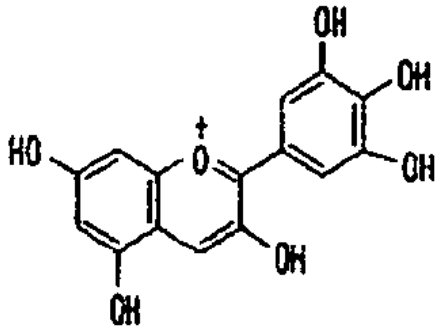
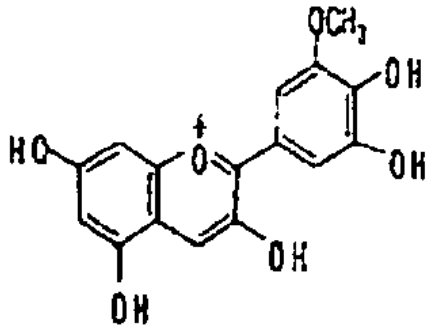
Anthocyanins

The term anthocyanin, initially coined to designate the substance responsible for the color of the cornflower (from the greek anthos=flower and kuanos=blue», applies to a group of water-soluble pigments responsible for the red, pink, mauve, purple,blue, or viole color of most flowers and fruits. These pigments occur as glycosides (the anthocyanins), and their aglycons (the anthocyanidines) are derived from the 2-phenylbenzopyrlium, a cation,more commonly referred to as the flavylium cation, a name that emphasizes the fact that these molecules belong to the vast group of flavonoids in the broad sense of the term.

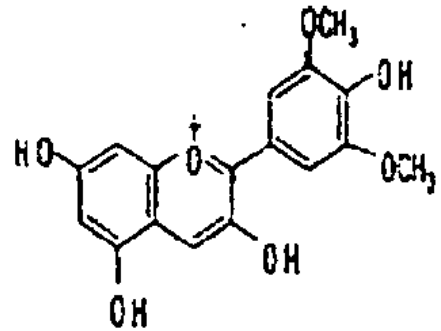
Anthocyanins, whose vivid colors attact insectsand birds, play a major role in pollination and seed dispersal. A high coloring power and the absence of toxicity lend to these natural coloring glycosides the potential to replace synthetic colors in food technology. The drugs containing anthocyanins are used for the extraction of anthocyanins for the preparation of galenicals designed to treat the symptoms linked to capillary and venous fragility.



