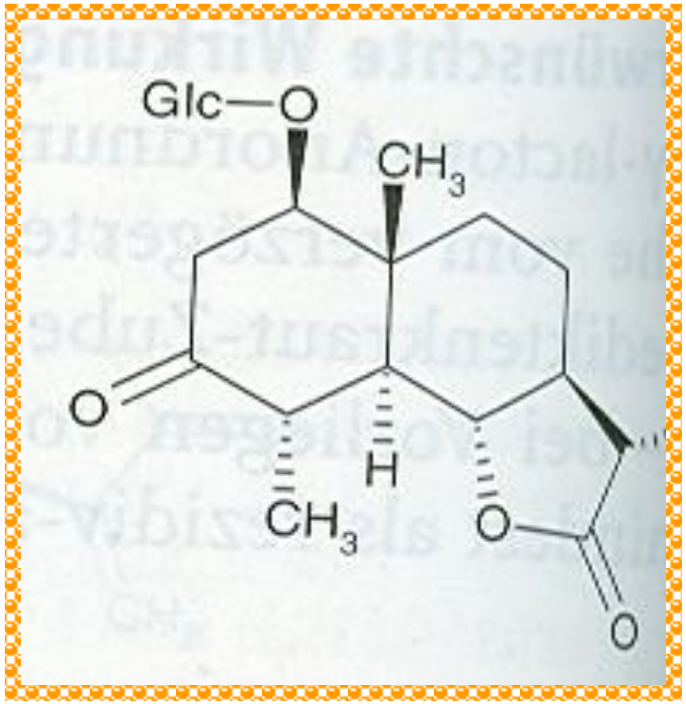
Taraxacum officinale

Karahindiba

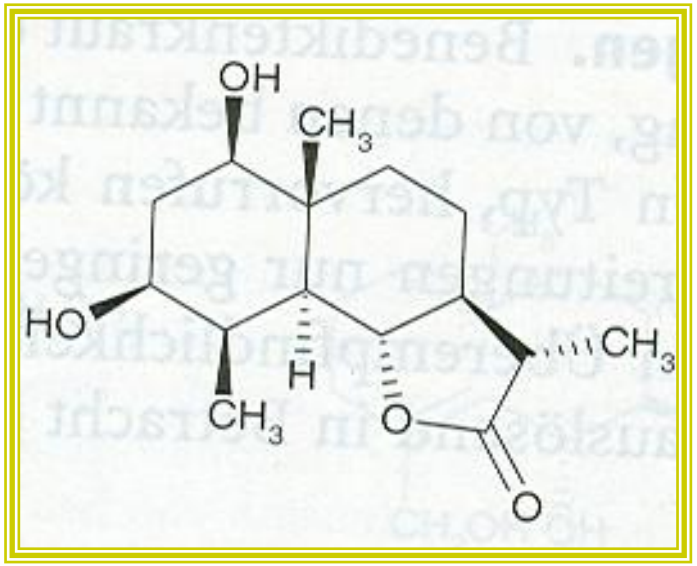
Taraxacum officinale, the **common dandelion** (often simply called **"dandelion"**), is a flowering herbaceous perennial plant of the family Asteraceae (Compositae). It can be found growing in temperate regions of the world, in lawns, on roadsides, on disturbed banks and shores of water ways, and other areas with moist soils. *T. officinale* is considered a weed, especially in lawns and along roadsides, but it is sometimes used as a medical herb and in food preparation.

Chemical Constituents : Active principles are sesquiterpenoid lactones (eudesmanolides), which have very bitter taste.

Sesquiterpenoid lactones of *Taraxacum officinale*



Taraxacolid-β-D-glucoside



Tetrahydroridentin B

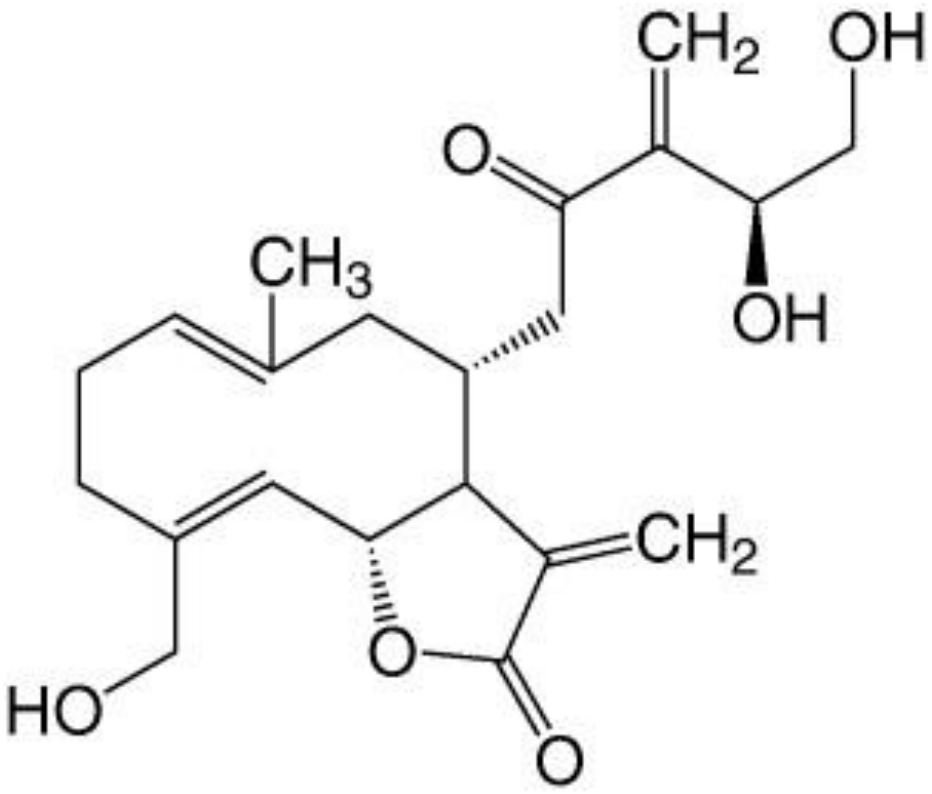
Historically, dandelion **(Taraxaci radix cum herba**) was prized for a variety of medicinal properties, and it contains a wide number of pharmacologically active compounds. Dandelion is used as a herbal remedy in Europe, North America and China.Empiric traditional application in humans of dandelion, in particular to treat digestive disorders, is supported by pharmacological investigations.

It has been used in herbal medicine to treat infections, bile and liver problems, and as a diuretic. A hepatoprotective effect in mice of chemicals extracted from dandelion root has been reported. Dandelion is used in herbal medicine as a mild laxative, for increasing appetite, and for improving digestion. The milky latex has been used as a mosquito repellent and as a folk remedy to treat warts. With very low or even no toxicity at all, taraxacum can be used as a drink like herbal tea on a daily basis.

Cnicus benedictus **Benedicti herba**

Blessed thistle **şevketibostan**

Blessed thistle (Holy thistle) consists of the dried aerial parts of *Cnicus benedictus* (Fam. Asteraceae), an annual, thistle-like herb with sharp thorns on the leaves and yellow flower-heads. It grows spontaneously in the Mediterranean region. The bitter compound is cnicin (a sesquiterpen lacton with germacranolide skleton) sesquiterpen lacton, which is present to the extent of about 0.2%. The bitterness value is approximately 1,500. Cnicin stimulates the secretion of saliva and gastric juice. Benedicti herba is supported by German Commission E for dyspeptic complaints and loss of appetite. The daily dosage is 4-6 g crude drug.



cnicin

FEVERFEW **TANACETI PARTHENII FOLIUM**

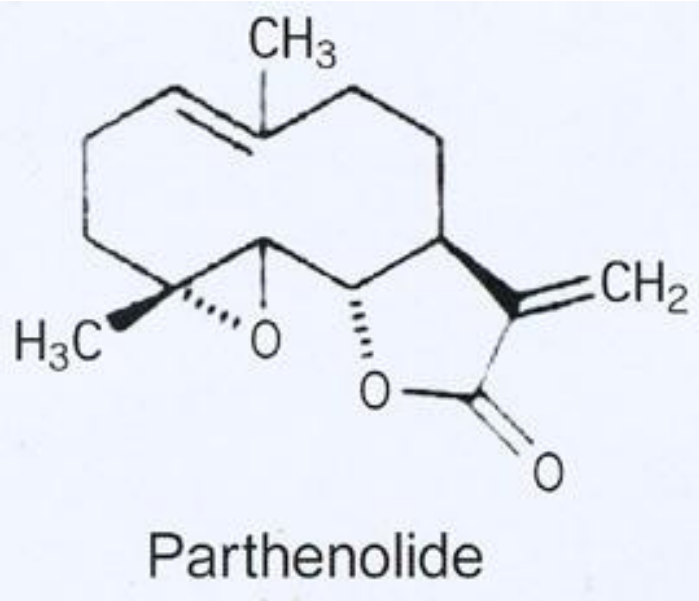
(gümüş düğme)

Tanacetum parthenium **Asteraceae**

Feverfew is a tall (70-80 cm) perennial herb, originally indigenous to Asia minor.

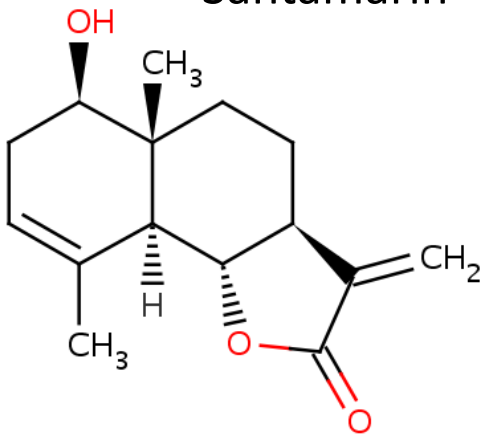
Chemical Composition : The strong odor of feverfew is due to an essential oil (3-8 ml/kg in the leaves) containing camphor and chrysanthemyl acetate as major constituents. Flavonoids, water soluble flavone glucuronates, and lipophilic methylated flavonoids are also found. A sesquiterpenoid lactone, a germacranolide, parthenolide, is thought to be the active principle.

Other sesquiterpenoid lactones in the drug are : santamarin (eudesmanolide), costunolide (germacranolide), guaianolides (canin, artecanin).

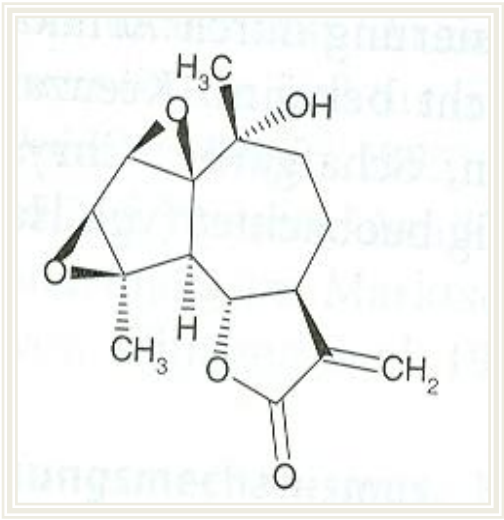


Parthenolide

Santamarin



Artecanin



Pharmacological Properties : Feverfew extracts inhibit platelet aggregation and the ADP- or adrenalin-induced release of seretonin, which would explain the activity against migraines traditionally attributed to the drug. It has been shown that parthenolide has a -weak- affinity for 5H2A receptors. There is also inhibition of the degranulation of polymorphonuclear leukocytes, of the release of enzymes involved in the inflammatory process, of phospholipase A2 and of prostoglandin synthesis, as well as a protective effect on vascular endothelial cells.

The initial clinical trials tended to show that feverfew leaf powder had an interesting potential to prevent the onset acute attacts of migraine headache.

