Plants containing flavonoids glycosides:

- **Ruta:** consists of the whole (entire) plant of Ruta graveolens family Rutaceae.

The Ruta plant contains mainly a flavonoids glycoside called Rutin.

- **Sophora:** consist of the flower buds of Sophora japonica family Fabaceae.

The plant Sophora is rich in Rutin about 20%.

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- **Lemon peel:** obtained from the fruit of Citrus limon family Rutaceae.

Dried lemon peel contains hesperidin and volatile oil.

- **Orange peel:** consists of the dried peel of Citrus aurantium family Rutaceae.

Orange peel also contains the flavonoids glycoside, hesperidin, and volatile oil.

Rutin, hesperidin (vitamin P) and related flavonoids decrease capillary bleeding, reduce capillary fragility and permeability induced by histamine or by tissue injury. Flavonoids characterized by having in their structures certain functional groups such as hydroxyl groups at C_3 and carbonyl group at C_4 or di-hydroxy groups at C_3', C_4' act as anti-oxidant by chelating of metal ions (Al, Cu, and Fe) and reduce the oxidizing effects of these elements.

Most of the citrus fruits and vegetables are sources in flavonoids and their derivatives which are important anti-oxidant compounds that are useful in preventing certain dangerous diseases, such as heart diseases, rheumatoid arthritis and other inflammatory conditions.

Cyanogenic or Cyanogenetic Or Cyanophor glycosides

These glycosides yield hydrocyanic acid (HCN) as one of the hydrolytic products. They are accompanied in the plant by enzymes (β-glucosidase) that catalyze the hydrolysis. The group is represented by amygdalin, which is found in large quantities in bitter almonds, in kernels of apricots, cherries, peaches, plums, and in many other seeds of the Rosaceae family.

Also prunasin is another Cyanogenic glycoside which occurs in Prunus serotina.

Both amygdalin and prunasin yield mandelonitrile as the aglycone plus sugar portion.

Amygdaline and other Cyanogenic glycosides are derivatives of mandelonitrile (benzaldehyde-cyanohydrins).

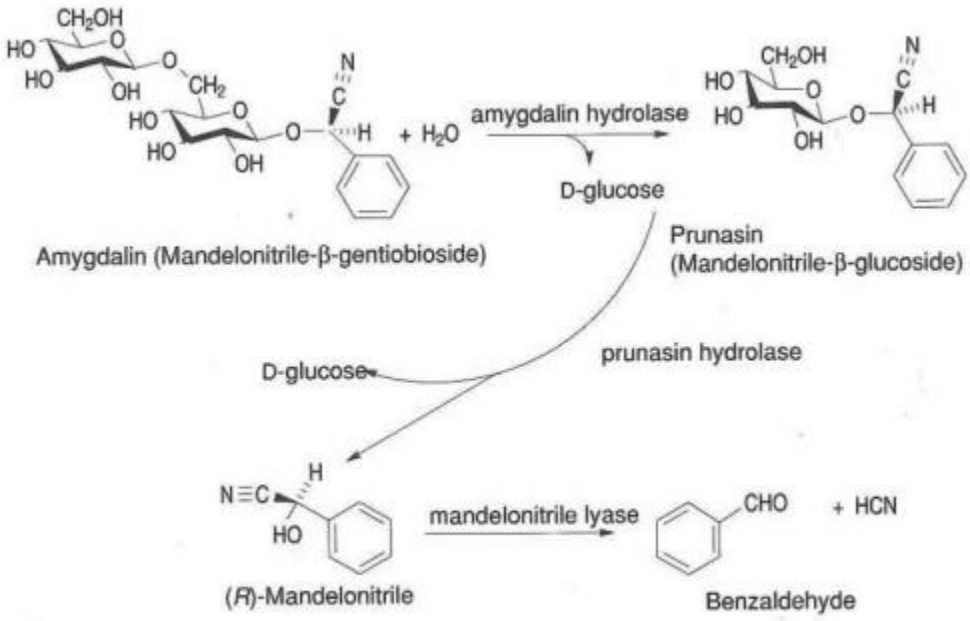


Fig. 4–4. Enzymatic hydrolysis (cyanogenesis) of amygdalin.

The enzyme β-glucosidase presents in the plants containing Cyanogenic glycosides is called emulsin which is a mixture of three different enzyme activities, Amygdalase (amygdalin hydrolase), Prunase (prunasin hydrolase) and mandelonitrile lyase.

Preparations from plant materials containing Cyanogenic glycosides are used as flavoring agents.

Plants containing Cyanogenic glycosides:

- **Wild Cherry bark:** is the dried bark of Prunus serotina family Rosaceae.

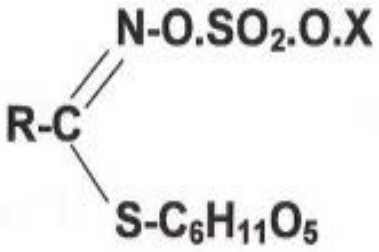
Wild cherry bark contains the Cyanogenic glycoside prunasin (mandelonitrile glycoside), a compound formed by partial hydrolysis of amygdalin. Also contains the hydrolyzing enzyme Prunase (prunasin hydrolase), tannins and resin. Wild cherry in the form of syrup is used as a flavoring agent in cough preparations, and as sedative expectorant.

- **Bitter almonds:** consists of kernels of Prunus amygdalus family Rosaceae.

The kernels of bitter almonds (Prunus amygdalus variety amara) which contain amygdalin and the hydrolytic enzyme β-glucosidase are toxic if ingested, while the kernels of sweet almonds (Prunus amygdalus variety dulcis) are not toxic, containing the enzymes but no Cyanogenic glycoside.

Isothiocyanate Glycosides

The seeds of several plants of the family Brassicaceae contain glycosides, the aglycones of which are isothiocyanate these glycosides are also termed glucosinolates and represent a group of bound toxins, like Cyanogenic glycosides. Upon hydrolysis by the enzyme myrosinase, glucosinolates give glucose and labile aglycone that rearranges spontaneously with the loss of sulphate to yield an isothiocyanate as the major product. The general structure of glucosinolates is shown below:



Glucosinolates have a distribution limited to a few plant families, and are characteristic of the Brassicaceae family which includes mustard, cabbage and turnips..... Etc.

Drugs containing isothiocyanate glycosides:

- **Mustard , or black mustard seeds:** Are the dried ripe seeds of Brassica nigra or of Brassica juncea family Brassicaceae (Cruciferae)

Black mustard seeds contain the glycoside sinigrin which is accompanied by the enzyme myrosinase (myrosin). Upon the addition of water to the crushed seeds, the enzyme myrosinase affect the hydrolysis of the sinigrin as shown in the following scheme:

The aglycones may be either aliphatic or aromatic derivatives formed from amino acids in the plant. Among these glycosides are sinigrin from black mustard and sinalbin from white mustard.