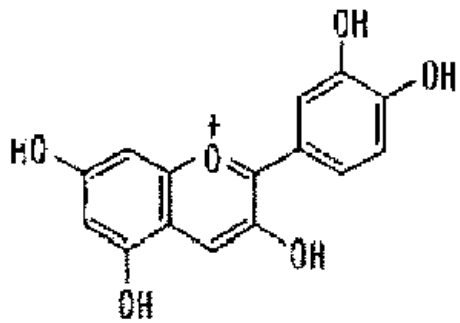
Delphinidin



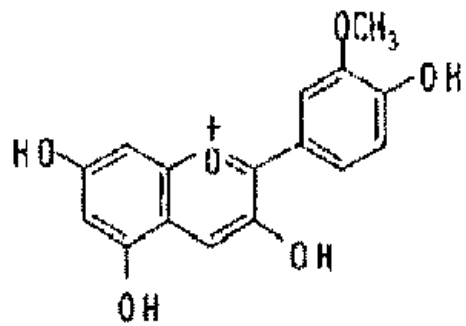
Petunidin



Malvidin

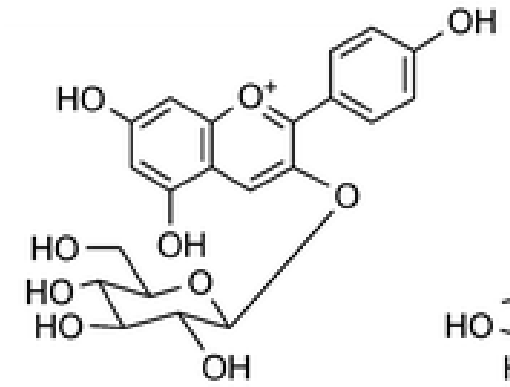


Cyanidin

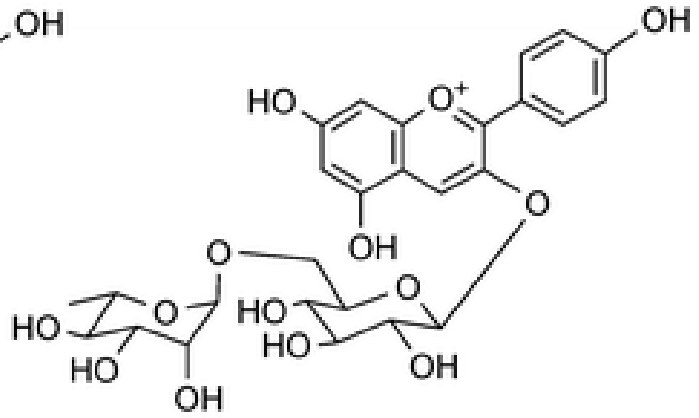


Peonidin

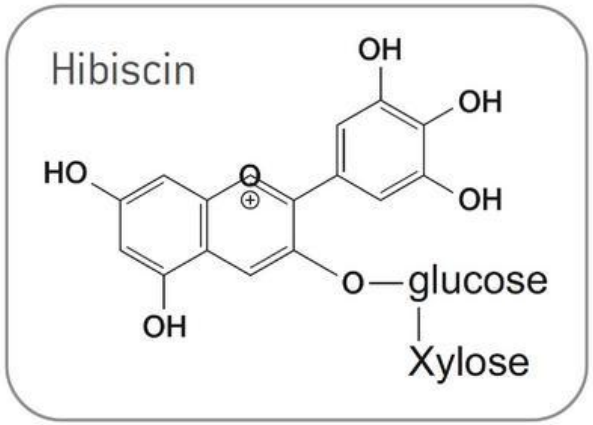
Structures of the chief anthocyanidins

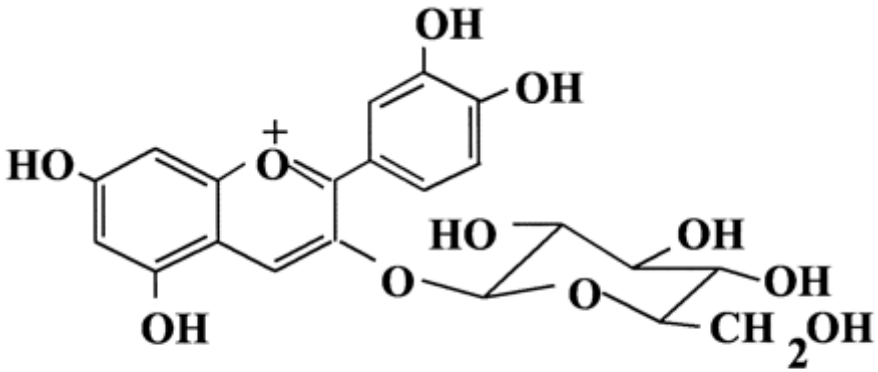


Pelargonidin-3-*O*-glucoside (



Pelargonidin-3-*O*-rutinoside

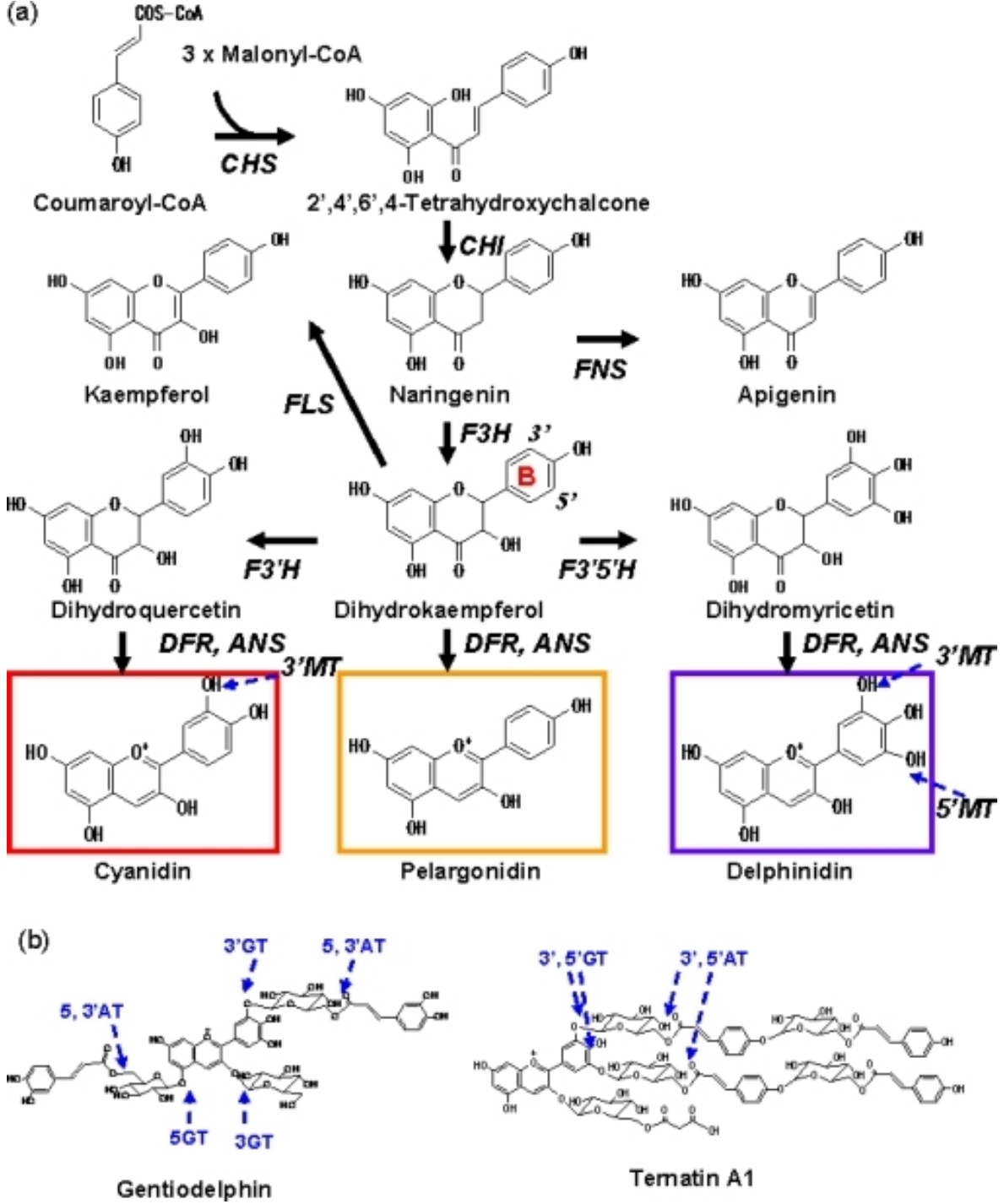




Cyanidin 3-*O*-β-D-glucoside

Structures of some anthocyanins

Biosynthetic pathway of anthocyanins



EXTRACTION AND CHARACTERIZATION

Anthocyanins are soluble in water and alcohols, insoluble in apolar organic solvents, and unstable in neutral or alkaline medium. They are generally extracted with an alcohol (methanol, preferrably ethanol if the product is intended for use in food) in the presence of a small amount (0.1-1%) of hydrochloric acid. Anthocyanin solutions are very unstable, and they can only be kept under nitrogen, at low temperature, and in the dark.

PHARMACOLOGICAL ACTIVITY AND USES

As in the case of flavonoids in the strict sense of the term, biological tests on based on the diffusion of dyes indicate that anthocyanins decrease capillary permeability and fragility. properties have been shown : antiedema activity and increase in regeneration of «visual purple» or rhodopsin. Like many other phenolic compounds, anthocyanin pigmwnts act like radical scavengers in vitro (antioxidant activity). These actons on capillaries and veins lead to the use of anthocyanins-containing drugs and the preparations based on them, for the symptomatic treatment of venous and lymphatic insuffiency and capillary fragility. Anthocyanins are also promoted in ophtalmology to treat circulatory disorders of the retina or choroid, and to improve vision at dusk.

Myrtilli fructus **bilberry, blueberry** **ligarba, mavi yemiş**

Vaccinium myrtillus **Ericaceae**

The bilberry (or blueberry), well-known for its tasty fruits, is used by the pharmacutical industry for the extraction of anthocyanins. The leaf and the dried fruit are used in phytotherapy.

Chemical Composition : Blueberries are rich in water (up to 90%), sugars, and organic acids. Phenolic acids, flavonoids(hyperin, quercitrin), proanthocyanidins (procyanidins B-1, and B-4), and monomeric flavan-3-ols (catechin and epicatechin) have been identified. The anthocyanin level in the fresh fruits is about 0.5%. These glycosides, about fifteen of them are C-3 O-glucosides, O-galactosides, and O-arabinosides of cyanidin, peonidin, delphinidin, malvidin, and petunidin.

The leaf is rich in flavonoids, phenolic acids, proanthocyanidins, and catechin.

Pharmacological Activity : Bilberry anthocyanins have, in animals, a vascular protective and antiedemic activity by the oral, as well as IP or IV route. They inhibit collagen induced platelet aggregation, and stimulate the prostacyclin activity of the vascular walls. In humans they are used for the treatment of vascular disorders (venous disorders, capillary disorders secondary to diabetes, ecchymoses, purpura and gingival hemorrhage). **Anthocyanins have also been tested for the treatment of retinopathies of hypertensive or diabetic origin.** The bilberry leaf (Myrtilli folium)is reputed to lower glycemia. In the diabetic rat, the hydroalcoholic extract of bilberry is hypolipidemic.

Uses: The pharmaceutical industry produces and markets a water-soluble bilberry powder titrated to contain 70% anthocyanins. The first step in the manifacturing process is the biological elimination of sugars by *Saccharomyces* spec.; the medium recovered from fermentors is clarified by on-line centrifugation and concentrated under vacuum at low temperature. The purification of this crude extract entails repeated treatment with boiling ethanol. Upon cooling of the ethanol solution, the insoluble anthocyanins precipitate and are recovered by centrifugation (the free anthocyanidins, organic acids, and other impurities remain in solution).

Extracts obtained form the bilberry fruits and enriched in anthocyanins are ingredients of drugs used to treat the functional symptoms of venous and lymphatic vessel insuffiency and cutaneous capillary fragility.

Vaccinii macrocarpi fructus **cranberry** **kranberi**

Vaccinium macrocarpon **Ericaceae**

Cranberry grows wild in eastern North America, from Carolinas to Canada. Cultivated in the United States since begining of the nineteenth century, it produces small dark red fruits, widely consumed as such (fresh or frozen) and as cranberry juice (pure or as a coctail sweetened with corn syrup), cranberry sauce, et so on. The fresh fruit is very rich in acids (citirc, quinic, benzoic): it also contains anthocyanins (3-O-galactosides and 3-O-arabinosides of cyanidin and peonidin), catechin, and flavonoids.