Feverfew causes no serious side effects in regular uses (ulcerations of the mouth, abdominal pain). It is rare for this Asteraceae to cause allergic dermatitis.

SESQUITERPENOID LACTONES AND ALLERGY

Asteraceae containing sesquiterpenoid lactones are frequently responsible for dermatitis, of allergic origin. This compounds act as haptens and bind to proteins to form allergens, which in turn induce the sensitilization of lymphocytes. Of course, this is due to the reactivity of the α-methylene-γ-lactone.

Produce species : artichoke, cardoon (cynaropicrin), endive (lactocopicrin), daisies, asters, cosmos, sunflowers,, and certain medicinal species, matricaria, yarrow, feverfew, arnica, or inula have caused various cases of occupational papulos dermatitis and conjunctivitis in farmers, horticulthurists, and florists.

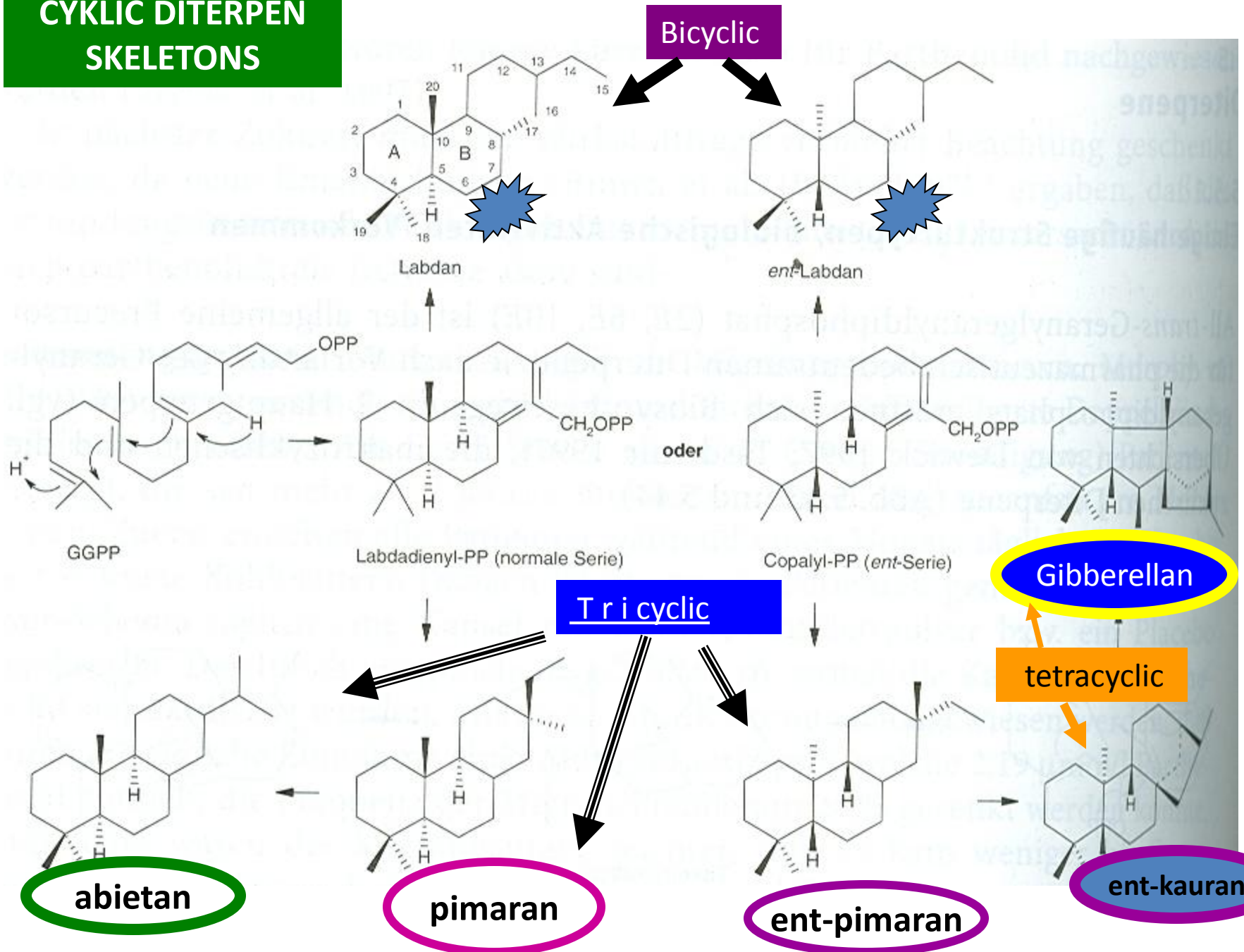
Also responsible for allergic dermatitis are perfumery products based on Asteraceae (arnica, camomile).

Diterpenes

Diterpenes constitue a vast group of C_{20} compounds arising from the metabolism of 2*E*,6*E*,10*E*-geranylgeranyl pyrophosphate. Found in some insects and in various animal organisms, they are especially widespread in plants. Some are ubiquitous (gibberellins), whereas others have a more limited distribution. They are partially abundant in the Lamiales and Asterales (over 1200 compounds have been reported in the Asteraceae),and they are more scattered in the Gentianales, Geraniales, and Fabales.

CHIEF STRUCTURAL TYPES

CYKLIC DITERPEN SKELETONS



Or

We can classify diterpenes as :

Diterpenes of the resins

Diterpenoid alkaloids

Toxic diterpenes

Gibberellins

INTEREST IN DITERPENES

Diterpenes have limited therapeutic application, except for the tricyclic terpenes from yews (taxol). Several diterpene-containing drugs are ingredients of therapeutic products or, as simple galenicals, ingredients of allopathic proprietary drugs.
Some diterpenes, do have some therapeutic potential, for example the following : forskolin from *Plectranthus barbatus* with its antihypertansive properties, prostatin from *Homalanthus nutans* with its antiretroviral properties.

Diterpenoid quinones from *Salvia miltiorrhiza*, of interest of various heart conditions.

The co-carcinogenic activity of the diterpenoid esters of the Euphorbiaceae and Thymeleaceae, and paradoxically, the cytotoxic activity of some of them suggest interesting research directions.

In addition to the therapeutic potential :

The antioxidant properties of the phenolic diterpenes of some Lamiaceae

The sweetening properties of stevioside from *Stevia rebaudiana*

The intense hallucinogenic properties of salvinorin, an active diterpene from the leaves of *Salvia divinorum.*

The physiological role of diterpenes, like that of many other secondary metabolites, is not well understood. Eccept for the gibberellins (which are known to be growth hormones).

DITERPENE-CONTAINING DRUGS USED IN THERAPEUTICS

YEW (porsuk ağacı) **TAXI CORTEX**

Taxus brevifolia, T. baccata **Taxaceae**

Taxus brevifolia

Taxus baccata

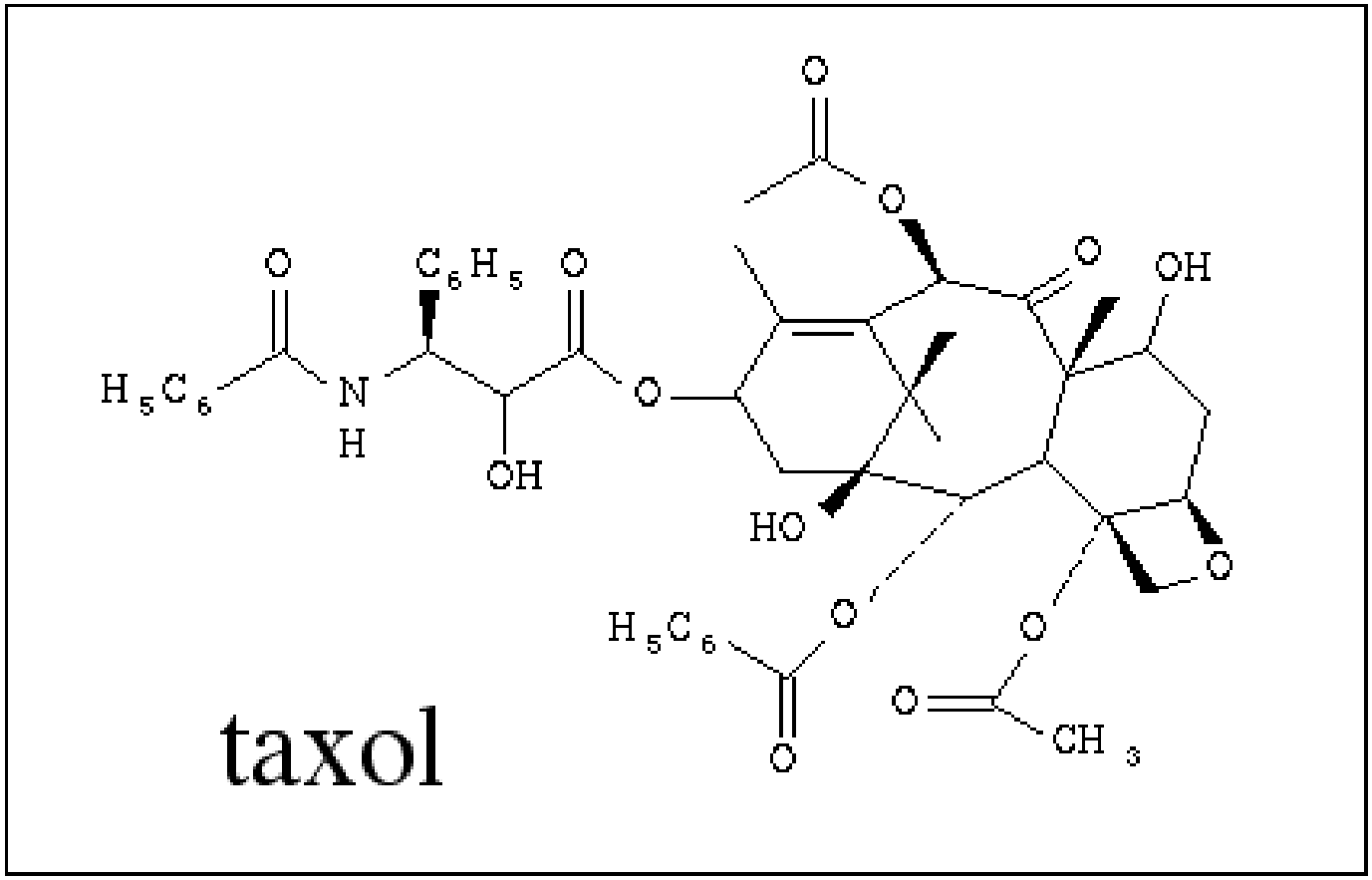
Yews have been known since remote antiquity for their toxicity to humans and domestical animals, and have been making medical headlines for a few years; directly or indirectly, they provide two diterpenoid anticancer compounds with a novel mechanism of action, namely paclitaxel and docetaxel

The eight species in this genus, which is only one in the Taxaceae family, are all found in the northern hemisphere.

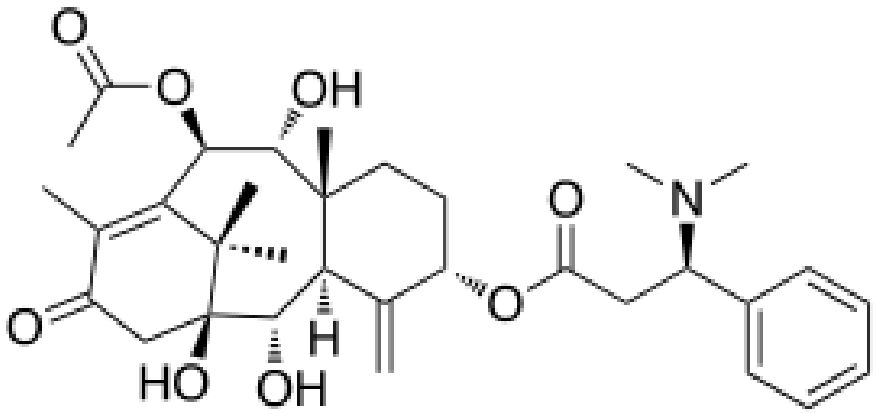
The European yew is *Taxus baccata*, the other important one is *T. breviifolia* from North America. All the species contain similar compounds.