In the above formulae, R represents CH_2=$CHCH_2$ in sinigrin and P-hydroxybenzyl (P-OH-$C_6H_4CH_2$) in sinalbin.

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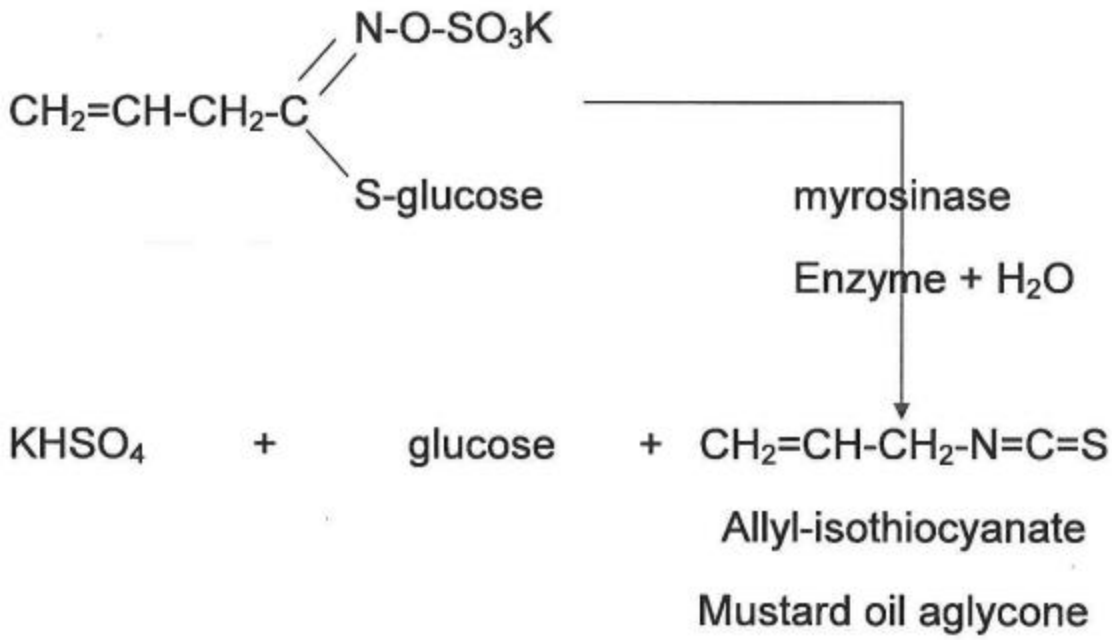
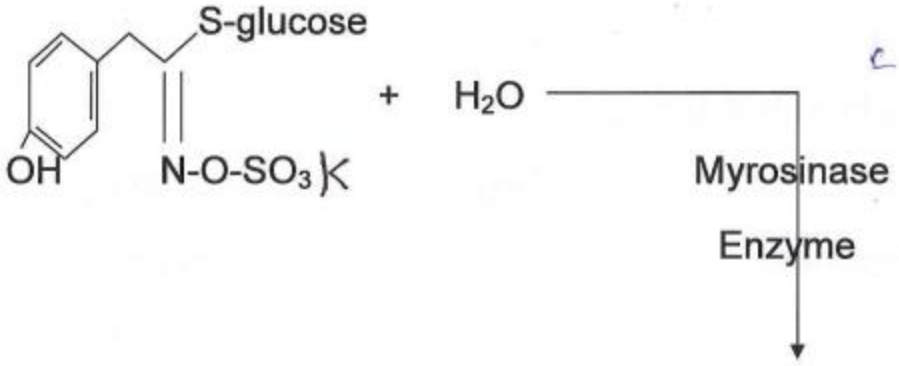


The allyl-isothiocyanate produced is volatile oil; it is commonly called volatile mustard oil. Black mustard is a

local irritant and emetic. Externally, the drug is a rubefacient. Commercially, it is used as a condiment (spices).

- **White mustard:** Are the dried ripe seeds of Brassica alba family Brassicaceae.

White mustard contains the glycoside sinalbin and the enzyme myrosinase. On treatment with water, the powdered seeds will give P-hydroxybenzyl isothiocyanate (aglycone) which has a pungent taste but the oil is less volatile than allyl-isothiocyanate of the black mustard variety.



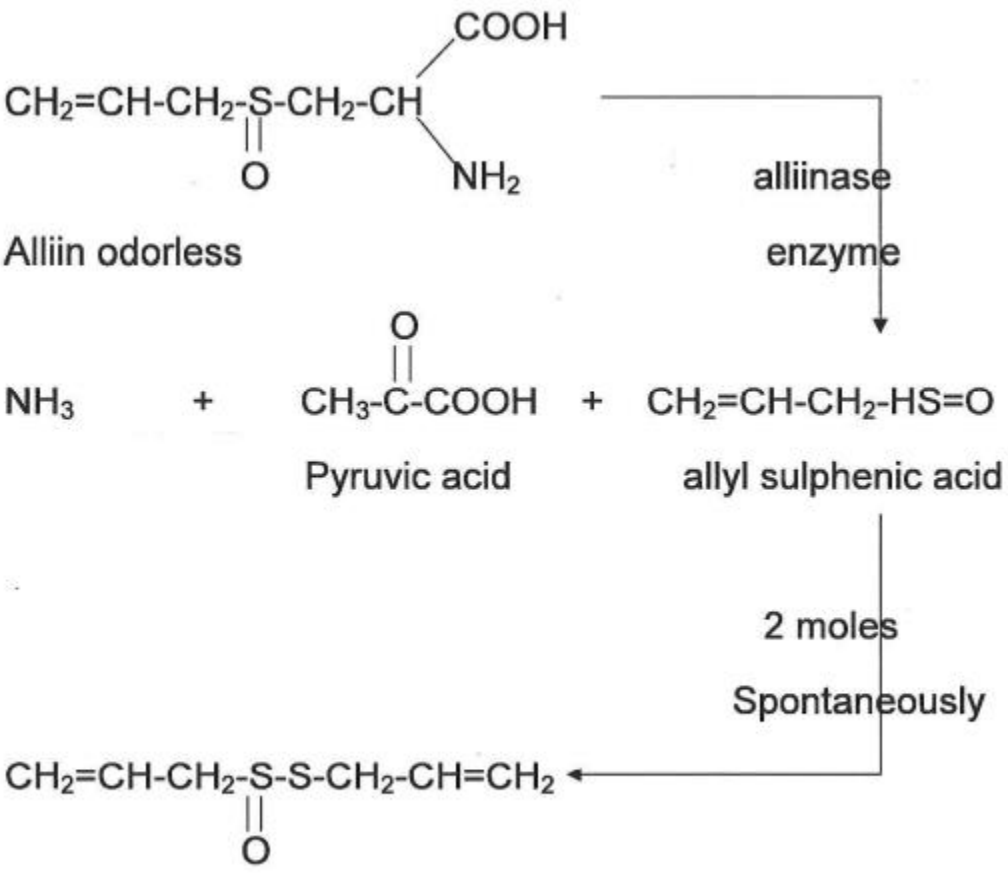
Acrinyl-isothiocyanate

White mustard seeds have the same use as black mustard seeds. Glucosinolates are found in many plants of the Brassicaceae (Cruciferae) family….etc. Consumption of the hydrolysis products from glucosinolates in food crops may induce goiter (an enlargement of the thyroid gland) by inhibiting iodine incorporation and thyroxin formation.