The beneficial-bacteriostatic-effect of cranberry juice in the treatment of urinary infections is confirmed by secular use; it was first attributed to urine acidification by the fruit acids and their metabolites. In the last years cranberry is also tested for breast cancer.

Ribes nigri fructus **black currant** **frenk üzümü**

Ribes nigrum **Grossulariaceae**

The durg is rich in sugars, organic acids, contains also flavonoids, and anthocyanidins (cyanidin and delphinidin glycosides). The fruit is used to prepare extracts enriched in anthocyanins; these extracts, and the proprietary drugs that contain them, have therapeutic indications identical to those of bilberry.

Vitis viniferae folium **vine** **asma (üzüm) yaprağı**

Vitis vinifera **Vitaceae**

The term «vine» designates cultivars with black grapes, red pulp, and leaves that turn red in the fall. The color of the vine leaves is of course linked to a high anthocyanin concentration, which varies as a function of time: it is maximal when the fruits are mature, and can reach, in some cultivars 0.3% of the dry weight. The chief constituents are 3-O-glycosides of cyanidin and peonidin. They ocur together with flavonoids, organic acids, proanthocyanidins, and hydrolyzable tannins.

Vine leaf-besed pharmaceuticals are traditionally used (orally and topically) to treat the functional symptoms of capilary fragility such as ecchymosis and petechiae, the subjective symptoms of venous insuffiency such as fullness in the legs, and the sypmtoms of hemorrhoids. Topically, they are traditionally used for eye irritation or discomfort of various etiologics (smoky athmospheres, eye strain etc.).

Sambuci fructus **elder** **mürver**

Sambucus nigra **Caprifoliaceae**

The berries contain anthocyanidin glycosides (especially cyanidin glycosides), and also flavonoids and organic acids. The drug is traditionally used orally to enhance the urinary and digestive elimination functions, as an adjunct in weight loss praograms, and to enhance the renal eimination of water. It is used in Germany for colds and coughs, because of its effect, an increase elimination elimination in bronchial secretions.

The flowers of *Sambucus nigra* (sambuci flos) are also used for medicinal purposes,for the same as the fruits, which are rich in flavonoids and organic acids.

Tannins

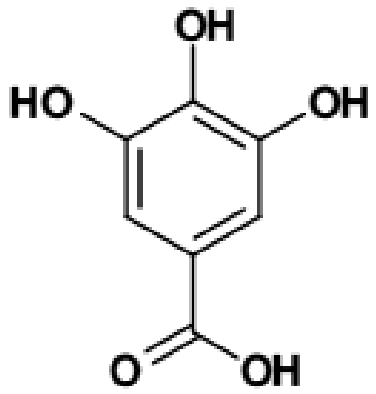
Prof. Dr. Ali Hikmet Meriçli

Historically, the importance of tannin-containing drugs is linked to their tanning properties, in other words their ability to transform fresh hides into an imputrescible material : leather. The consequence of tanning is the formation of bonds between the collagen fibers in the hide, which imparts resistance to water, heat, and abrasion. This capability of tannins to combine with macromolecules explains why they precipitate cellulose, pectins, and proteins; it also explains their characteristic astringency and tartness; by precipitating the glycoproteins contained in saliva, tannins make the latter lose its lubricating power. These properties are the basis of the classic difinition of tannins : «water soluble phenolics of molecular weight between 500 and 3000, which, in addition to displaying the classic reactions of phenols, can precipitate alkaloids, gelatin, and other proteins».

CLASSIFICATION OF TANNINS

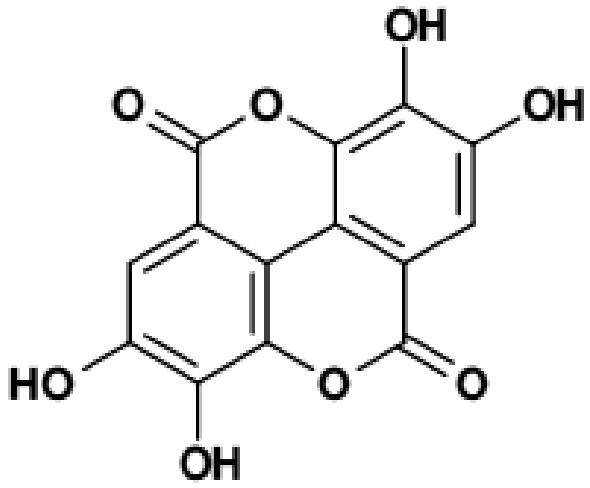
In higher plants, two groups of tannins are generally distinguished, which differ by their structure, as well as their biogenetic origin : hydrolyzable tannins and condensed tannins.

Hydrolyzable tannins : **Hydrolyzable tannins are esters of a sugar (or related polyol) and of a variable number of phenolic acid molecules. The sugar is most generally glucose. The phenolic acid is either gallic acid, in the case of gallotannins, or else hexahydroxydiphenic acid (=HHDP) and its oxidized derivatives(dehydrohexahydroxydiphenic acid (DHHDP); chebulic acid, in the case of the tannins conventionally referred to as ellagitannins.**