Chemical Composition : Different categories of metabolites are represented in the leaves and stems : saccharides, polysaccharides, fatty acids, sterols, bisflavonoids, proanthocyanidins, and cyanogenetic glycosides.

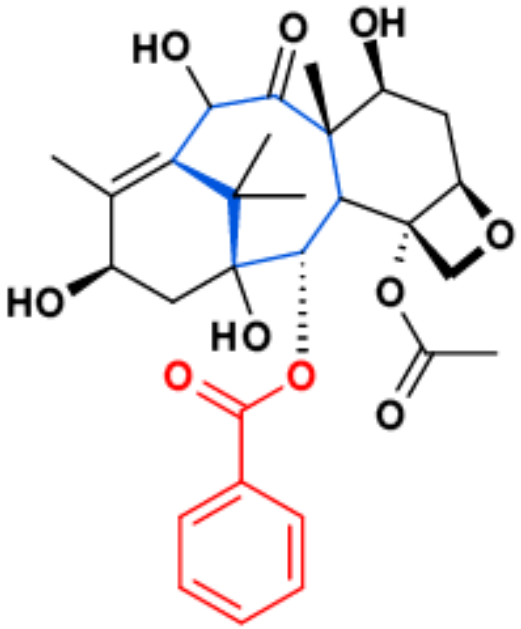
The most interesting constituents are tricyclic diterpenes with a taxane nucleus, including taxusines, taxagifin, baccatin III and derivatives, taxin (a comples mixture of taxine A, B, and their derivatives), taxoltaxicines and derivatives. Some are strictly diterpenoids (baccatins), whereas others have an amide function (taxol), or are esters of 3-dimethylamino-3-phenylpropionic acid (taxines), so they are sometimes considered to be pseudoalkaloids. Biogenetically, taxoids arise from the cyclase-catalysed cyclization of geranylgeranyl diphosphate to bicyclic verticillene, then to taxa-4(5),11(12)-diene. The latter becomes functionalized in various ways.



Taxol = Paclitaxel



Taxine B

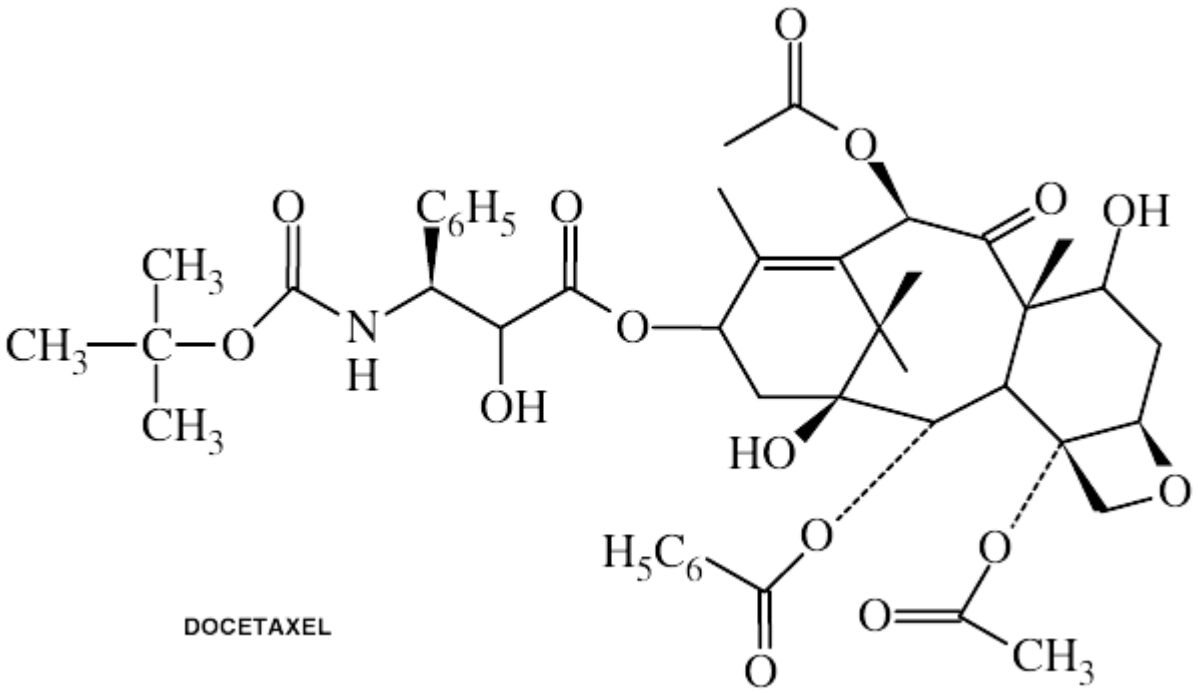


10-deacetyl Baccatin III

Taxol Sources : Taxol (paclitaxel) was initially isolated from the bark of the trunk of Pacific yew (*Taxus brevifolia*) but was found only in traces (0.01%): at best a hundred year old tree would produce about 3 kg of bark, in other words 300 mg of taxol. Even with optimized extraction methods, about 7 t of dried bark would be required to yield 1 kg of taxol. Thus the compound cannot be produced on an industrial scale without eventually destroying the species.

Systematically screening the *Taxus* genus resulted in the selection and cultivation of cultivars whose leaves contitute an exploitable source of taxol : in the case of *T. x media*, the taxane concentration of the leaves exceeds 0.1% and the taxol concentration can reach 0.06%, particularly in the "*hicksii*" cultivar. The yield of taxol is closely dependent on the drying process (40-50^{0}C). It is also quite feasible to prepare taxol by semisynthesis from structural analogs such as 10-deacetylbaccatin III. This is a diterpene found in substantial quantities (0.02-0.1%) İn an easily sustainable starting material : the leaves of the European yew *T. baccata* or of various cultivars of other yews (*T. wallichiana, T. uspidata, T. x media*).

Synthetic work has also led from the same 10-deacetylbaccatin III to esters at C-13, in which N-benzoyl-3-phenylisomerine is replaced by a structual analog. One of these analogs, N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol (=docetaxel).



DOCETAXEL

Compound : Paclitaxel (Taxol)

Commercial Product : Taxol

Compound : Docetaxel

Commercial Product : Taxotere

Pharmacological Properties and Uses of Paclitaxel and Docetaxel

Paclitaxel : Paclitaxel, like some other natural substances, is a mitotic spindle poison, but its mode of action is very spesific : it promotes the assembly of tubulin dimers into microtubules, which it stabilizes by inhibiting their depolimerization.

The first indication of paclitaxel was the treatment of advanced ovarium tumors. Other indications 1. treatment of metastatic breast cancer 2. advanced ovarian tumors in combination with cis-platinum.

Posology : 135-175 mg/m^2, depending on the indication; by infusion every 3 weeks, after appropriate pre-medication. The toxicity is non-trivial, and includes nutropenia, peripheral neuropathy, cardiovascular problems,nausea, vomiting, and hypersensitivity to the solvent, polyethoxylated castor oil.

Docetaxel : The indication of docetaxel is the single-drug therapy of breast cancer, locally advanced, or metastatic and resistant, or in relapse, after chemotherapy that has a induced an anthracycline (posology : 100 mg /m^2 by infusion every 3 weeks after appropriate pre-medication). Like its natural homolog, docetaxel is highly toxic: adverse effects include severe neutropenia, hypersensitivity reactions, cutaneous reaction and water retention

Yew : a toxic plant

The toxicity of the yew has been exploited for war (arrow poison), to commit murders. This toxicity is also well known to veterinarans and farmers.

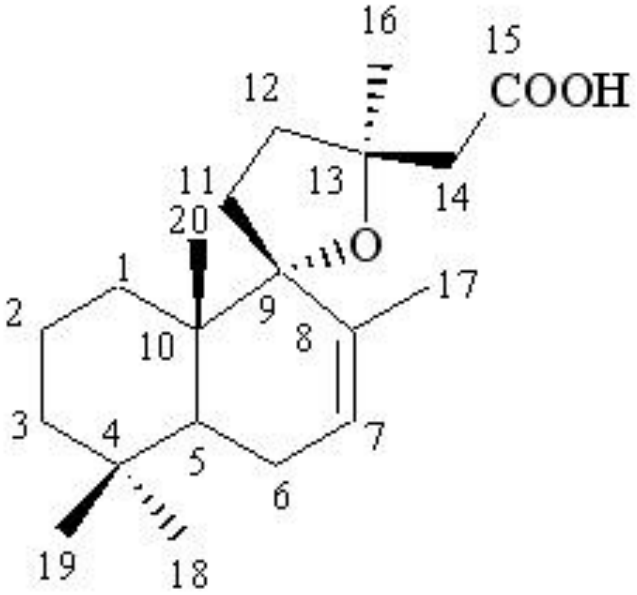
The intoxication by the leaf (or the seed) begins with digestive symptoms (nausea, vomiting, abdominal pains, diarrhea) and neurological symptoms (sleepiness, lethargy), and is characterized by hypotension and bradycardia. There is no spesifical treatment.

GUM PLANTS **GRINDELIAE FLOS**

Grindelia robusta, G. squarrosa **Asteraceae**

The official gum plants are Californian species. Gum plants resin contains diterpenoid acids. Grindelic acid and about twenty other compounds with a labdane skleton have been characterized in the various species, which also produce sesquiterpenes. The drug also contains phenolic acids, flavonoids, and saponins.

The drug has a reputation for being an antitussive and a spasmolitic, and is traditionally used to treat cough.



Grindelic acid

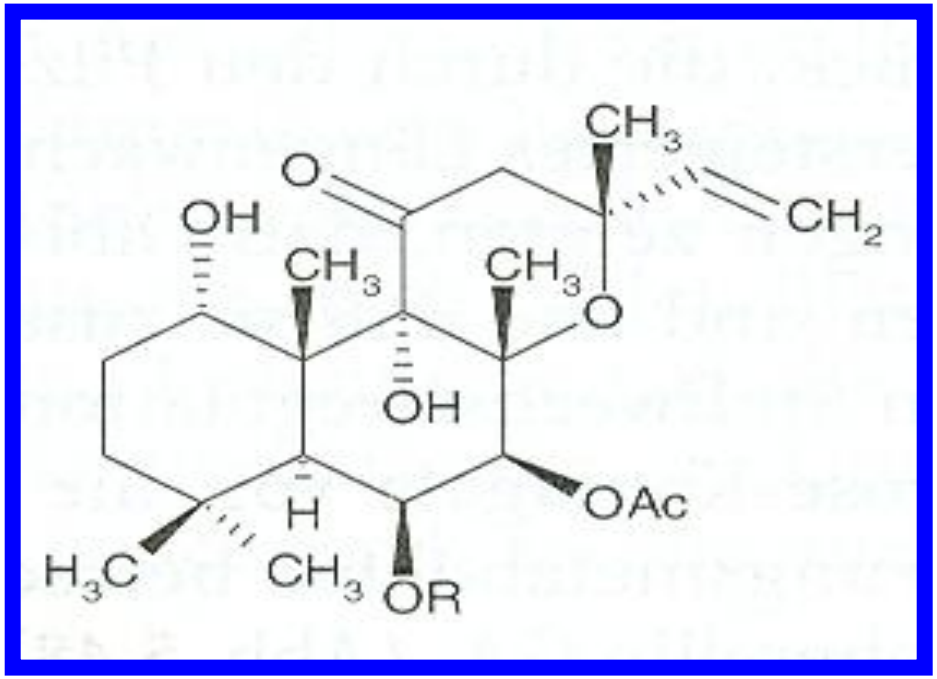
DITERPENE-CONTAINING DRUGS OF POTENTIAL INTEREST

COLEUS **COLEI RADIX**

Plectranthus barbatus = Coleus forskohlii

Lamiaceae

This *Plectranthus* species grows wild in the warm and subtropical temperate areas of India, Burma and Thailand. The roots contain diterpenes whose basic skeleton is 11-oxo-manoyl oxide (8,13-epoxy-labd-14-en-11-one). The chief constituent is forskolin, initially isolated under the name coleonol. This compound has a positive inotropic action on the myocardium and by decreasing peripheral vascular resistance, it exerts an antihypertensive activity. Furthermore, forskolin possesses bronchodilating properties which could be of interest to treat asthma. The drug is also used in Ayurveda.