Other Organo-Sulphur drugs:

- **Garlic:** consists of the bulb of the Allium sativum family Liliaceae.

The intact cells of garlic contain the odorless, sulphur-containing amino acid derivative S-allyl-cysteine sulphoxide. This compound is called alliin and occurs in garlic in concentration of up to 1.2% of fresh weight. When the cells are crushed, it comes into contact with the enzyme alliinase which is stored in different cells, and is converted to allicin (di-allyl thiosulphinate) as shown in the following scheme:



Alliin odorless

Allicin characteristic odor of garlic

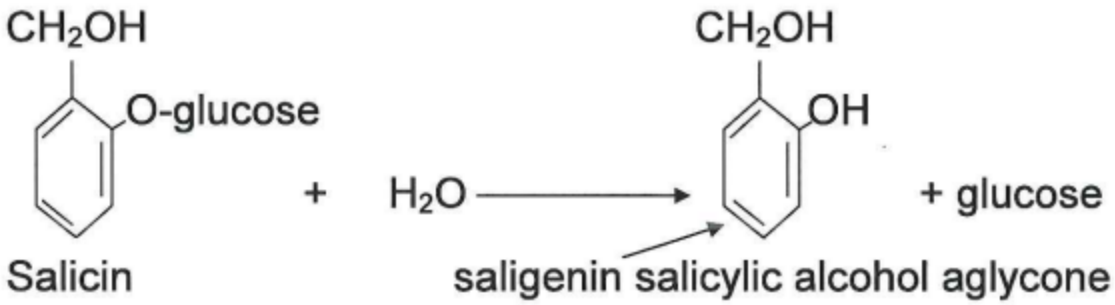
Allicin has potent anti-bacterial activity. It is also responsible for the characteristic odor and flavor of garlic. Garlic also possesses anti-hyperlipidemic activity and enhances blood fibrinolytic activity and inhibits platelet aggregation, reducing the risk of heart attacks.

Daily doses with a range of one to five cloves (4 grams fresh weight per clove) have been recommended. Enteric coated tablets or capsules have enhanced activity because stomach acid inactivates alliinase, thus preventing the conversion of the inactive alliin to the bio-active products.

Alcohol Glycosides

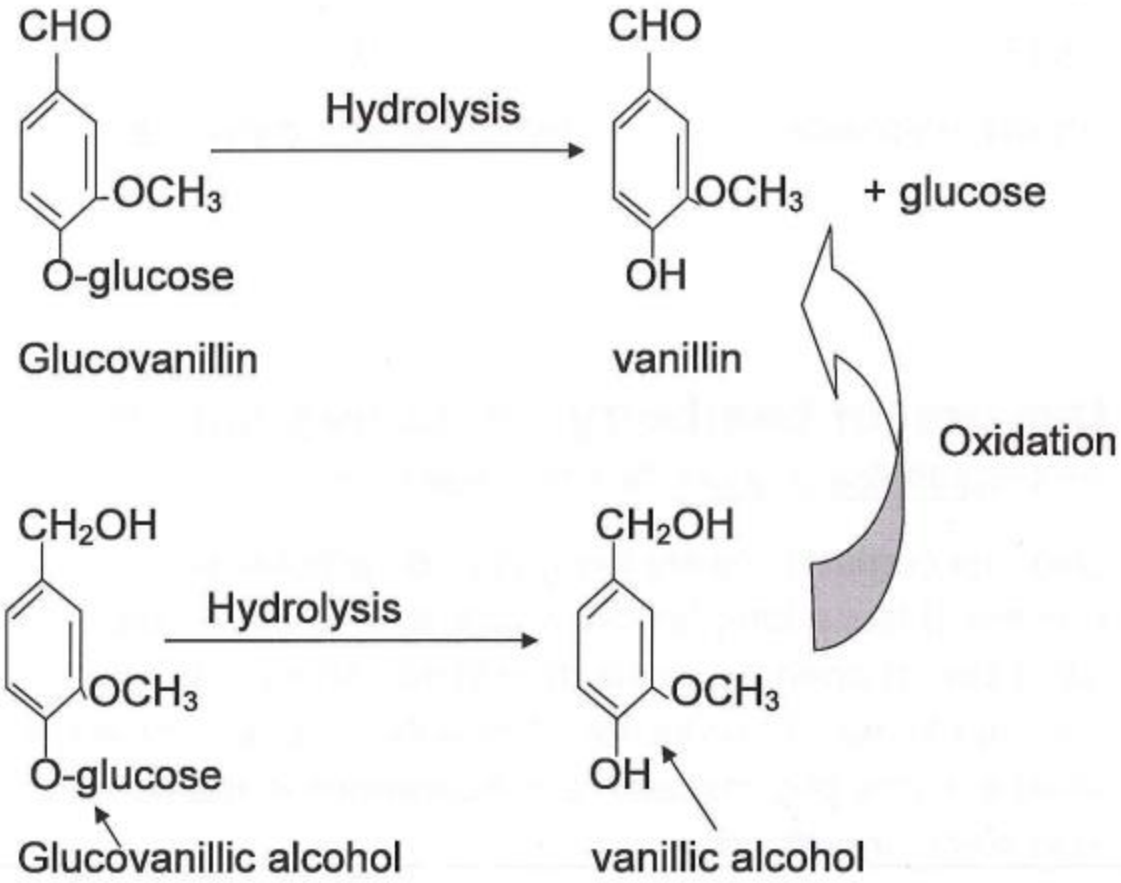
This group of plant glycosides is represented by Salicin. Salicin is obtained from several species of Salix and Populus. Most willow and poplar barks yield salicin, but the main sources are Salix purpurea and Salix fragilis family Salicaceae.

Salicin is hydrolyzed into saligenin (aglycone) and glucose by the enzyme emulsin. Salicin has anti-rheomatic properties. Its action closely resembles that of Salicylic acid, and it is probably oxidized to salicylic acid in the human system.