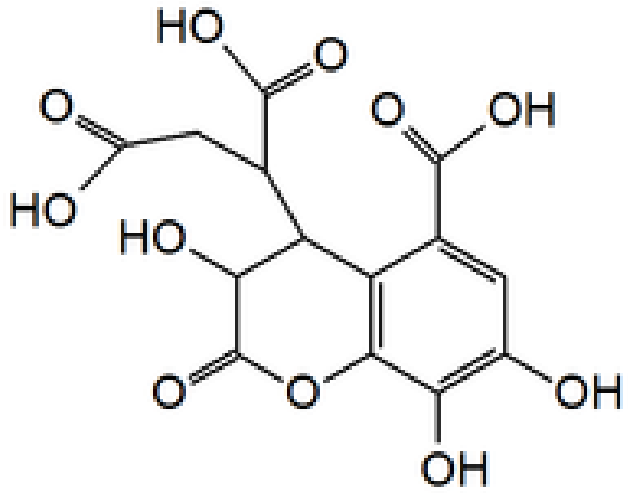


Gallic Acid

3,4,5-TriHydroxyBenzoic Acid

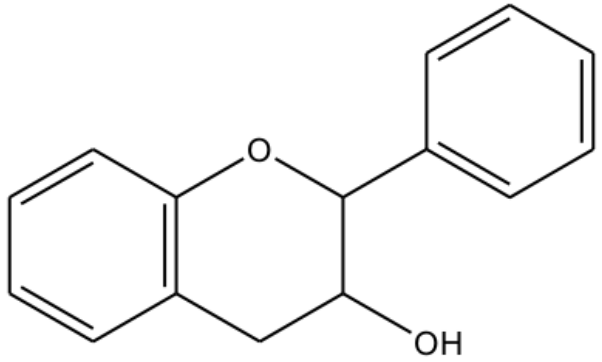


Ellagic Acid

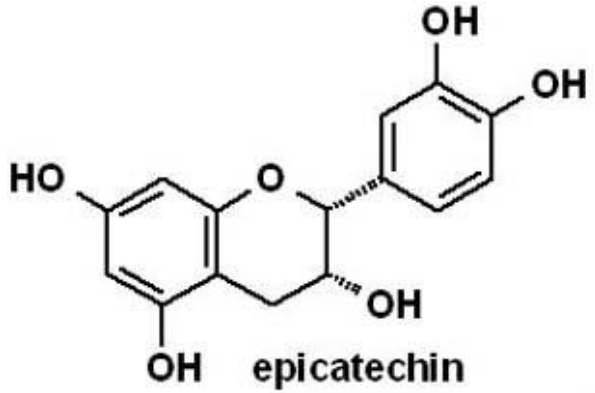


Chebulic acid

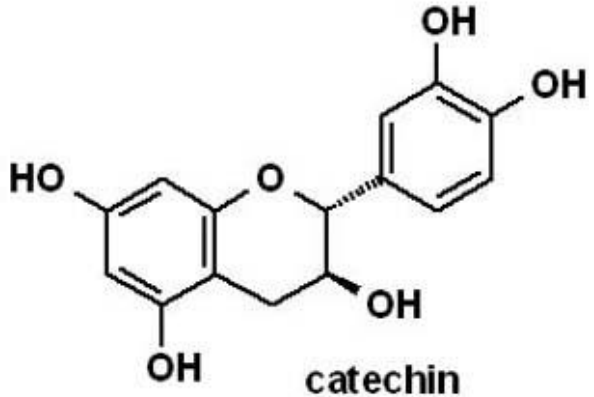
Condensed tannins : Condensed tannins or proanthocyanidins are polymeric flavans. They consist of flavan-3-ol units linked together by carbon-carbon bonds, most often 4→8 or 4 →6, which result generally a flavan-3-ol.



flavan 3-ol

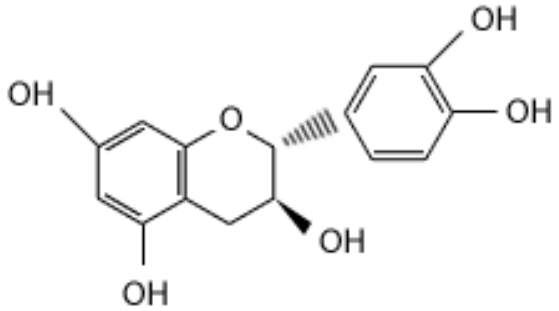


epicatechin

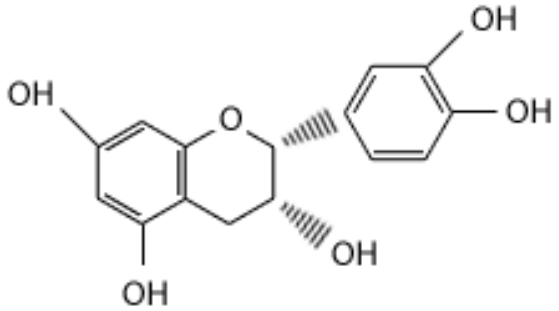


catechin

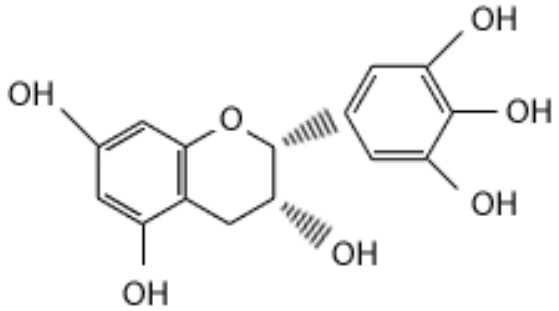
Flavan-3-ols



(+)-Catechin



(-)-Epicatechin



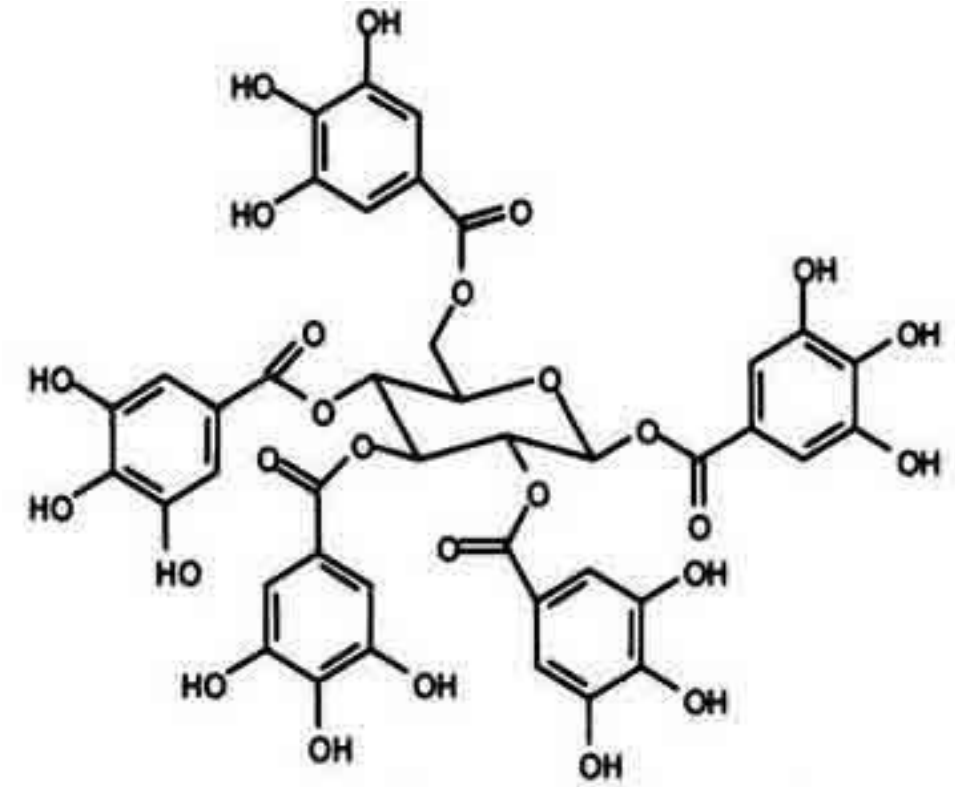
(-)-Epigallocatechin

STRUCTURES OF HYDROLYZABLE TANNINS

In general, gallotannins are sters of gallic acid and glucose. However, mono and digalloyl glucoses are devoid of the classic properties of tannins, because their molecular weight is too low. These properties, particularly the ability to precipitate proteins, are only true for triesters and their homologs. Biogenetically, gallic acid (=3,4,5,-trihydroxybenzoic acid) arises from the metabolism of shikimic acid.

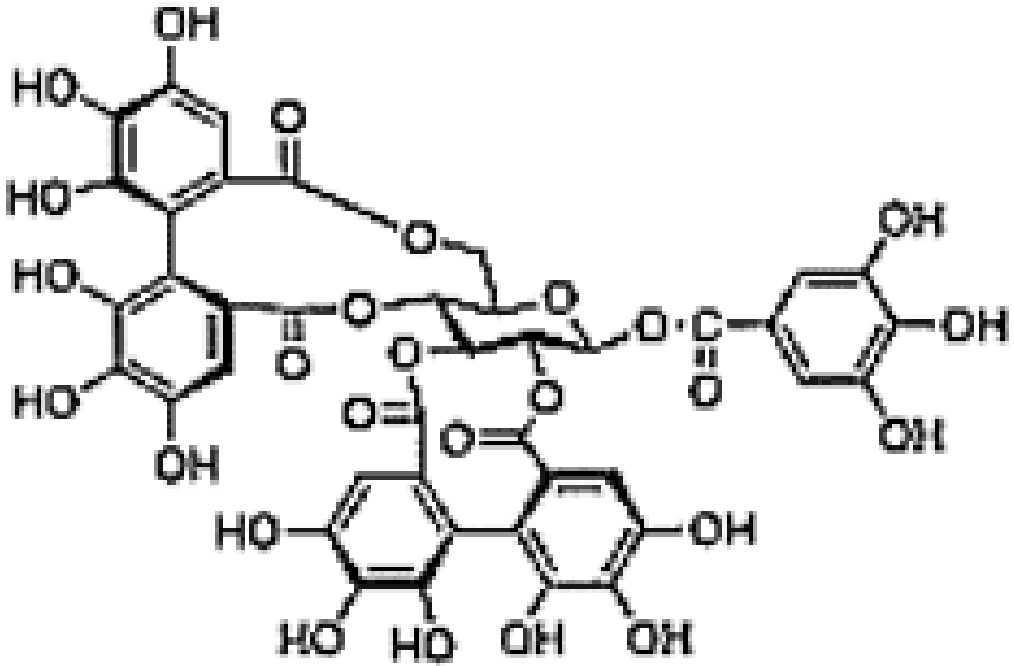
A.MONOMERIC HYDROLIZABLE TANNINS

The pentaester (1,2,3,4,6-penta-O-galloyl-β-D-glucose) is the most common tannin, it plays a central role in the metabolism of tannins because most plants can metabolize it.