Forskolin

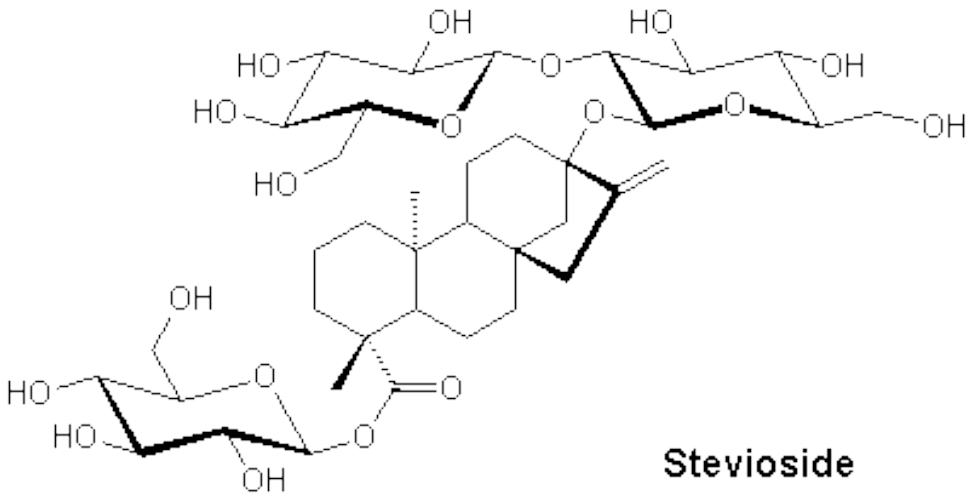
STEVIA **STEVIAE FOLIUM**

Stevia rebaudiana **Asteraceae**

The plant is indigenous to the high altitude regions of Brasil and Paraguay; it is cultivated in Brazil, Israel,Japan, China (Turkey-Alanya).

The leaves contain a series of glycosides formed from an *ent*-kaurenoid alcohol : steviol (consider stevioside, rebaudiosides, and dulcoside). The glycosides can represent up to 10% of the weight of the leaf. It can be extracted with water, re-extracted with butanol, and it is generally purified by filtration (charcoal) and crystallization.

Stevioside as a sweetener is approximately 200 times more potent than sucrose; it seems devoid of toxicity. A weak antihormonal activity had been reported only. Currently used in Japan, stevioside is also marketed in Brazil, Paraguay and other countries including Turkey.

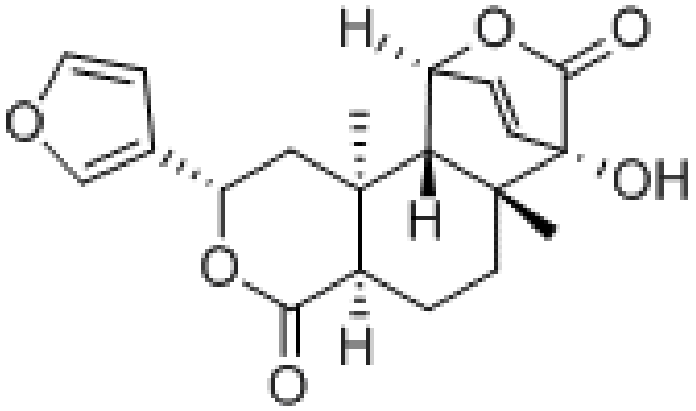


Stevioside

Calumba root **Güvercin kökü** **Calumbae radix = Colombo radix**

Jateorhiza palmata **Menispermaceae**

The roots of this climbing herbaceous plant from the eastern coast of Africa contain 2-3% total alkaloids, chiefly protoberberins (palmatine, jatrorrhizine, columbamine), as well as furanoditerpenoid lactones which impart to it a very bitter taste (columbin, palmarin). The drug was formerly used as a bitter tonic.



columbin

DAN SHEN (CHINA), TAN-JIN (JAPAN)
SALVIAE MILTIORRHIZAE RADIX

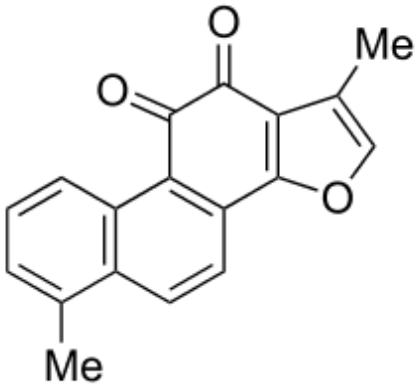
Salvia miltiorrhiza **Lamiaceae**

The roots of this plant, have been used as a traditional remedy in eastern medicine.They have a reputation for being a sedative, bactericide, cardiac stimulant (stasis, edema), and are used, among other things, to treat certain cardiac disorders.

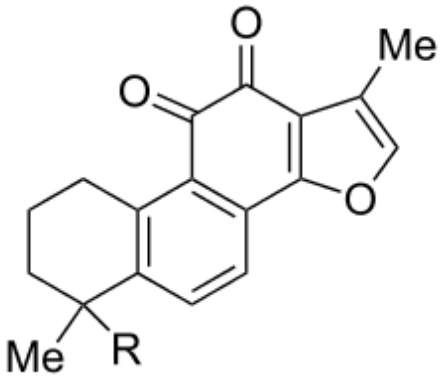
Their composition is well known, or at least of the pigments, which impart their reddish-brown color to the subterranean parts. These pigments are diterpenoid lactones with an abietane skleton.

Orthoquinones (tanshinones), and paraquinones (isotanshinones) occur alongside lactone derivatives. Phenolics have also been isolated.

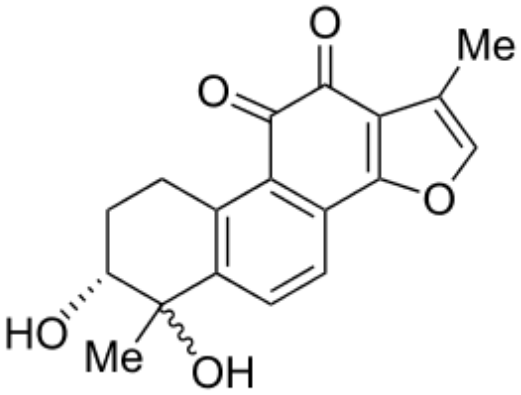
Dan-shen quinones are antioxidants, and many of them are bacteriostatics and active against various dermathophytes. Tanshinones prevent the complications of myocardial ischemia.



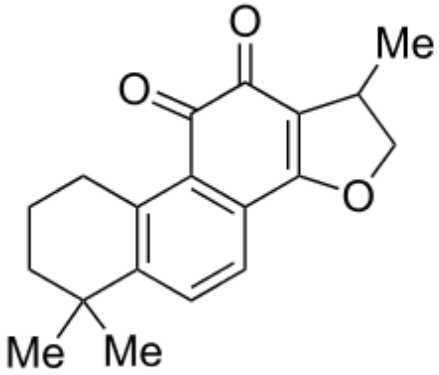
Tanshinone-I



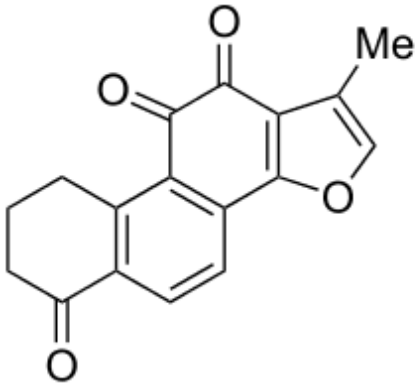
Tanshinone-IIA (R = Me)
Tanshinone-IIB (R = CH_2OH)



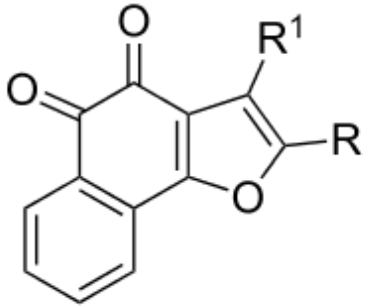
Tanshindiol-B (*cis* diol)
Tanshindiol-C (*trans* diol)



Cryptotanshinone



Nortanshinone



R = H, R^1 = Me
R = H, R^1 = Me

DITERPENE-CONTAINING TOXIC PLANTS : ESTERS OF PHORBOL AND OF INGENOL AND RELATED COMPOUNDS

Several plant species owe their toxicity to diterpenoid esters of complex structure, of the tigliane, ingenane, or daphnane type. The distribution of these compounds is restricted to two families, the Euphorbiaceae and Thymelaeceae.

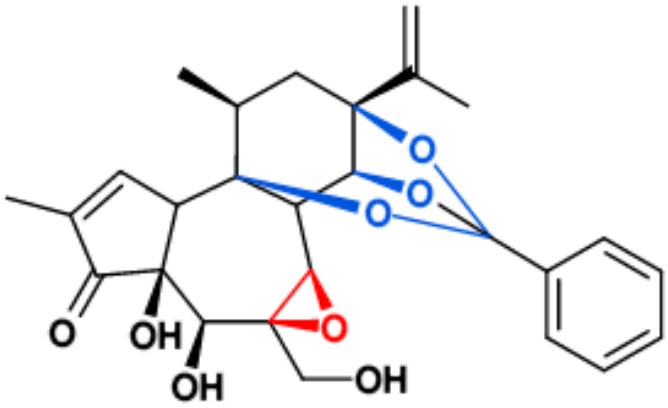
The concentrations are generally low and the composition is always very complex. Almost all of these compounds are toxic : they are drastic cathartics, and induce, by contact with the skin or with the mucosal membranes, an intense inflammatory reaction; they are also co-carcinogens

THYMELEAECEAE

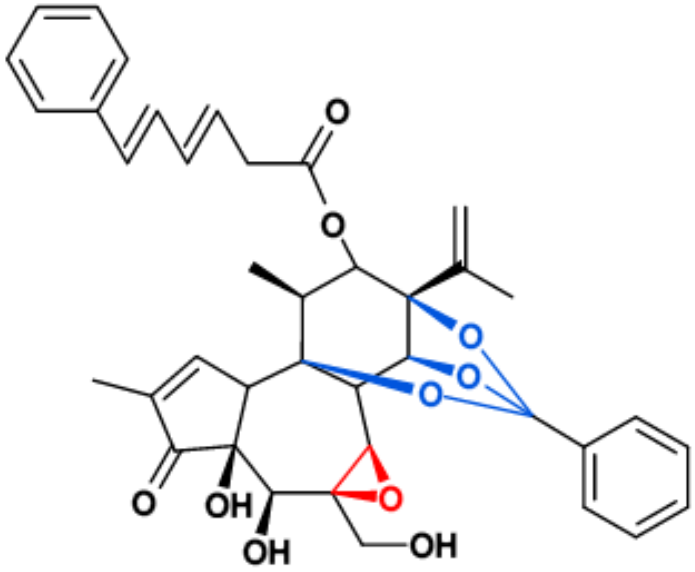
This small heterogeneous family of about fifty genera is represented in western Europe by a dozen species from two genera : *Thymelaea* and *Daphne*. Especially *Daphne mezereum* is wide distributed in Europe and Turkey.