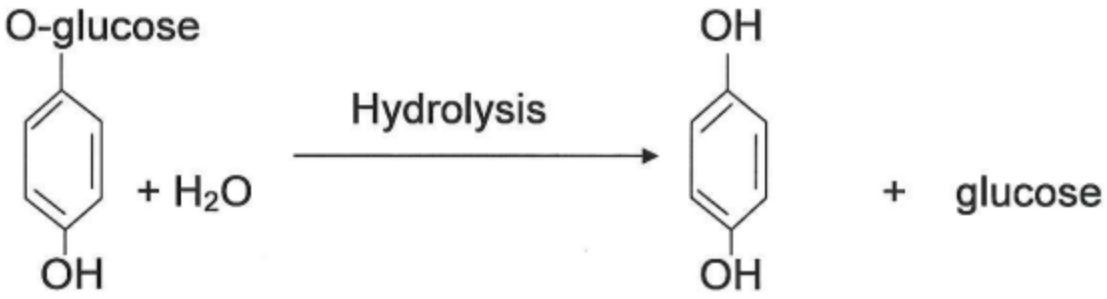
Aldehyde Glycosides

Vanilla is a drug that has an aldehydic aglycone as its main constituents. Vanillin is the aglycone formed during the curing of vanilla beans. **Vanilla or vanilla beans:** is the cured, fully grown unripe fruit of Vanilla planifolia family Orchidaceae. Green vanilla contains two glycosides, glucovanillin and glucovanillic alcohol. Glucovanillin is hydrolyzed an enzyme during the curing process into glucose and vanillin, and glucovanillic alcohol is similarly hydrolyzed into glucose and vanillic alcohol, which is, in turn oxidized to vanillic aldehyde (vanillin). Vanilla is used as a flavoring agent and as pharmaceutics aid. It is a source of vanillin.


CHO
Hydrolysis
OCH3
O-glucose
Glucovanillin
CHO
OCH3
+ glucose
OH
vanillin
Oxidation
CH2OH
Hydrolysis
OCH3
O-glucose
Glucovanillic alcohol
CH2OH
OCH3
OH
vanillic alcohol

Phenol Glycosides

The glycone groups of many of the naturally occurring glycosides are Phenolic in character. Thus, arbutin, hesperidin….etc. are examples of phenol glycosides. Arbutin which is found in Uva ursi gives hydroquinone and glucose upon hydrolysis.



Arbutin glycoside hydroquinone aglycone

Uva ursi or bearberry: Are the dried leaves of Arctostaphylos uva-ursi family Ericaceae.

Uva ursi contains mainly the glycoside arbutin, and tannins. It has a long history of use as anti-septic and astringent properties, in addition to its use as a diuretic material for weight reduction. The aglycone hydroquinone used in some pharmaceutical preparations in the form of skin bleaching cream.

Resins and

Resin combination

The term resin is applied to more or solid, amorphous products of complex chemical nature. On heating they soften and finally melt. They are insoluble in water, but they dissolve more or less completely in alcohol, ether and chloroform. Chemically, resins are complex mixtures of resin acids, resin alcohols, resin phenols, esters and chemically inert compounds called resenes.

Resins are usually formed in special cells, ducts or cavities, and they represent end products of metabolism. Resins often occur in more or less homogenous mixtures with volatile oils, and the mixtures are called oleo-resins. Natural oleo-resins are exemplified by Turpentine. Oleo-resins also occur in mixtures with gums, these mixtures are called oleo-gum-resins, example myrrh.

Pharmaceutic resins are usually obtained by:

- Extracting the drug with alcohol and precipitating the resin in water.
- Or separating the oil from oleo-resin by distillation.

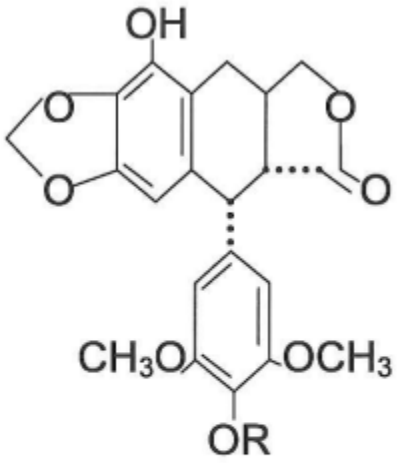
Drug containing resins:

- **Podophyllum:** consists of the dried rhizomes and roots of Podophyllum peltatum or Podophyllum hexandrum (Pod. Emodi.) Family Berberidaceae.

Podophyllum hexandrum found in India, China ….etc and yields Indian podophyllum.

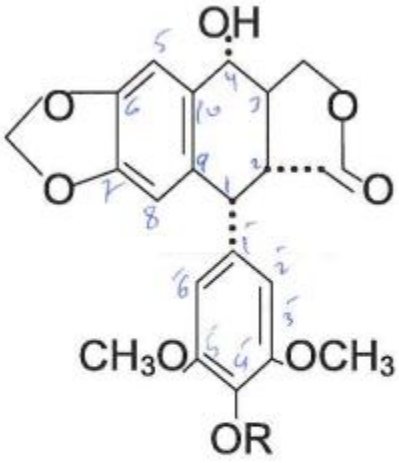
Podophyllum peltatum comes from North America and called American podophyllum. The roots contain cytotoxic compounds and their glycosides. American podophyllum contain 2-8% of resins, and the Indian podophyllum contains 6-12% resins, the resins of podophyllum are sometimes called podophyllim. The Indian roots contain chiefly podophyllotoxin, and 4\'-dimethyl podophyllotoxin.

The main constituents of the American roots are podophyllotoxin, β-peltatin and α-peltatin.



R = CH_3 = β-peltatin.

R = H = α-peltatin.



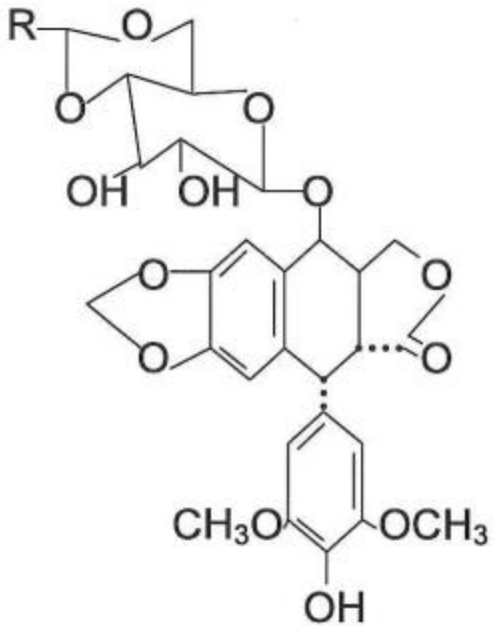
R = CH_3 = podophyllotoxin

R = H = 4'-demethyl podophyllotoxin.

Podophyllum resin was used as purgative. The discovery of cytotexic activity of podophyllum has made podophyllum an important drug plant.

Podophyllum resin preparations are used for the treatment of skin warts, and also as paint for several warts.

Semi-synthetic derivatives obtained from podophyllotoxin such as Etoposide and Teniposide are used as anti-cancer agents. Etoposide (4'-dimethyl podophyllotoxin derivative) is used in the treatment of small-cell lung cancer as well as Lymphomas and Leukaemias. Teniposide has similar anti-cancer properties; it has value in pediatric Lymphocytic Leukaemia, and brain tumor in children.