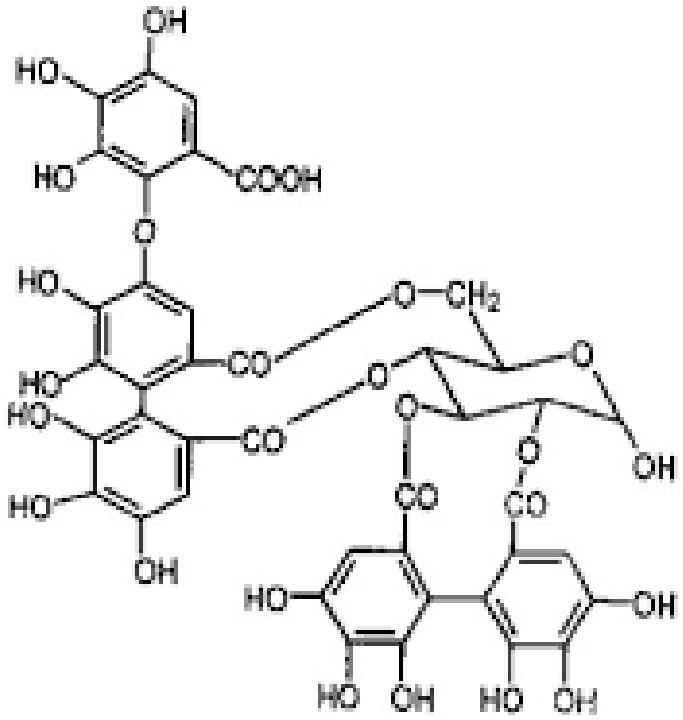


Penta-1, 2, 3, 4, 6-O-galloyl-beta-D-glucose (PGG)

Examples of structures of hydrolyzable tannins



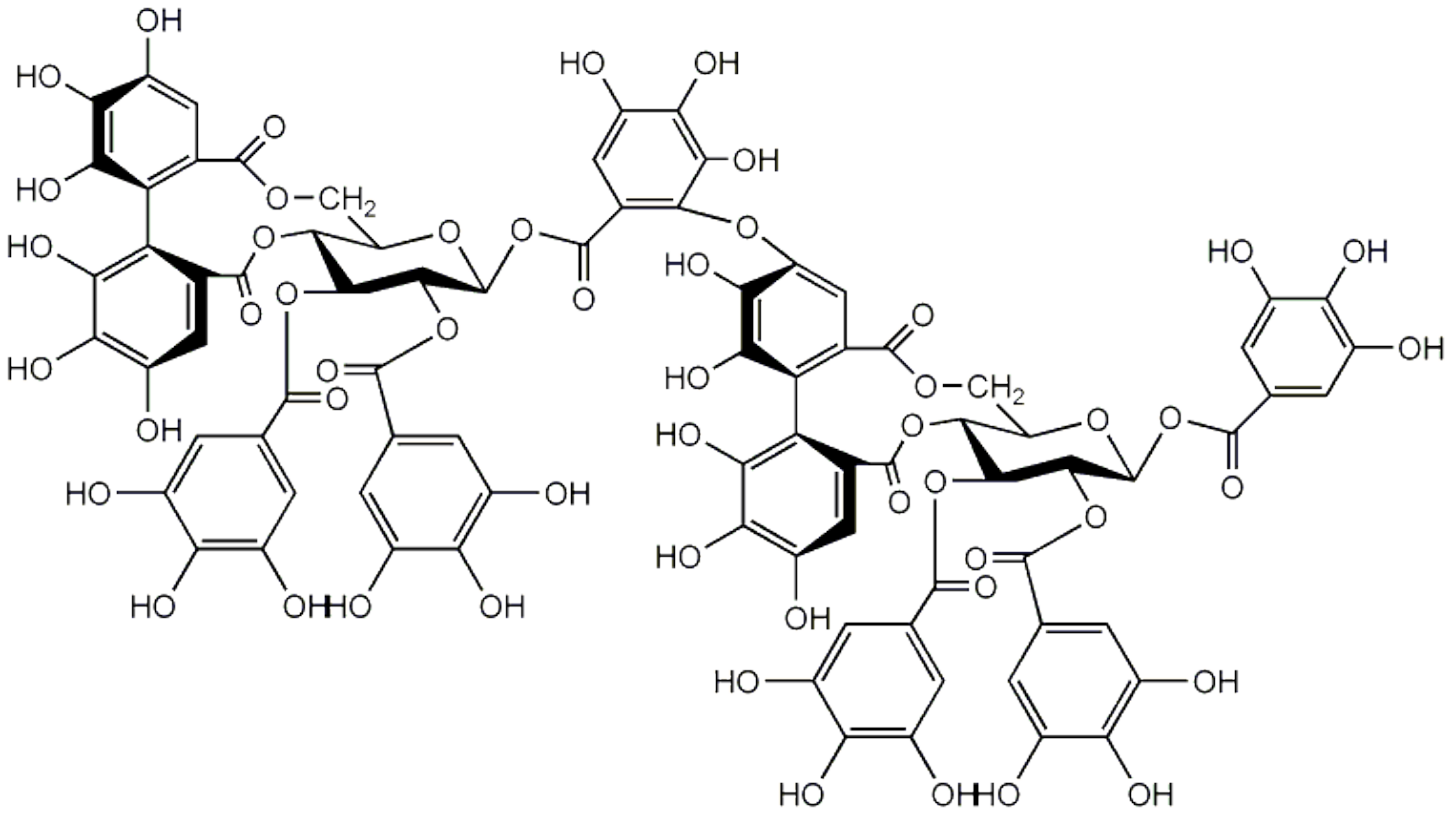
Pedunculagin



Praecoxin

B. OLIGOMERIC HYDROLYZABLE TANNINS

Intermolecular oxidative coupling (C-C or C-O-C) explains the existence of a large number of oligomeric ellagitannins of molecular weight between 2000 and 5000. Thus rugosin D, isolated from *Filipendula ulmaria* and from other Rosaceae, has a molecular weight of 1874.