The toxic substances are daphnetoxin (bark) and mezerein (seeds). The barks, upon contact with the skin or mucosal membranes cause substantial irritation. The ingestion of the fruits precipitetes an ulceration of the mucosas of the digestive tract. The symptoms include violent digestive spasms, hypersalivation, and vomiting, swallowing difficulties, diarrheas, headaches,nausea, and neurological symptoms (convultions).

The treatment is essentially symptomatic. The toxin is removed, the inflammation of the mucosas is treated with astringents and the neurological symptoms are treated with barbiturates.



Daphnetoxin

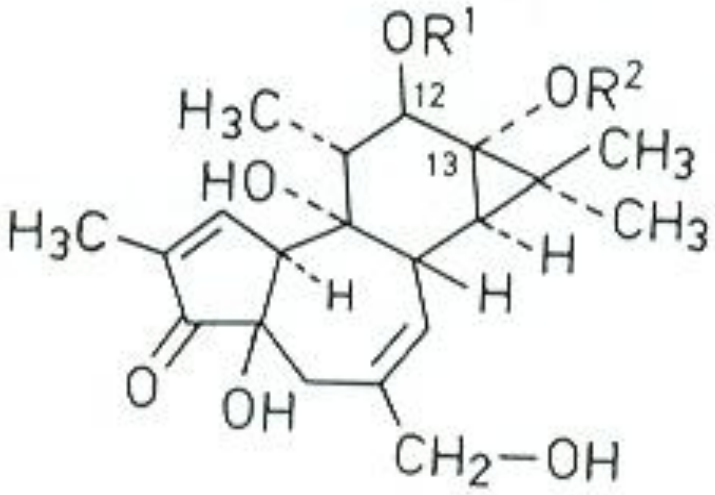


Mezerein

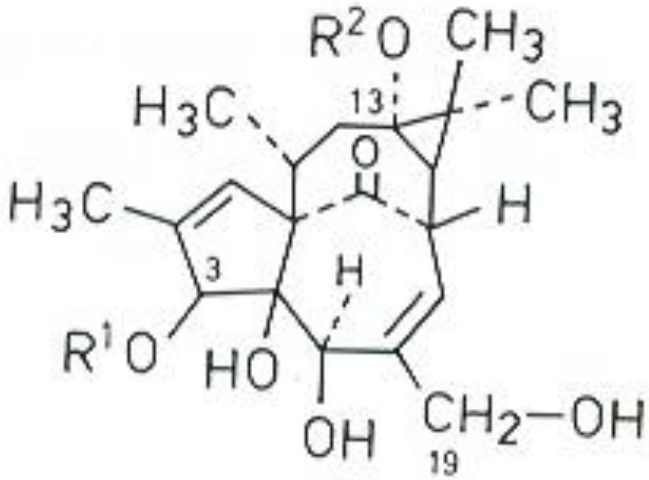
EUPHORBIACEAE

Toxic diterpenes are found in at least 14 of the 300 genera in this family, including *Euphorbia* (sütleğen), *Croton, Jatropha,* and *Sapium.*

The concentrations of the toxic compounds are normally very low (0.05-0.1%). All of them are irritans for the skin and the mucosal membranes, and have substantial toxicity when taken orally by animals and humans.



Phorbol



13,19,dihydroxyingenol

Some *Euphorbia* species are wide distributed in Turkey and Cyprus. They secrete an irritating milky latex and are known for their drastic purgative properties, their toxicity to fish, their aggressive action on the skin, and their ability to induce serious conjunctivitis. They contain diterpenoid esters of forbol and ingenol type.

Accidents due contact with the skin are the most frequent : redness, swelling, and the formation of vesicles are the main symptoms. If the latex gets into an eye, immediate and profuse rinsing is necessary, and medical attention must be sought (topical antibiotic therapy).

Some *Euphorbia* species growing in Cyprus

Euphorbia peplus

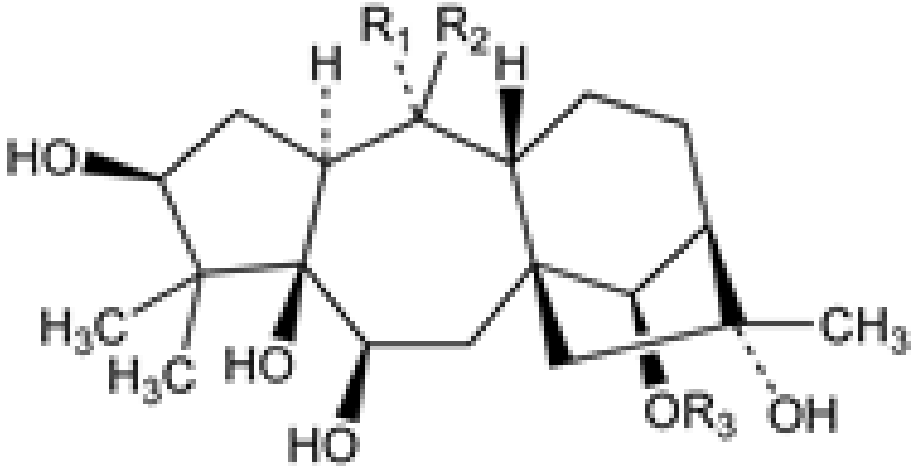
Euphorbia pubescens

TOXIC HONEYS

Especially in Turkey several case reports have been recorded following the ingestion of honey made by bees gone honey-gathering on *Rhododendron ponticum* and *R. flavum* (orman gülü) (Ericaceae). The toxic principle in these species is grayanatoxin I (=acetyl andromedol), which causes nausea, vomiting, hypotension, bradycardia, perturbations of the cardiac rhythm, extreme fatigue, dizziness and loss of consciousness.

Rhododendron ponticum

Rhododendron flavum



	R_1	R_2	R_3
Grayanotoxin I	OH	CH_3	$COCH_3$
Grayanotoxin III	OH	CH_3	H
Grayanotoxin II	$R_1R_2 = =CH_2$		R_3 = H

Grayanatoxins bind to and modify the sodium channels of cell membranes, leading to prolonged depolarization and excitation. Modification of the sodium channels favors calcium movement into cells and results in a positive inotropic effect similar to that of digitalis.

Detoxification : Emesis is used where appropriate. Activated charcoal should be administered repeatedly the first day.

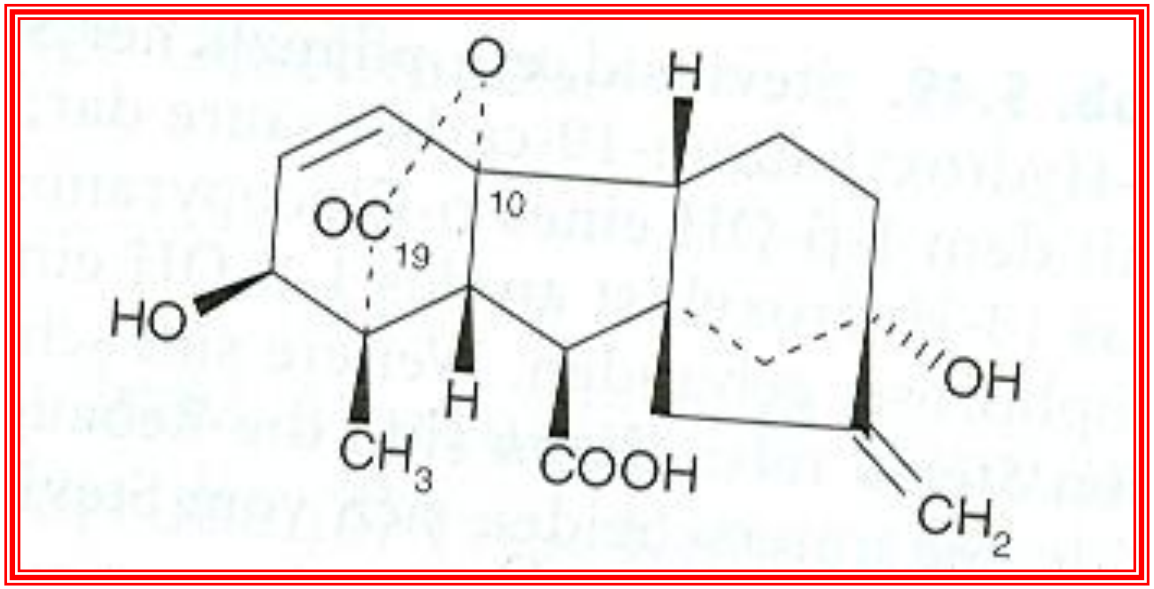
Supportive therapy : Fluid replacement therapy and respiratory support may be necessary. Atropine is recommended for severe bradycardia. Isoproterenol or sodium channel blockers (e.g. Quinidine) may be used to treat heart block.

Honey made from the plants has been reported to cause cardiac arrhythmias, emesis, mild paralysis and convultions in humans and is known as «mad honey».

In 401 B.C., Xenophon of Athens, one of Socrates' students, marched off to back the wrong contender in a Persian civil war, and had to lead a retreat through hostile territory. He wrote a best-seller about it, the "Anabasis

"Here, generally speaking, there was nothing to excite their wonderment, but the numbers of bee-hives were indeed astonishing, and so were certain properties of the honey. The effect upon the soldiers who tasted the combs was, that they all went for the nonce quite off their heads, and suffered from vomiting and diarrhoea, with a total inability to stand steady on their legs. A small dose produced a condition not unlike violent drunkenness, a large one an attack very like a fit of madness, and some dropped down, apparently at death's door. So they lay, hundreds of them, as if there had been a great defeat, a prey to the cruellest despondency. But the next day, none had died; and almost at the same hour of the day at which they had eaten they recovered their senses, and on the third or fourth day got on their legs again like convalescents after a severe course of medical treatment."

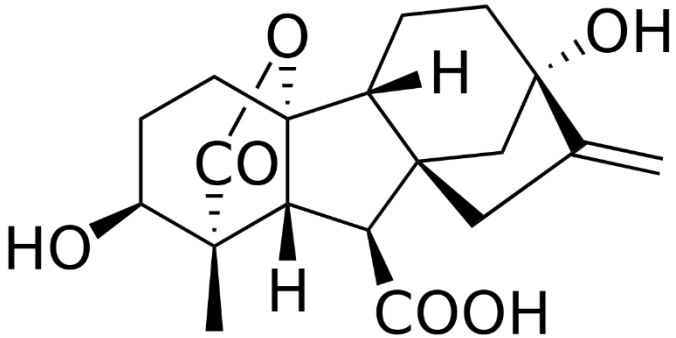
Gibberellins : They are plant growth hormones. They are obtained some tiny mushroms like *Gibberella fujikuroi* and are used in horticulture and greenhouse processes.



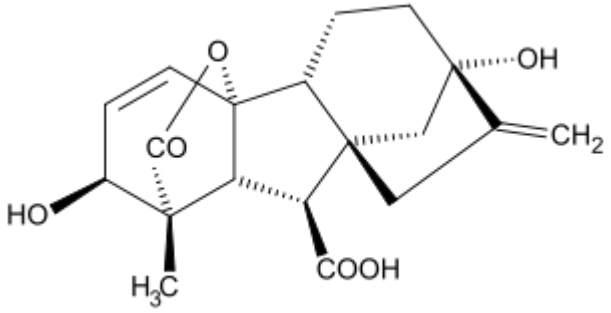
Gibberellin A_3

All known gibberellins are diterpenoid acids that are synthesized by the terpenoid pathway in plastids and then modified in the endoplasmic reticulum and cytosol until they reach their biologically-active form. All gibberellins are derived via the *ent*-gibberellane skeleton, but are synthesised via *ent*-kaurene. The gibberellins are named GA_1 through GAn in order of discovery. Gibberellic acid, which was the first gibberellin to be structurally characterized, is GA3.
As of 2003, there were 126 GAs identified from plants, fungi, and bacteria.