R = CH_3 = Etoposide

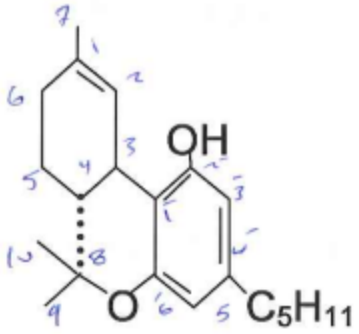
R =  = Teniposide

- **Cannabis, Indian hemp, Hashish, Marihuana:** consists of the flowering and fruiting tops of Cannabis sativa family Cannabaceae (Moraceae).

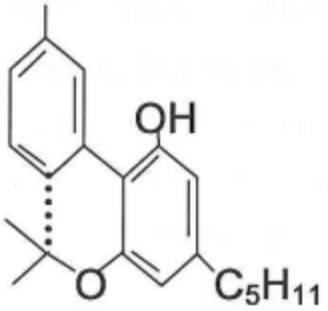
About 15-20% resin produced (narcotic resin) by the flowering tops of high quality Indian cannabis. The major constituents in cannabis are called cannabinoids; a group of structurally related compounds termed terpenophenolics. The main compound is a psychoactive agent called tetra-hydrocannabinol (THC).

Also the plant contains cannabinol (CBN) and cannabidiol (CBD) which negligible psychoactive properties. Smoking of cannabis produces euphoria, relaxation and sense of

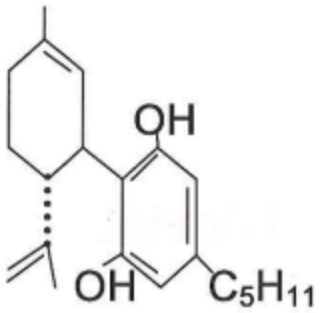
well-being. Cannabis can cause psychoactive dependence and can lead to hallucination and depression.



Tetra-hydrocannabinol (THC)



Cannabinol (CBN)



Cannabidiol (CBD)

Cannabis has been used medicinally as analgesic and tranquilizer it has anti-emetic properties which reduce the side effects of nausea and vomiting caused by cancer chemotherapeutic agents. The activity is due to the THC.

Cannabis is now outlawed in all world countries and generally classified with narcotic such as Morphine and other abused psychoactive drugs like Cocaine.

Drugs containing oleo-resins:

Oleo-resins are homogenous mixtures of resins and volatile oils.

- **Turpentine:** is the oleo-resin obtained from Pinus palustris and other species of the pine tree trunk, family Pinaceae.

The oleo-resin used externally as counter irritant. The pure resin, called rosin or colophony is obtained after distillation of the oleo-resin, and used as a stiffening agent in plasters and ointment (in pharmacy). Commercially, the resin (rosin) is used in the manufacture of varnish and paint dryers, sealing wax, and floor covering.

- **Ginger:** are the dried rhizomes of Zingiber officinale family Zingiberaceae.

The main constituents are oleo-resin (resin and volatile oil) the aroma is due to 1-3% of volatile oil.

Ginger is used as flavoring agent, condiment, an aromatic stimulant and carminative. The characteristic pungency of the drug is due to the ginger oleo-resin.

Drugs containing oleo-gum-resins:

Oleo-gum-resins are homogenous mixtures of oleo-resins and gum (mixture of resin, gum and volatile oil):

- **Myrrh or gum myrrh:** is an oleo-gum-resin obtained from Cammiphora molmol, or from other species of Cammiphora, family Burseraceae.

The plant is a small tree; the name myrrh is from the Arabic Murr (bitter). The plant is of two types, African myrrh (Somali myrrh), and Arabian myrrh (Yemen myrrh).

Myrrh contains mainly oleo-gum-resin consisting of a volatile oil that has the characteristic odor of myrrh, resin, and gum. Myrrh is used as a protective agent, stimulant and stomachic. It is also employed as mouthwashes and an astringent.

- **Asafoetida:** is an oleo-gum-resin obtained from the rhizomes and roots of Ferula foetida and other species of Ferula, family Umbelliferae.

Asafoetida consists of volatile oil, resin and gum. It is used as carminative, expectorant.

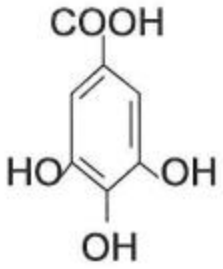
Tannins

Tannins constitute a large group of complex substances that are widely distributed in the plant kingdom. Chemically, tannins are complex substances, they occur as mixtures of polyphenols that are difficult to separate because they don't crystallize.

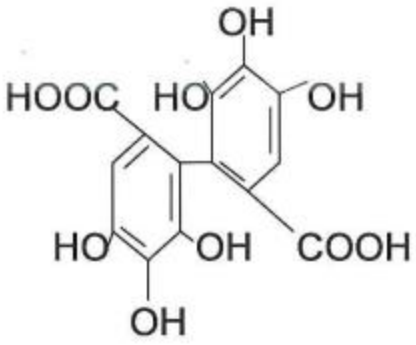
The term tannin was used to denote substances present in plant extract which were able to combine with protein of animal hides, prevent their putrefaction and convert them into leather.

Tannins are usually divided into two chemical classes, based on the identity of the Phenolic nuclei involved and on the way they are joined.

- **Hydrolysable tannin:** members of this class consist of the Gallic acid and hexahydroxydiphenic acid and their derivatives esterified with glucose, that is to say. They are formed from several molecules of Phenolic acid which are united by ester linkages to a central glucose molecule. Because such esters are readily hydrolyzed to give the Phenolic acids and the sugar, they are called hydrolysable tannins.

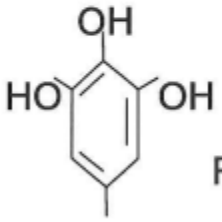


Gallic acid



Hexahydroxydiphenic acid

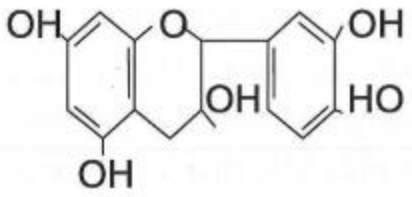
Like Gallic acid their solutions turn blue with iron salts. They were formerly known as pyrogallol tannins because on dry distillation, Gallic acid and similar components are converted into pyrogallol.