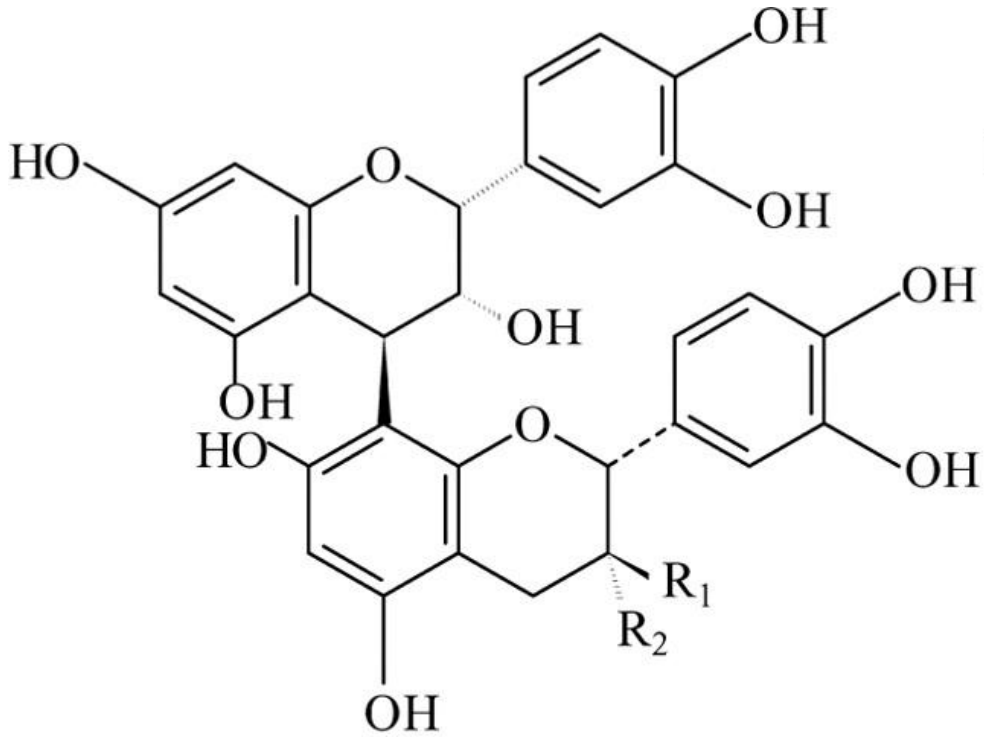


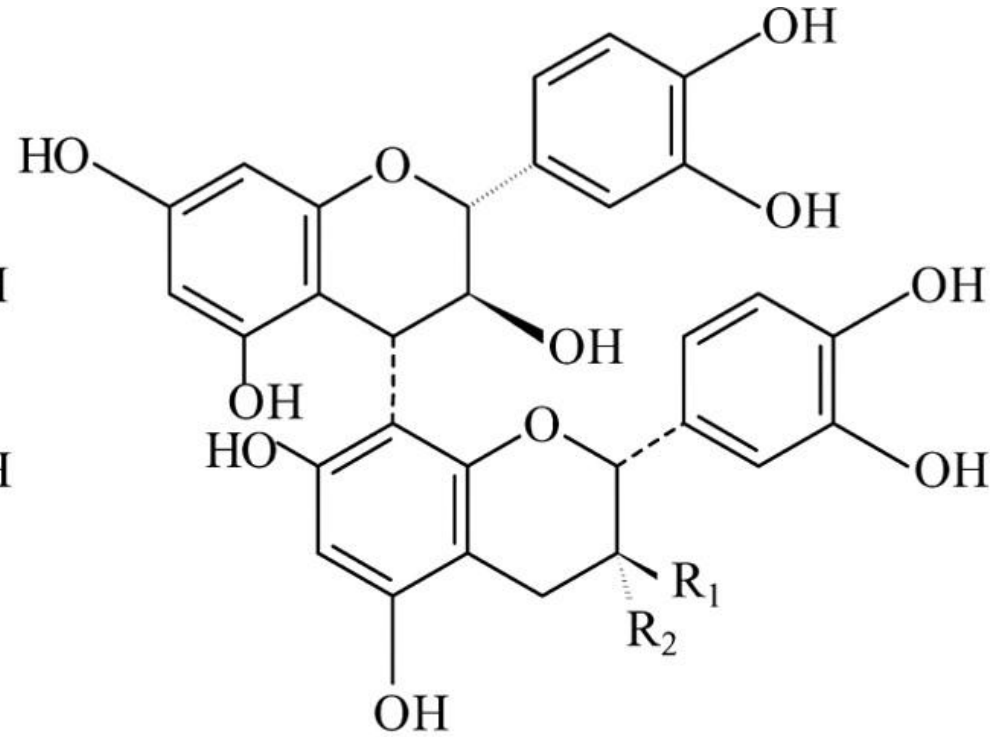
STRUCTURES OF CONDANSED TANNINS (PROANTHOCYANIDINS)

The proposed proanthocyanidin nomenclature was initially based on the name of the anthocyanidin that is formed when the polymer is treated with an acid at high temperature : procyanidin, prodelphinidin, or propelargonidin. The basic structural element of these polymers is a flavan-3-ol: especially catechin and epicatechin (3,5,7,3’,4’-pentahydroxylated, constituents of procyanidins) and gallocatechin and epigallocatechin (3,5,7,3’,4’,5’-hexahydroxylated, constituents of prodelphinidins).

Biogenetically, these flavan-3-ols arise from the metabolism of **flavonoids**. They are formed by the 3-hydroxylation of a **flavanone**. Chemically the formation of oligomers and polymers involves flavan-3,4-diols: these molecules, highly reactive because of the benzylic character of their 4-hydroxyl group, readily form a carbocation which immediately reacts, either with the nucleophilic C-8 or C-6 of a flavan-3-ol. The repetition of this mechanism leads to oligomers and polymers.

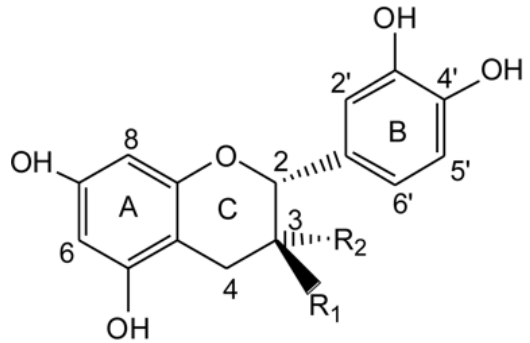
Type B proanthocyanidins : The simplest dimers are procyanidins B-1, B-2, B-3 and B-4, in other words proanthocyanidins consisting of two units catechin-epicatechin, or one of two units with a 4→8 linkage in an α (B-3 and B-4) or β (B-1 and B-2) configuration. These procyanidins ocur in the free state, and widely distributed.

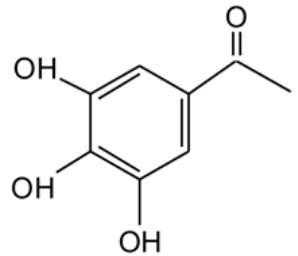




	R_1	**R_2**
Procyanidin B1	OH	H
Procyanidin B2	H	OH
Procyanidin B3	OH	H
Procyanidin B4	H	OH

Type A proanthocyanidins : Another important group of procyanidins consist of dimers with a double interflavonoid linkage: C-4→C-8 and
C-2 →O →C-7. the best known are aesculitannins, which are procyanidins from the seminal tegument of the horse chestnut (*Aesculus hippocastanum*); they are also found in the bark of cassia cinnamon (*Cinnamomum cassia*).