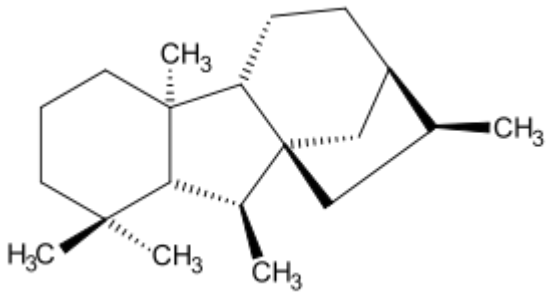
Gibberellins are tetracyclic diterpene acids. There are two classes based on the presence of either 19 or 20 carbons. The 19-carbon gibberellins, such as gibberellic acid, have lost carbon 20 and, in place, possess a five-member lactone bridge that links carbons 4 and 10. The 19-carbon forms are, in general, the biologically active forms of gibberellins. Hydroxylation also has a great effect on the biological activity of the gibberellin. In general, the most biologically active compounds are dihydroxylated gibberellins, which possess hydroxyl groups on both carbon 3 and carbon 13. Gibberellic acid is a dihydroxylated gibberellin.



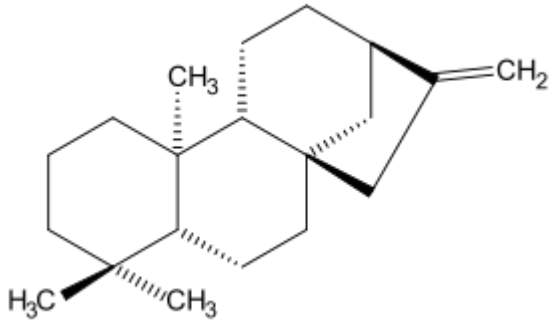
Gibberellin A_1



Gibberellic acid



Ent-gibberellane



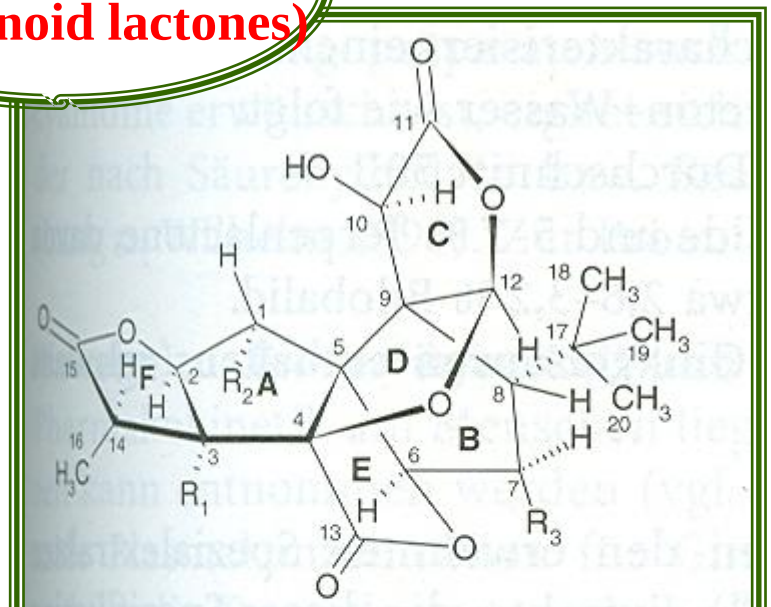
Ent-kaurene

Gibberella fujikuroi

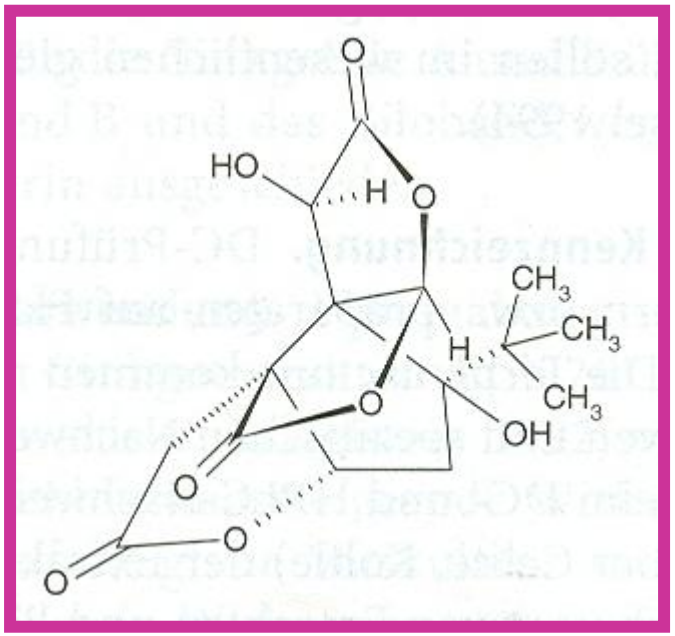
REMEMBER *GINKGO BILOBA*

GINKGO BILOBAE FOLIUM

Ginkgolids (diterpenoid lactones)



R_1	R_2	R_3	Ginkgolid
OH	H	H	A
OH	OH	H	B
OH	OH	OH	C
OH	H	OH	J
H	OH	OH	M



Bilobalid
Sesquiterpenoid lacton

The commercial *G. biloba* leaf extract;must contain 6% lactones and 24 % flavonoids. Active principles are the lactones.

Phytotherapy of Arterial Occlusive Diseases

Ginkgo

Botany/Key constituents Ginkgo consists of the leaves of the Chinese tree *Ginkgo biloba* L. (Fam. Ginkgoaceae). The *Ginkgo biloba* tree, cultivated in various parts of the world including France, USA, Japan, Korea and China, is the oldest tree on the earth: more than 200 million years old. Individual ginkgo trees sometimes live more than 1.000 years. The leaves are fanshaped with bifurcated ribs and glabrous.They are fresh green to golden yellow in autumn. Ginkgo contains terpenoids (bilobalide, ginkgolides), flavonoids and other compounds like amino acids.

Main pharmacological properties of ginkgo

Antioxidant properties

Ginkgo has been shown to induce the destruction of various free radicals and to inhibit lipid peroxidalion. The flavone component may mediate ginkgo‘s ability to protect from reactive oxygen species. This may be useful in treating the effect of blood lipoprotein oxidation that result in the deposition and aggregation of atherosclerotic plaques.

Anti platelet activating factor (anti-PAF) activity

Ginkgolides are competitive antagonists of PAF This finding is important due to the role played by PAF in the pathophysiology of infiammation and hypercoagulable states.

Anti-Ischemic properties

Ginkgolides prevent the metabolic damage caused by experimental cerebral ischeamia. They reduce the infarct size in experimental myoaardial occlusion.

Bilobalide has demonstrated a potent neuroprotective effect against ischemic damage, which is stronger than ginkgolide B.

Ginkgo posesses neuroprotective properties under conditions such as hypoxia/ischemi and nerve damage.

Clinical evidence of ginkgo from randomized clinical trials. Analysis of systematic reviews or meta-analysis

Dementia

Dementia is defined as "acquired global impairment of intellect, memory, and personality, but without an impairment of consciousness . Pharmacological treatments for dementia are still being developed. Conventional drug used (e.g. cholinesterase inhibitor) have given modest clinical benefits and serious adverse effects. The result of a recent systematic review' which included nine double-blind, randomised, placebo controlled trials suggest that ginkgo is more effective for dementia than placebo . The findings are encouraging and warrant large scale confirmatory and comparative trials.

Alzheimer's Disease

Alweimer‘s disease is the most common cause of dementia ,accounting for 50-60% of all cases . Pharmacological tratment for Alzheimer‘s disease include drugs which increate the endogenous levels of acetylcholine (acetylcholine precursors,releasers or inhibitors of its degradation). Serious adverse effects have been noted, including severe liver toxicity. Of more than 50 articles identified, the overwhelming majority were excluded primarily because of lack of clear diagnoses of Alzheimer's dementia. Only 4 studies involving a total of 424 subjects were analysed. Based on a quantitative analysis of these

studies there is a small but significant effect of 3- to 6-month treatment with 120 to 240 mg of ginkgo extract on objective measures of cognitive function in Alzheimer‘s disease.

Tinnitus

Tinnitus is the perception of sound in the absence of an external source. Causes include musculoskeletal and vascular sound porducing tinnitus, and disorders of the peripheral and central auditory system, which usually produce tinnitus . Anti-tinnitus drugs include oral local anesthetics (tocainide), which can have serious adverse effect on the heart, benzodiazepines,which should be used sparingly because they can be habituating and tricyclic antidepressants, which have antimuscarinic and cardiac adverse effects . The result of a recent systematic review which included five double-blind, randomized, placebo-controlled trials (n = 541 subjects) suggest that ginkgo is more effective than placebo. Although not fully conclusive, the findings are promising and warrant large scale confirmatory studies.

Interminent claudication

Interminent claudication is a condition caused by sclerosis of the arteries of the leg; it is characterized by a cramping pain in the calf muscles brought on by walking a short distance. Treatment is usually conservative and consist largly of regular physical exercise (regular walking is effective. but compliance is often poor) and pharmacological interventions (pentoxyfylline has a modest clinical effect). A recent meta-analysis identified eight randomized, placebocontrolled, double blind trials involving at total of 415 patients .The result suggests that ginkgo extract (120-160 mgl daily for 24 weeks) is superior to placebo in the symptomatic treatment of intermittent claudication. However, the size of the overall treatment effect is modest.

Ginkgo and memory in healthy subjects

Ginkgo is promoted as a “smart" drug and hence used by healthy individuals. A recent systematic review identified nine controlled trials of the cognitive effect of ginkgo in young subjects (n = 224 subjects ; 20-40 years old) without cognitive deficits. All the trials were double-blinded and eight used a randomized design. The duration of the treatment was in general short (the longest had a treatment period of 30 days). In the nine studies reviewed, there is no evidence for a consistent positive effect of ginkgo upon any particular aspect of cognitive performance in healthy people. The use of ginkgo as a “smart" drug cannot be recommended on the basis of the evidence available to date,and there is a particular need for longer-term trial .

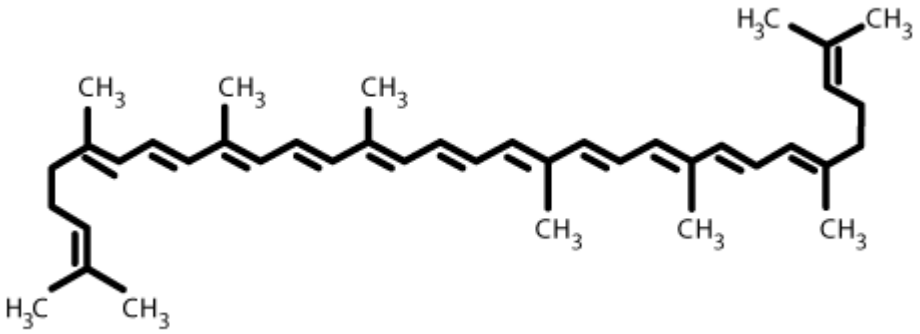
Macular degeneration

Loss of vision occurs frequently with advancing age. Age -related macular degeneration, the most common cause of visuaI loss in the elderly, is thought to result in part from oxidative damage to the retina. One published triaI has been identified. Although a beneficial effect was observed, as only 20 people were enrolled in the triaI, and assesment of outcome was not masked, its result must be considered equivocaI.