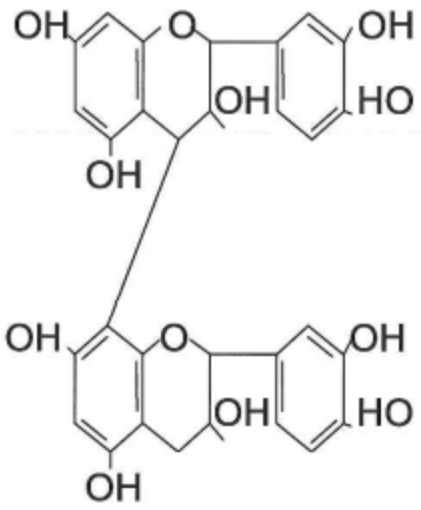
R = OH = Gallic acid

R = glucose = glucogallin ester of gallicacid

- **Non-hydrolysable tannins condensed tannins:** unlike the hydrolysable tannins, these are not readily hydrolyzed to simpler molecules and they do not contain sugar unit. They are related to the flavonoids compounds and have polymeric flavan-3-ol structures. Basically, these tannins contain only Phenolic nuclei, but frequently are linked to carbohydrates or proteins. Most such tannins result from the condensation (polymerization) of two or more flavan-3-ols such as Catechin. When treated with hydrolytic agents, these tannins form insoluble, red products called phlobaphenes (phlobatannins), which give red color to many plant drugs such as red cinchona bark.



Catechin



A dimeric form

On dry-distillation they give Catechol and these tannins are therefore sometimes called Catechol tannins. Like Catechol itself, their solutions turn green with ferric (iron) salts.

Properties and uses:

1. Tannins are soluble in water, alcohol and acetone. They form with water a colloidal solution having n acid reaction and a sharp or astringent taste.
2. Tannin solutions precipitate heavy metals, alkaloids and gelatin.
3. They form dark blue or greenish brown soluble compounds with ferric salts.
4. Tannins ppt. proteins from solution and combine with proteins making them resistance to proteolytic enzymes. This property is utilized in leather industry.
5. They are used in ink industry due to the color they produce with iron salts.

6. They are used in alkaloidal poisoning, they ppt. alkaloids by the formation of insoluble tannate.
7. Tannins are used in medicine as astringent, in the treatment of burns, and as antiseptic, and protective for skin bruises.

Drugs containing tannins:

- **Hamamelis leaves or witch hazel leaves:** consists of the dried leaves of Hamamelis virginiana family Hamamelidaceae.

Hamamelis leaves contain hamamelitannin (gallitannins, ellagitannins) and free Gallic acid, volatile oil and bitter principles. Hamamelis leaves have astringent and haemostatic properties, also used as an antiseptic for wounds and bruises.

- Galls or nut-gall: galls are vegetable growth formed on the young twigs of Quercus infectoria family Fagaceae.

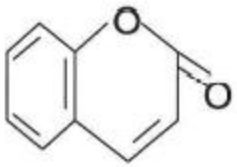
Galls contain 50-70% of the tannin called gallotannic acid (tannic acid), also the galls contain Gallic acid, ellagic acid and starch.

Tannic acid is hydrolysable tannin; it gives Gallic acid and glucose on hydrolysis. Galls are the main sources of tannic acid, used for tanning and dyeing industry and in the manufacture of inks. Medicinally, tannic acid has astringent and antiseptic properties, for bed sores, mild wounds, minor ulceration, and also used as anti-dote in alkaloid poisoning.

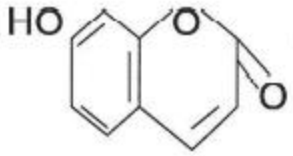
Tannic acid is not a single compound; it is a complex mixture of esters of Gallic acid with glucose.

Coumarins

Coumarins are derivatives of benzo-α-pyrone. Coumarins are the lactone of O-hydroxycinnamic acid such as Umbelliferone. Coumarins are found in plants as free and as glycosides (Phenolic derivatives). They give blue, blue-green or violet fluorescence under ultra violet (UV) light or in ammoniacal solution.



Benzo-α-pyrone

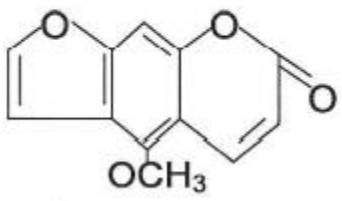


Umbelliferone

Umbelliferone occurs in belladonna, stramonium of the family solanaceae, and also in Ferula species.

Furanocoumarins (or furocoumarins) are closely related to Coumarins, example bergapten from Ammi majus.

Bergapten is a Furanomehtoxycoumarin:

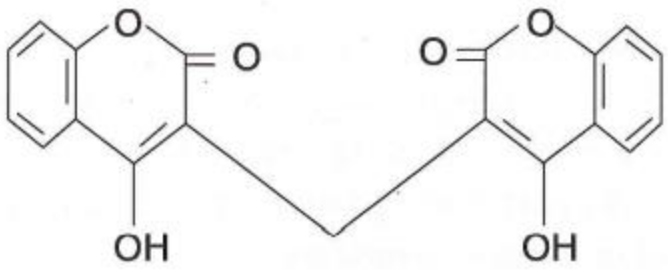


Bergapten

The Furanocoumarins occur particularly in the Rutaceae and Umbelliferae, for example Ruta graveolens, and in the peels of most citrus fruits, and celery fruits, Coumarins and coumarin derivatives have anti-coagulant properties.

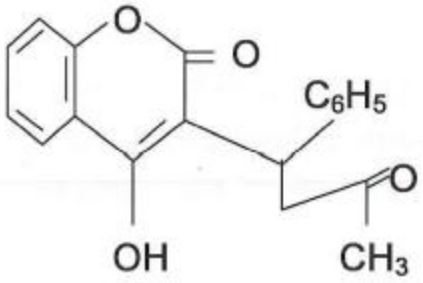
Bicoumarins or dicoumarol: is a drug related to coumarin. It is formed from two coumarin units and the linkage may occur in a no. of ways.

It was isolated from crude leaves and flowering tops of Mililotus officinalis family Lamiaceae.



Bicoumarins

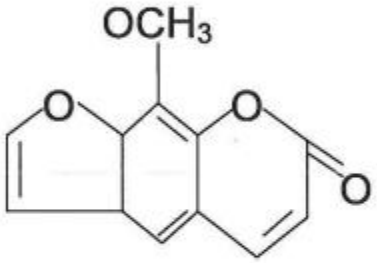
Natural dicoumarol and synthetic derivatives has been used as an oral blood anticoagulant in the treatment of thrombosis. These compounds (drugs) has been replaced by salts of warfarin which is synthetic drug obtained from the natural product. An overdose of warfarin may be countered by injection of vitamin K.



Warfarin

Psoralens: are photosensitizing Furanocoumarins that occur in a no. of plant families including Apiaceae (Umbelliferae) and Rutaceae, where they are a common cause of phototoxicity. The most common examples of Psoralens are: bergapten, and xanthotoxin. Plants containing Psoralens have been used internally and externally to promote skin pigmentation and skin-tanning, Psoralen compounds absorb in the ultra violet and allow this radiation to stimulate formation of melanin pigments.

Methoxsalen, 8-methoxypsoralen, or xanthotoxin, a constituent of the fruits of Ammi majus family Umbelliferae (Apiaceae) is used medicinally to facilitate skin repigmentation in idiopathic vitiligo (leukoderma) and for symptomatic control of serve psoriasis.