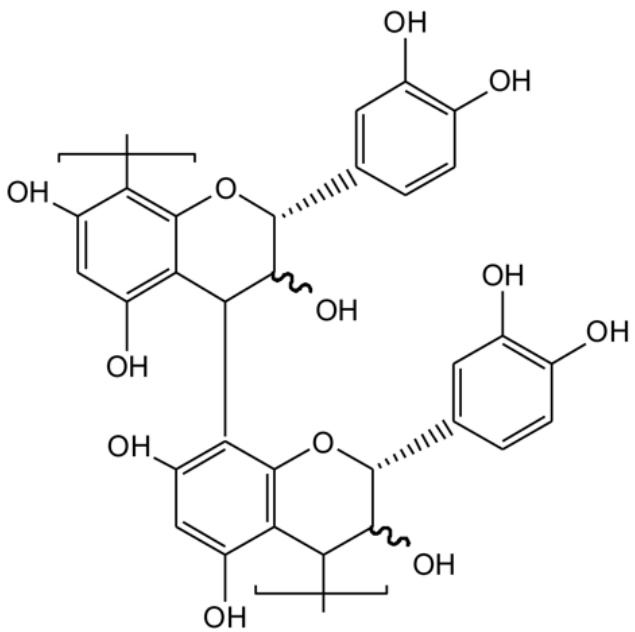
G: Galloyl group

R_1 = OH, R_2 = H, Catechin

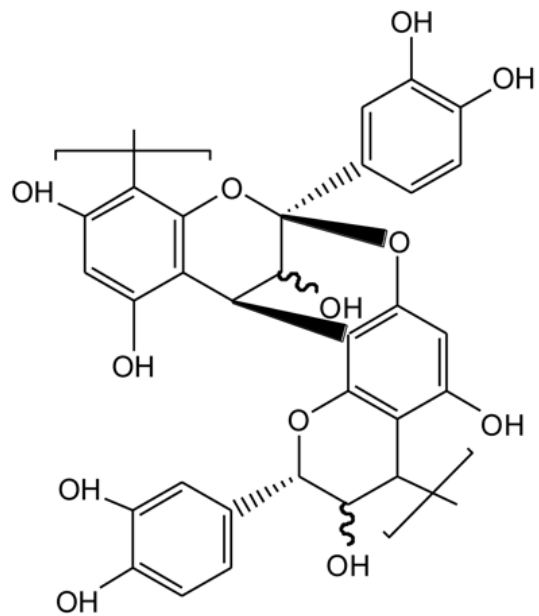
R_1 = H, R_2 = OH, Epicatechin

R_1 = OG, R_2 = H, Catechin gallate

R_1 = H, R_2 = OG, Epicatechin gallate



B-type linkage



A-type linkage

PHYSICO-CHEMICAL PROPERTIES, EXTRACTION, CHARACTERIZATION, AND QUANTITATION

A. Properties

Tannins dissolve in water to form colloidal solutions, but their solubility varies with their degree of polymerization. They are soluble in alcohols and acetone. The stability of the aqueous solutions varies with the structure, and is generally moderate. Like all phenols tannins react with ferric chloride. Heavy metal salts and gelatin make them precipitate out of aqueous solutions. Hydrolizable and condensed tannins may be distinguished based on their behavior in acidic medium at high temperature.

Hydrolizable tannins are polyesters of glucose, and upon hydrolysis, they release the sugar, and either gallic acid, hexahydroxydiphenic acid, or both. The latter acid rapidly lactonizes to ellagic acid (which explains the traditional terminology of ellagitannins).

Condensed tannins, under same experimental conditions, will see their interflavonoid bond cleaved, and in the presence of air, the carbocation that is formed leads to an anthocyanidin.

B. Extraction

Tannins are generally extracted with a water and acetone mixture (methanol is to be avoided because it causes the methanolysis of galloyl depsides). After eliminating the acetone by distillation, the pigments and lipids are removed from the aqueous solution by a solvent extraction (e.g., with dichloromethan). Next, an ethyl acetate extraction of the aqueous solution separates the dimeric proanthocyanidins and most gallotannins. The polymeric proanthocyanidins and high molecular weight gallotannins remain in the aqueous phase. To obtain pure compounds, the appropriate chromatographic techniques are used.

C. Characterization

With ferric salts, gallotannins and ellagitannins give **bluish-black** colors and precipitates, and condensed tannins give **greenish-brown** precipitates.

Gallotannins give a pink color with potassium iodate (whereas free gallic acid gives an orange color with this reagent). Ellagitannins are colored by nitrous acid in the presence of acetic acid (pink at first, the color turns purple, then blue), and condensed tannins turn red with vanillin and hydrochloric acid.

D. Quantitation

Quantitation methods involving protein precipitation

- One of the most frequently methods is the hemolyzed blood method. It is based on the fact that tannins form a combination with hemoglobin, and that the residual , non-precipitated hemoglobin can be estimated colorimetrically against a blank in a part of the spectrum where interferences are unlikely.
- There is closely related method in which the hemoglobin is replaced with bovine serum albümin.
- The traditional method using hide powder is also based on the fact that tannins react with proteins.

Quantitation of condensed tannins: Proanthocyanidins can be quantitated by measuring the color (absorbance) obtained upon conversion to anthocyanidins by boiling in n-butanol in the presence of hydrochloric acid. Proanthocyanidins can also be quantitated as vanillin addition products in methanol in the presence of hydochloric acid.

Quantitation of hydrolizable tannins: Gallotannins can be hydrolized in the presence of sulfuric acid; following the reaction of the resulting gallic acid with rhodamine, the absorbance of the product can be measured.

Total phenol quantitation: The general methods for total phenol quantitation are sometimes used, in conjunction with the hide powder precipitation technique, to measure the total tannins in a drug.

BIOLOGICAL PROPERTIES OF TANNINS

Most of the biological properties of tannins are linked to their ability to form complexes with macromolecules, particularly with proteins.

Therapeutic activities due to the astringency : The applications of tannin-containing drugs are limited, and result from their affinity for proteins. **Externally**, the waterproof of the external layers of the skin and the mucosas, thus protecting the underlying layers; they also have a vasoconstrictor effect on small superficial vessels. By limiting fluid losses, and by preventing external aggressions, tannins enhance tissue regeneration in case of superficial wound or burn. **Internally**, they are undoubtedly **antidiarrheals**. Regardless of the route of administration, these molecules have clearly demonstrated antiseptic effects (antibacterial and antifungal), which are of interest in the treatment of infectious diarrheas and dermatitis.

Antioxidant activity: Many tannins, especially hydrolizable tannins, inhibit the lipid peroxidation induced by ADP and ascorbic acid. Antioxidant flavanols and proanthocyanidins from grape juice and wine are widely considered to be the main principles responsible for the preventive effect on cardiovascular disease of a moderate and regular intake of red wine.

Enzymatic inhibition: Generally speaking, tannins are enzyme inhibitors, they block 5-lipoxygenase.

Other activities: A few ellagitannins counteract the mutagenicity of certain carcinogens. Procyanidin dimers, considered responsible for the positive inotropic and coronary vasodilator activities of the flowering tops of hawthornsimilar to those of flavonoids.

Toxicity: The potential toxicity of tannins to humans is not very well known.

Gall	**Gallae**	**Quercinae**	**Meşe mazısı**
***Quercus* infectoria**		**Fagaceae**	

Official tannin can be prepared from the nutgalls of an oak found on the eastern side of the Mediterranean rim including Turkey and Cyprus (*Quercus infectoria*). The formation of the galls is a consequence of the deposition of the eggs of hymenoptereus insects (*Cynips*) in the oak tissues: the developing larva induces cellular proliferation in the host tissues. Galls contain hydrolizable tannins in high proportion (50-70%), free gallic and ellagic acids, sterols and triterpenes and starch. **Official tannin, also known as «tannic acid»,** is prepared by extracting the galls with an ether and alcohol mixture saturated with water, separating the phases, and evaporating the aqueous layer.

Tannin may be used externally as an astringent for burns and dermatitis; it is also a hemostatic agent. It is incompatible with many other products (e.g., ferric salts, oxidants, proteins, alkaloids, glycosides).