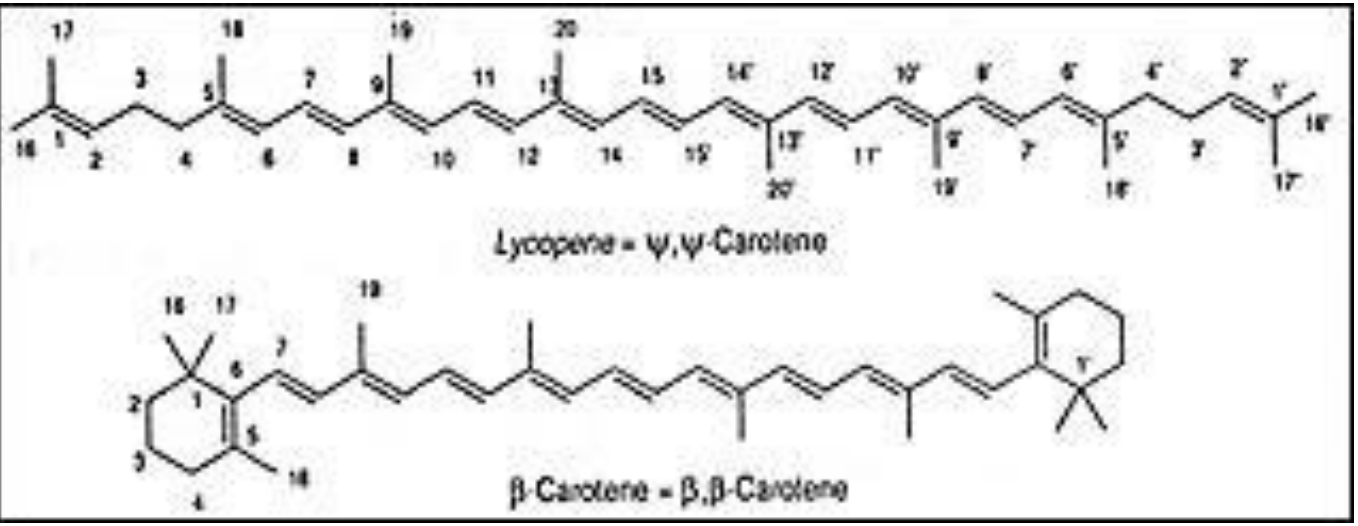
Carotenoids

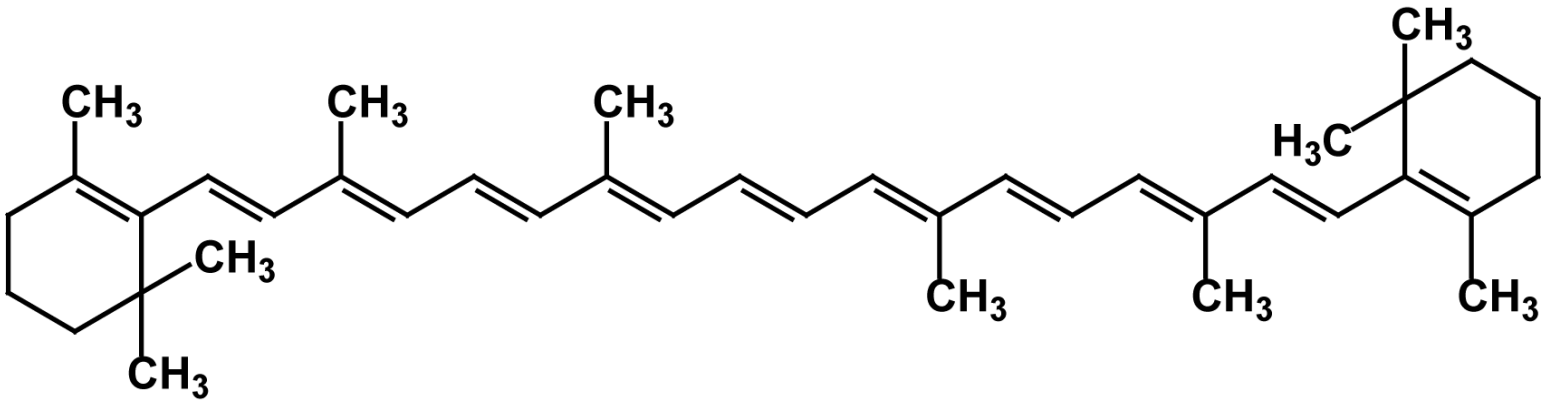
The carotenoid group includes several hundred tetraterpenoid compounds consisting of a sequence of eight isoprene units. Their characteristic chromophore –at least ten conjugated double bonds- explains their yellow or orange color and their extreme tendency to get oxidized.

Among these compounds, the hydrocarbons are collectively referred to as carotenes, and the hydroxylated derivatives as xanthophylls. Since there are multiple unsaturations, there could be multiple geometrical isomers : in reality, most carotenoids have a poly-E configuration.



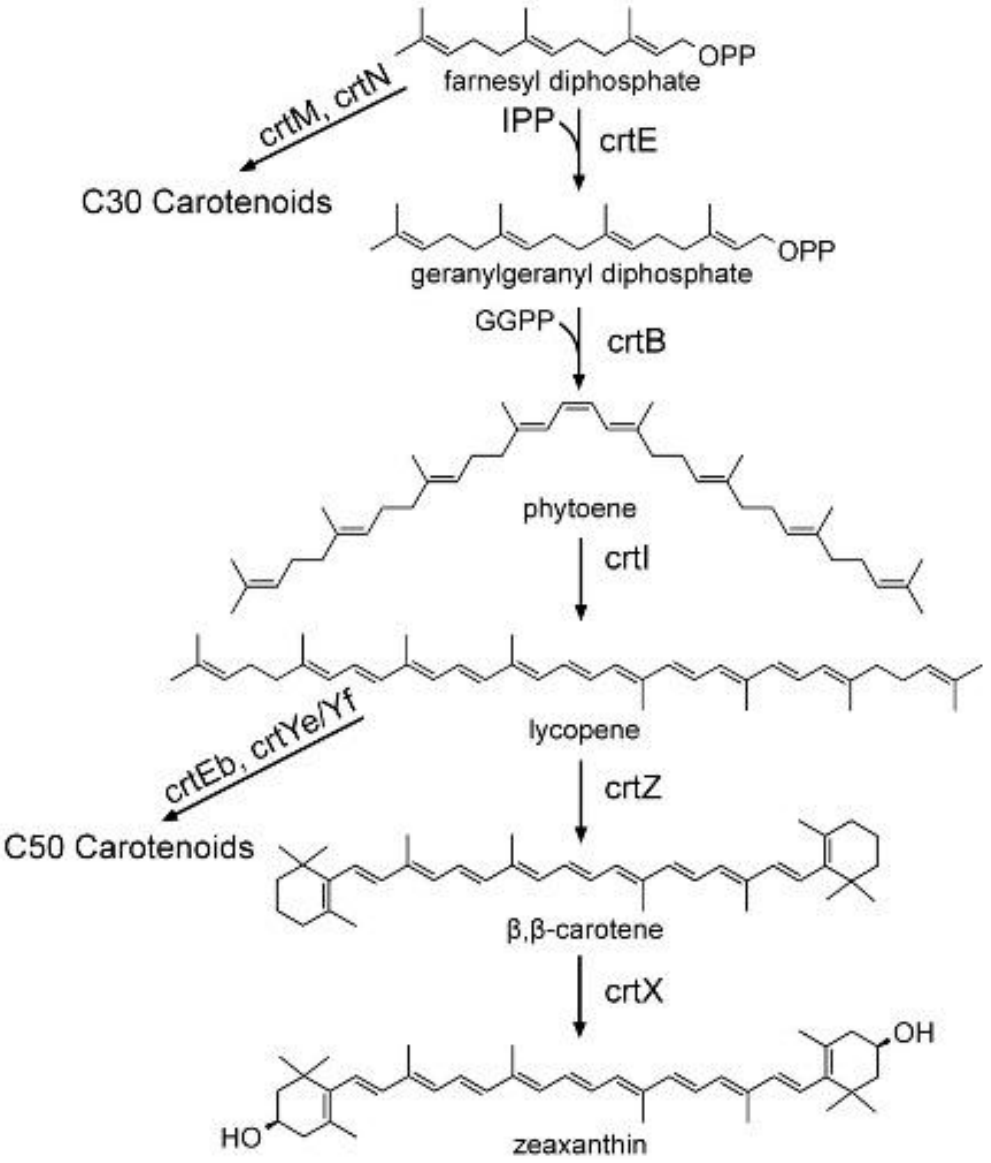
Lycopene = Ψ,Ψ-Carotene





β-Carotene = β,β-Carotene

Carotenoid Biosynthesis



INTEREST IN CAROTENOIDS AND USES

The interest in carotenoids has multiple justifications

- β-carotene and closely related compounds are degrated; at the level of the human intestinal mucosa, to retinol (vitamin A): this contributes to the value of some fruits and vegetables (carrots, spinach, mangos, tomatoes, bell peppers, squash, Citrus, melons), and also some animal products (eggs, liver, fish), or palm oil (margarine).

- Carotenoids are thought to exert a preventive action against degerenative disorders. The results of many epidemiological studies designed to assess the relationship between the consumption of fruits and vegetables containing –among others- carotenes and different cancers suggest, in an aggregate sense, that dietary carotenoids might have a protective role against various cancers. There is clearly an inverse relationship between blood levels of carotenes and the risk of lung cancer, but for all other cancers, the results are inconclusive.

- Carotenoids, because their interfere with photo-oxidation processes, may be of use in the treatment of photosensitization linked to porphyria, and also in cases of dermatitis of phototoxic origin : drug induced photosensitization, sun-induced urticaria, or lupus erythematosus summer flares. These products (β-carotene, canthaxanthin, in combination) are used orally; they are contraindicated in case of retinal disease or glaucoma.

- Carotenes are ingredients of tanning pills: in sufficient doses, they color the skin where they are deposited.

- In the pharmaceutical as well as food technology industry, carotenoids have applications as natural, efficacious, and non-toxic colorings

The natural products are commercially avelaible as extracts.

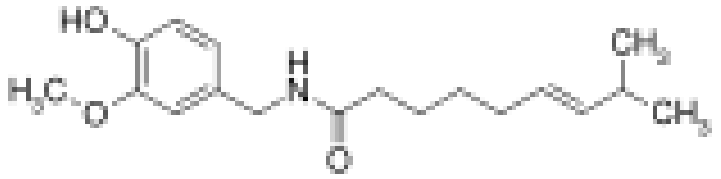
Pure carotenoids are avelaible in two forms : a microcrystalline suspension in a vegetable oil or powder to be dispersed in water. The chief applications, outside of the pharmaceutical and cosmetic industry, are in the food industry : cold meat products, dairy products, seasonins, soups, candy, pastries, liquors, beverages and syrups among others.