Methoxsalen or xanthotoxin

Methoxsalen may be applied topically or taken orally. Therapeutic use requires cautious patient exposure to UV radiation (sunlight) to minimize the risk of skin cancer.

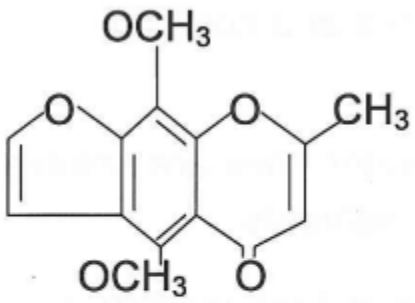
Parsley (Petroselinum crispum family Umbelliferae), and Ruta graveolens, family Rutaceae contain Psoralens such as bergapten and xanthotoxin.

Khellin and Visnagin

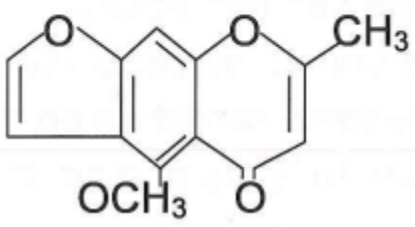
Are furanochromones found in the fruits of Ammi visnaga, family Umbelliferae (Apiaceae).

Khellin is the most important constituents (2%) of the plant. It is 2-mehtyl-5, 8-dimethoxy-furanochromone, Visnagin (0.1%) and Khellol glucoside (0.3%). The plant grows in Mediterranean countries, and has been used as antispasmodic and anti-asthmatic agent, also for urethral spasm and renal colic.

Khellin is a potent coronary vasodilator and bronchodilator is the treatment of coronary insufficiency, angina pectoris and bronchial asthma.



Khellin



Visnagin

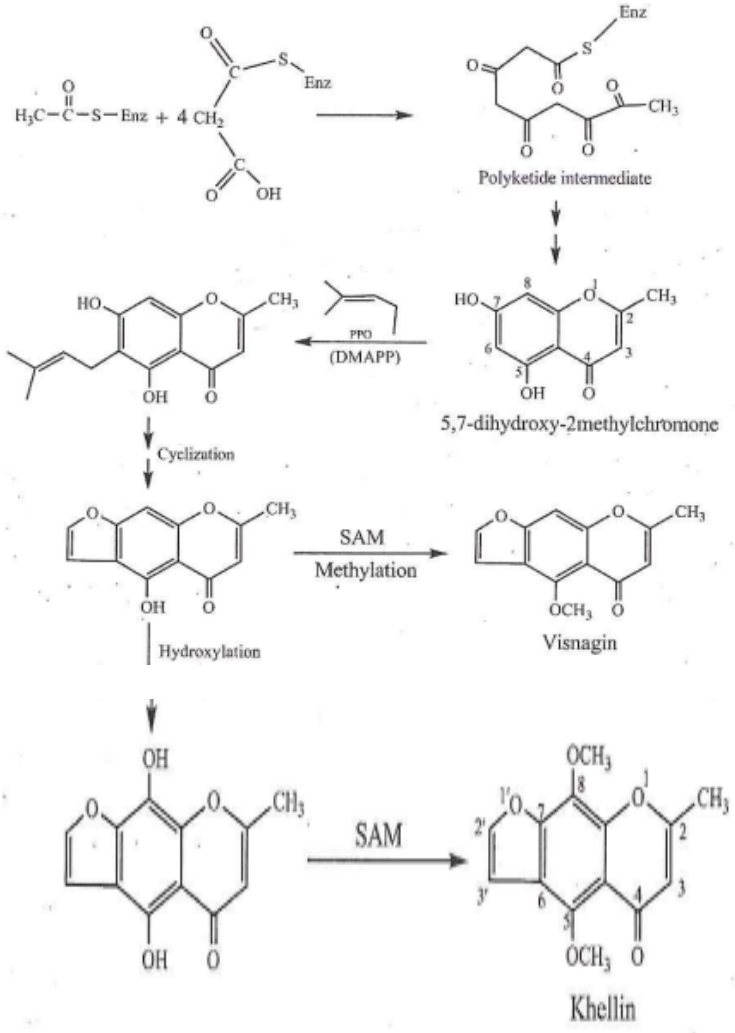
Natural products derived from the acetate (polyketide) pathway .

Anthraquinone Glycosides:

A number of glycosides with aglycones related to anthracene are present in such drugs as Cascara , Aloe , Rhubarb and Senna . These drugs contain natural products (anthraquinone glycosides) used as cathartics. Biosynthesis studies have shown that these products are derived from the acetate (polyketide) pathway by head-to-tail condensation of 8 acetate / malonate units. The polyketide chain produced gives rise to the various oxygenated aromatic compounds such as emodin , aloe-emodin , rhein , …..etc (see page .

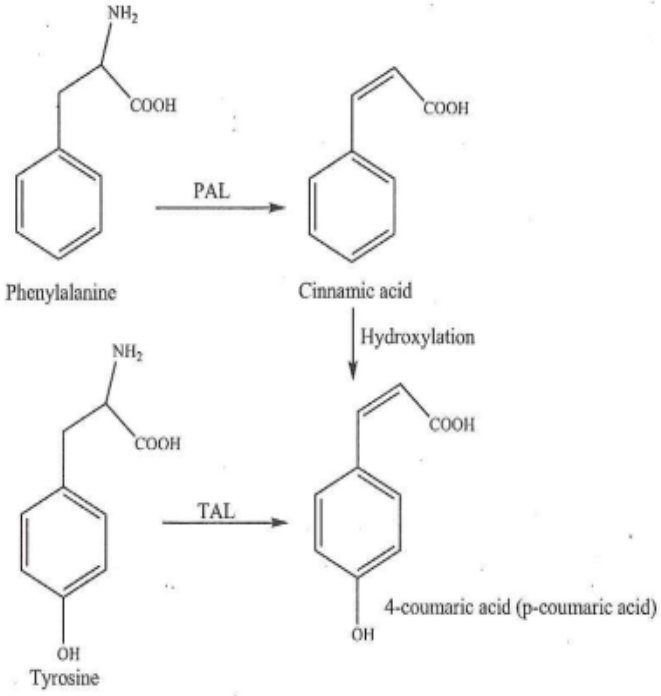
Chromones and furanochromones:

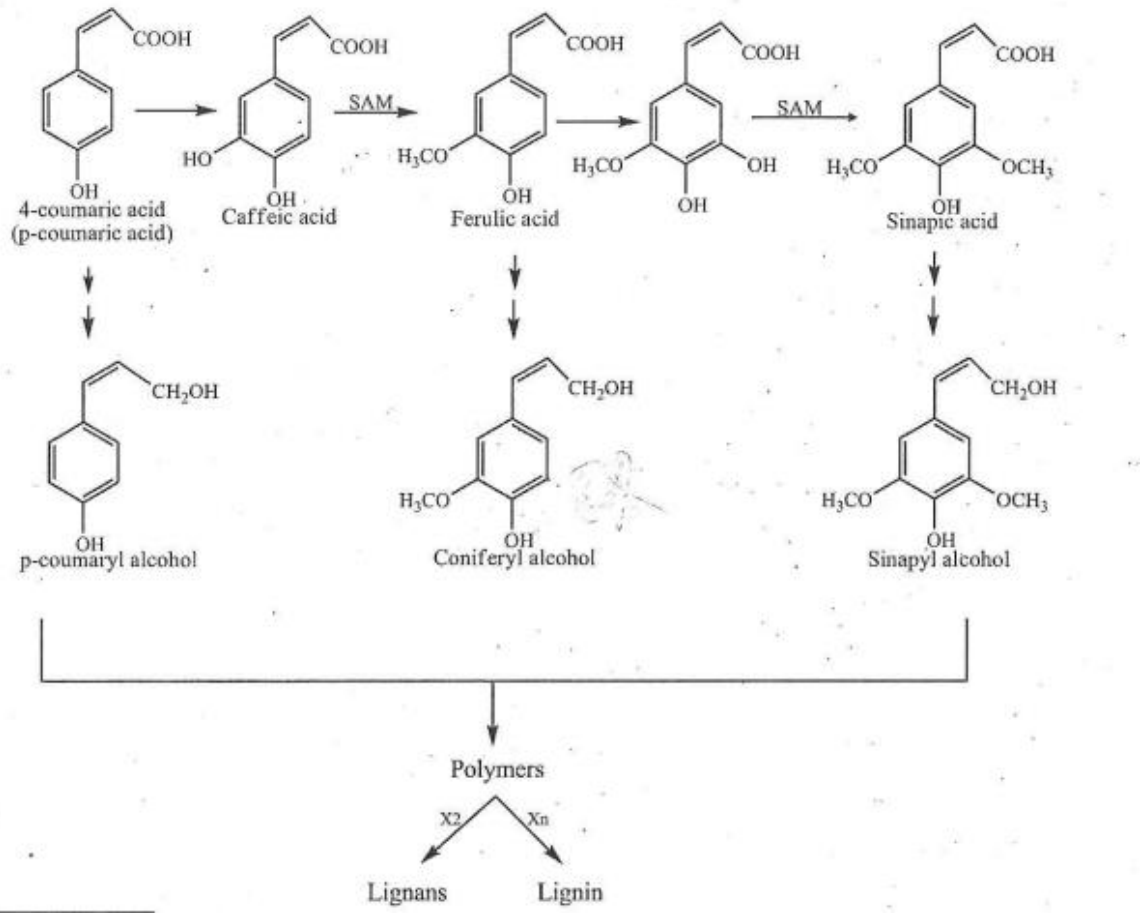
Khellin and visnagin are furanochromones found in the fruits of *Ammi visnaga* family umbelliferae, Apiaceae, and the active principles of a crude plants drug which has a long history of use as antispasmodic, antiasthmatic agent, and for the treatment of ***Angina Pectorise***[1]. These compounds are biosynthetically derived from the acetate pathways as shown in the following diagram. Other natural products such as *tetracyclines*, erythromycins, *graiseofulvin* and other ***marcolides***[2] are also derived from the acetate pathway. They are all antibiotics produced by microorganisms (fungi), i.e. they are not phytochemical compounds.



:: Natural product derived from the Shikimate pathway ::

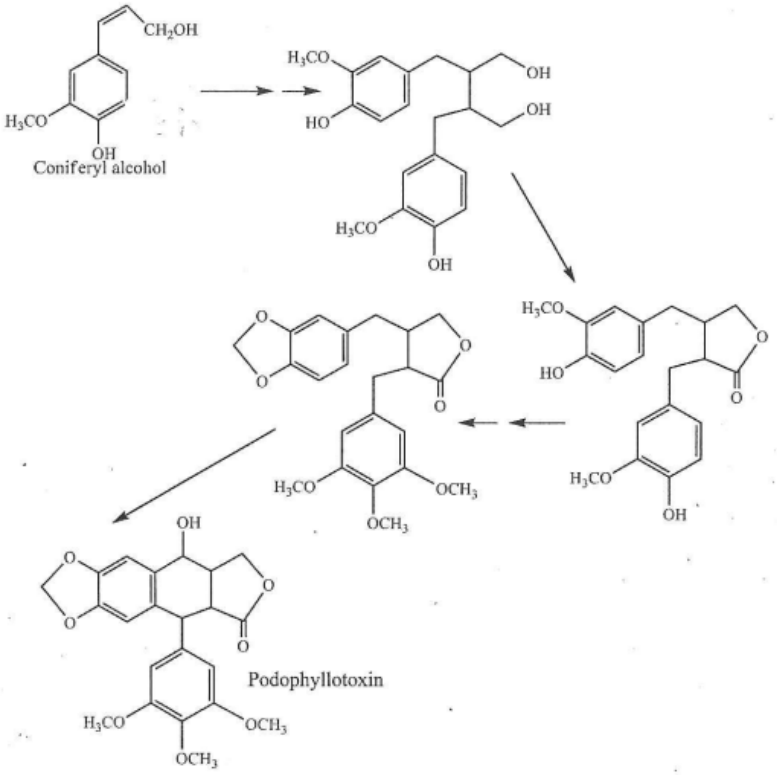
Phenylalanine[1] and *Tyrosine*[2], as C_6C_3 building blocks are precursors for a wide range of natural products. In plants the first step is the elimination of ammonia from the side chain of phenylalanine to form Cinnamic acid, whereas Tyrosine gives 4-coumari acid (p-coumaric acid). All plants appear to have the ability to deaminate phenylalanine via the enzyme phenylalanine ammonia lyase (PAL). Tyrosine is deaminated by another enzyme called Tyrosine ammonia lyase (TAL). Other Cinnamic acids are obtained by further hydroxylation and methylation reactions, build up substitution patterns typical of Shikimate pathway metabolites. i.e. an ortho oxygenation pattern some of the more common natural cinnamic acid are shown at right.





The plant polymer, ***Liginin***[1] is a strengthening material for plant cell wall which acts as a matrix for cellulose. Lignans are formed by coupling (dimerization) of two ***Coniferyl alcohol***[2] molecules in which the two phenylpropane units are coupled at the central carbon of side chain.

Cyclization and other modification can lead to the formation of a wide range of Lignans of different structural types. One of the most important of the natural Lignans having useful biological activity is *Podophyllotoxin*[3] which is derived from Coniferyl alcohol as shown in the following pathway.



Podophyllotoxin and related Lignans are found in the root of *podophyllum* species family Berberidaceae and have clinically useful cytotoxic and anticancer activity, example the drugs Etoposide and teniposide.