CAPSICUM (kırmızı biber) **CAPSICI FRUCTUS**

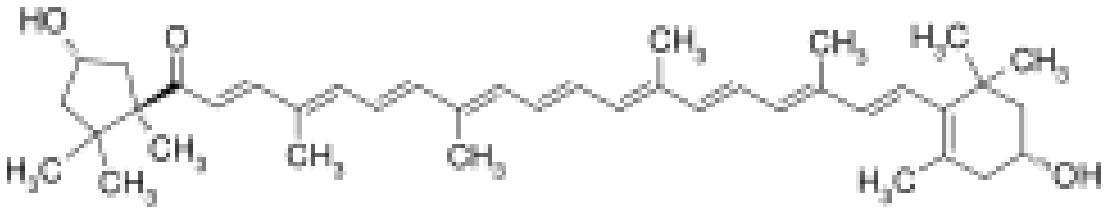
Capsicum annuum, ***C. frutescens***

Solanaceae

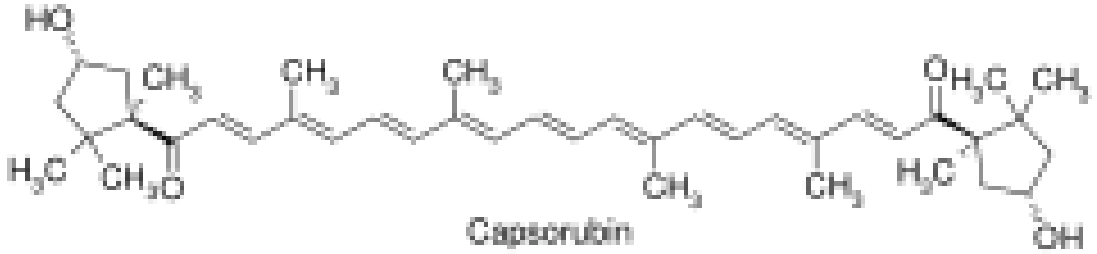
Capsicums are rich in ascorbic acid, they also contain diterpenoid glycosides (capsianosides) and a furostanol glycoside (capsioside). The color is due to the presence of carotenoids with a terminal cyclopentane ring, the level of which increases during ripening : among them capsanthin and capsorubin. The pungent flavor of hot and extra hot peppers is due to amides, found in a wide range of concentrations, namely capsaicinoids. The chief constituent in this series is capsaicin.



Capsaicin



Capsanthin



Capsorubin

The potential therapeutic applications of capsaicin are a subject of active research, particularly in the context of exploring the functions of certain types of neurons. Capsaicin application on the skin causes a burning sensation which turns to anesthesia by inhibition of neurotransmission by C fibers.

Capsicum oleoresin is an ingredient of pepper sprays used for self-defense.

Topically *Capsicum* is traditionally used for the symptomatic treatment of minor pain in the joints.

SAFFRON (safran) **CROCI STIGMATA**

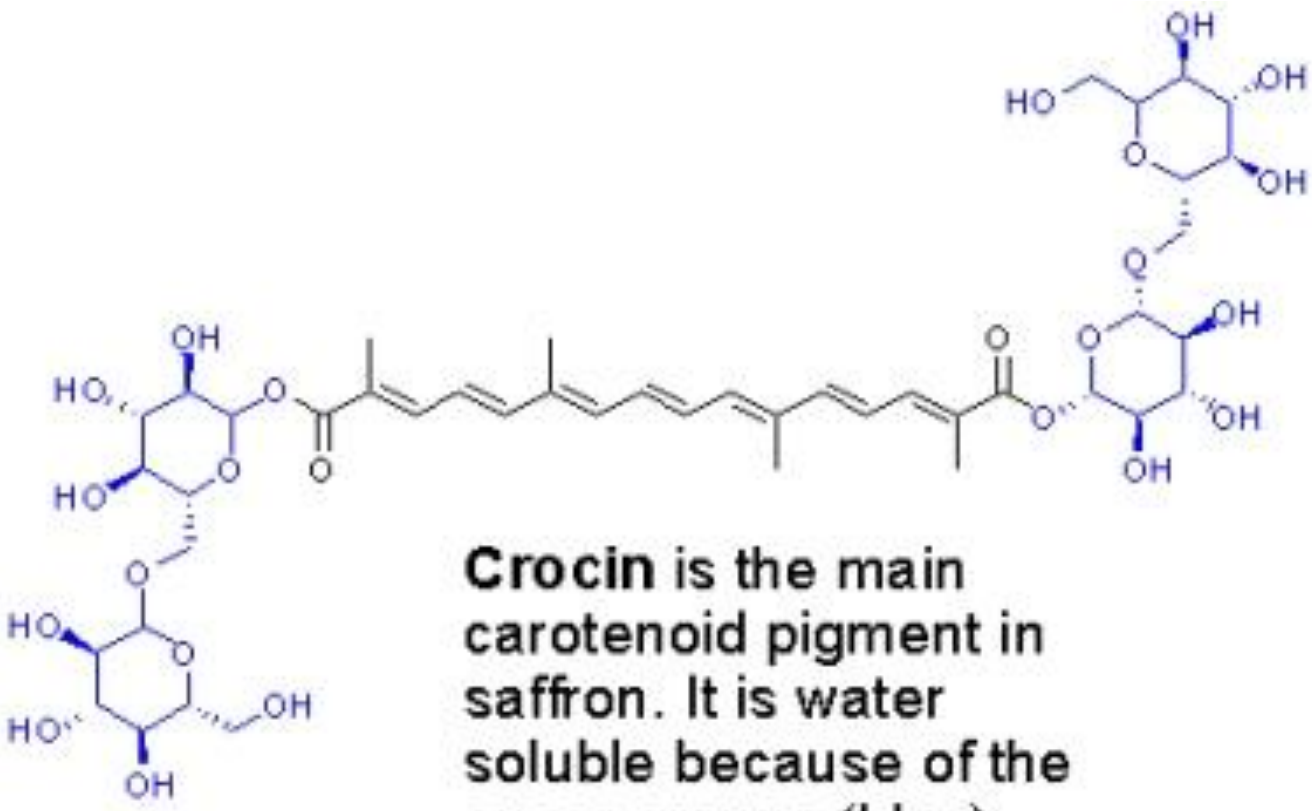
Crocus sativus **Iridaceae**

CROCUS

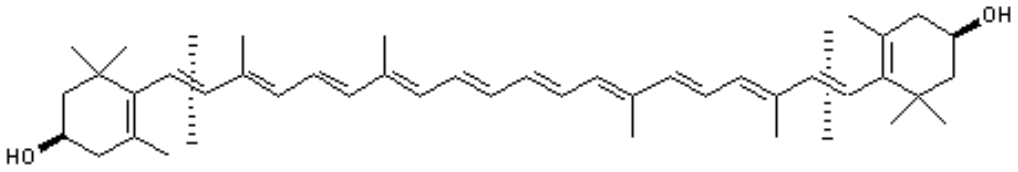
SAFFRON

In Safranbolu province of Turkey, *Crocus sativus* is cultivated but there are many wild *Crocus* species in Turkey and bulbs are eaten as chestnuts in some districts.

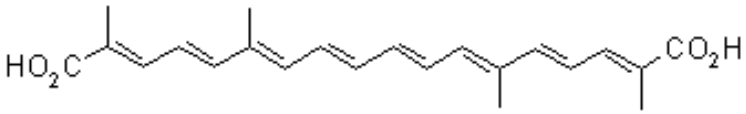
This small plant of oriental origin grows from a bulb and is used for its stigmas. These have an aromatic odor, and slightly bitter and pungent taste. The color of the drug is due to carotenoids, chiefly represented by crocin (2%), which is a diester of crocetin and of gentiobiose. Other constituents include picrocrocin (4%), which is the glucoside of 4β-hydroxycyclocitral, a small amount (1%) of essential oil in which safranal dominates.



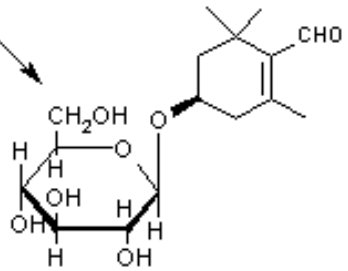
Crocin is the main carotenoid pigment in saffron. It is water soluble because of the sugar groups (blue)



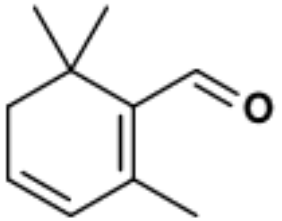
Zeaxanthin



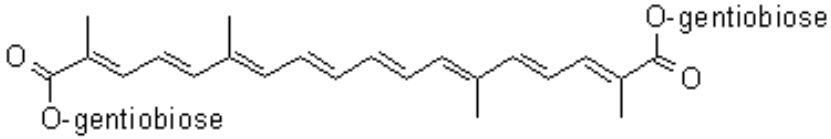
Crocetin



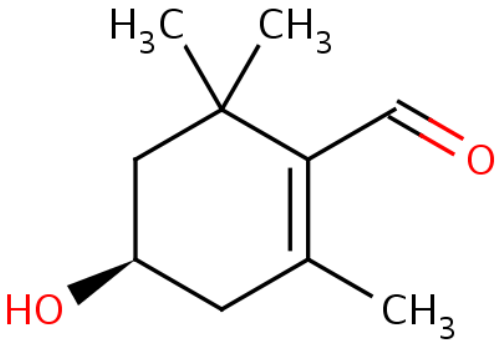
Picrocrocin



Safranal



Crocin



4β-hydroxycyclocitral

Because the high price of the drug leads to illicit attempts at substitution or addition. Sometimes *Carthamus tinctorius* flowers are used as saffron (false saffron).

Carthamus tinctorius
(aspir)

Saffron stigmas are seldom used in pharmacy.
The German Commission E monograph describes that saffron stigma is a traditional nervous sedative.

Saffron has been used traditionally since ages and has references in the oldest Ayurvedic Charaka Samhita & Sushruta Samhita (approx. 500 B.C).It is commonly known as Kumkum or Kesar. It takes about 150,000 flowers to produce one kilogram of dried saffron, traded by weight making it the most expensive spice in the world.

Iran, Spain, India, Greece, Azerbaijan, Morocco and Italy are major saffron spice producing countries. Iran and Spain produce approximately 85% of the total world crop.

Saffron is as important ingredient of large number of Ayurvedic medicines because of its antipoisonous, anticancer and antitumor (F. Abdullaev), aphrodisiac, cardiotonic, carminative, diaphoretic, diuretic, febrifuge, stimulant, lactogogue, livotonic, nervine tonic, sedative properties. It is used in acne, apoplexy, arthritis, asthma, colic, cough dyspepsia, hemierania, insect bites and stings, liver disorders, mental disorders, neurasthenia, oedema, painful menstruation, phthisis, prolapse of anus, sore throat and splenic disorders

The use of Saffron in Western countries for medicinal purposes dates back to the sixteenth century. The Ebers Papyrus (Ca. 1550 B.C) has mentioned it as an ingredient in case of kidney problems (Baumann.1960). Dioscorides of Anazarb attributed magical medicinal properties to Saffron if worn as an amulet. Pliny (1st century) ascribed general panacean properties to it when taken internally. In the centuries to follow it was recommended as an addition to meals to give cheering cardiac medicament effect. In regulated doses, it is said to increase appetite and to ease headaches and hangovers,a valuable remedy for catarrhal infections, useful in otitis, melancholia, enlargement of liver and spleen, as a nerve sedative, carminative.

Some endemic

Crocus Species

growing in Turkey

Crocus abantensis

Crocus hittiticus

Crocus antalyensis

Crocus baytopiorum

Crocus asumaniae

Crocus hartmannianus and C. veneris grow in Cyprus

PALM OIL as coloring

Elaeis guineensis, African oil palm

E. oleifera American oil palm

Palmaceae

Elaeis guineensis

Palm oil is added to margarines in some countries as coloring agent.

Palm oil can also be a good source of carotenes. The oil is transesterified by methanol, which allows the separation of the esters (for the detergent industry) and a fraction enriched in carotenes.

Reference Books :

Main Book

Bruneton, J., Pharmacognosy, Phytochemistry, Medicinal Plants, TEC & DOC Editions, Paris 1999

Other Books

- Hänsel, R., Sticher, O., Pharmakognosie – Phytopaharmazie, Springer Medizin Verlag, Heidelberg 2010
- Evans, W.C., Trease and Evans Pharmacognosy, Elsevier Limited, Edinburgh, London 2002
- Baytop, T., Farmakognozi I-II, İstanbul Üniv. Yay. No. 2783, Eczacılık Fak. No.29, İstanbul 1980
- Tanker, M., Tanker N., Farmakognozi I-II, Ankara Üniv. Eczacılık Fak. Yay. No. 63, Ankara 1990