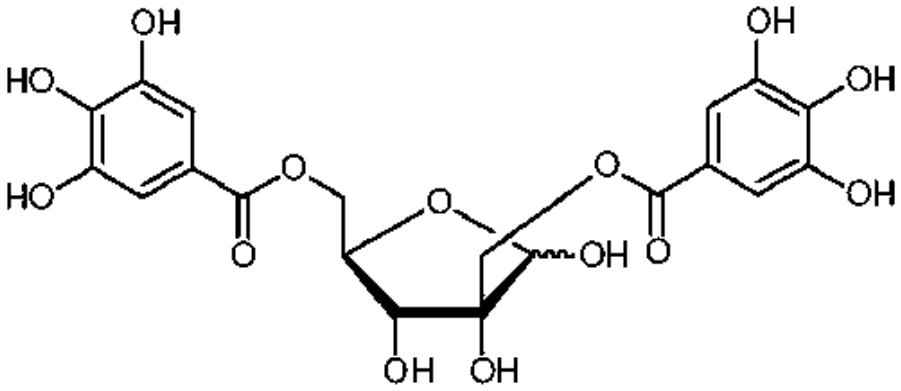
Oak bark = Querci cortex = Meşe kabuğu : The drug contains tannins in a wide range of concentrations (8-20%). In Germany Commission E recognizes astringent and virostatic properties for oak bark and specifies under uses : externally, for skin disorders (except in case of extensive damage); internally, for acute diarrhea; on the mucous membranes (throat, vagina) in case of moderate inflammation. There are no contraindications for internal use.

Hamamelidis folium **witch hazel** **cadı fındığı**

Hamamelis virginiana **Hamamelidaceae**

The drug is used for its astringent and vasoconstrictor properties. The stem bark (Hamamelidis cortex) is also used for the same properties, mostly in Germany.

Hamamelidis folium contains flavonol glucosides, and up to 10% tannins, gallic acid, polygalloylglucose, hamamelitannin and proanthocyanidins. The chief polyphenolic constituents of the leaves are procyanidins and procyanidin-prodelphinidin copolymers. The bark of the stems is also rich in tannins.



hamamelitannin

Pharmacological Properties : In vitro, Hamamelis extract is bacteriostatic and toxic to molluscs. It also has an inhibitory effect on human polynuclear leucocyte elastase.

Uses : Hamamelidis leaf based phytomedicines are traditionally used , orally, as well as locally, to treat the subjective symptoms of venous insufficiency such as fullness in the legs, and the symptoms of piles. The German Commission E monographs for the drugs (leaf and bark) list astringent, anti-inflammatory, and local hemostatic properties, and the uses are the same for both (phlebitis, hemorrhoids, skin disorders)

The drug is also used in cosmetic formulation as Hamamelis water or Distilled Witch Hasel Extract, and promoted as an astringent.

Ratanhiae radix **Rhatany** **Ratanya kökü**

Krameria lappacea* = *Krameria triandra **Krameriaceae**

The drug contains 10 to 15% condensed tannins. The hydroalkoholic extract is an antibacterial and can be used traditionally 1. for the symptomatic treatment of cutaneous capillary fragility, 2. for the subjective symptom of venous insufficiency, such as fullness in the legs. Locally, the drug may be used as a mouthwash for oral hygiene. In Germany, Commission E authorizes only one use for the decoction, namely the treatment of inflammations of the mucous membranes of the mouth and throat (gingivitis, stomatitis).

Agrimoniae flos, Agrimony, *Agrimonia eupatoria* Rosaceae
Alchemillae herba, Lady's mantle, *Alchemilla glabra* Rosaceae
Fragariae rhizoma, Strawberry, çilek, *Fragaria vesca* Rosaceae
Rosae gallicae flos, French rose, Kırmızı gül, *Rosa gallica* Rosaceae
Rubi fruticosi folium, Blackberry, böğürtlen, *Rubus fruticosus* Rosaceae
Corylli avelanae folium, Hazel, fındık, *Coryllus avellana*, Corylaceae

Agrimonia eupatoria *Alchemilla glabra* *Rosa gallica*

DIMERIC PROANTHOCYANIDIN-CONTAINING DRUGS

Crataegus sp. *Crataegus monogyna, C.laevigata* (*C. oxyacantha*)

Hawthorn Alıç Rosaceae

Crataegus monogyna

Crataegus laevigata

Drugs :

Crataegi flos

Crataegi folium

Crataegi folium cum floribus

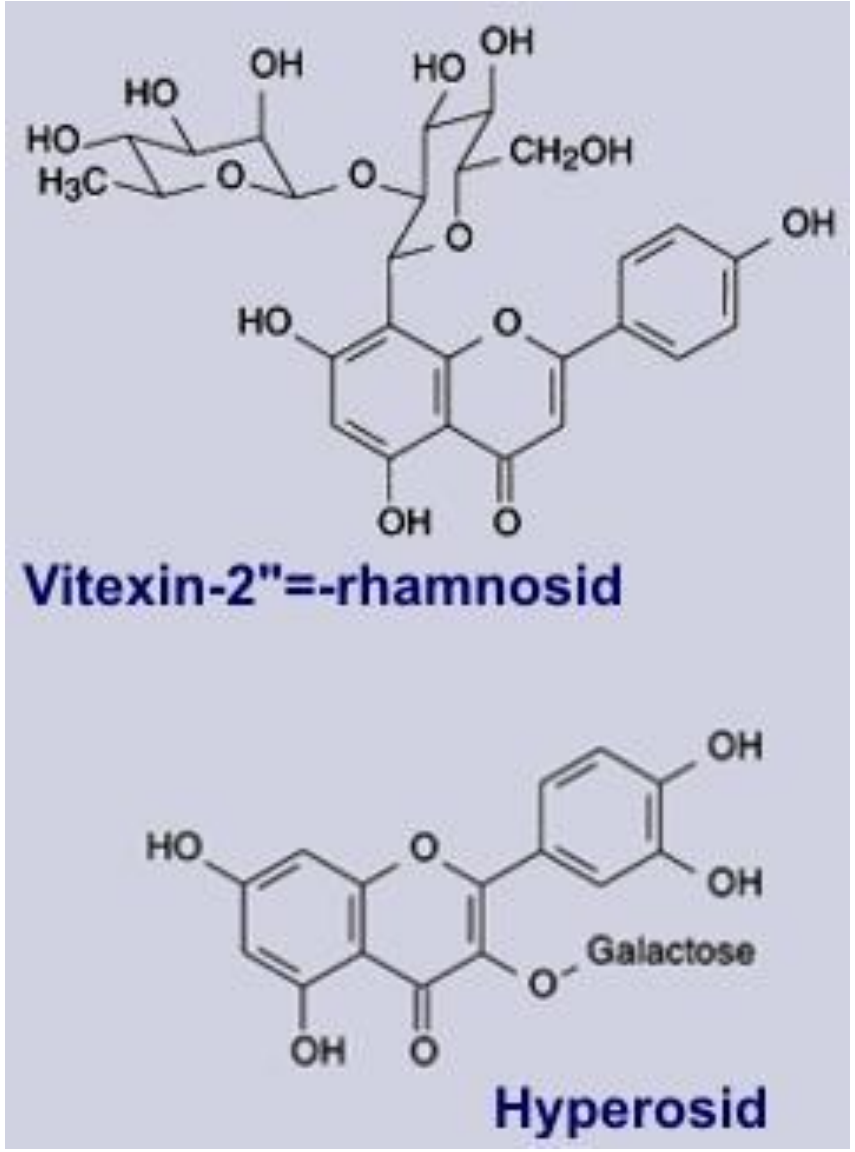
Crataegi fructus (unripe)

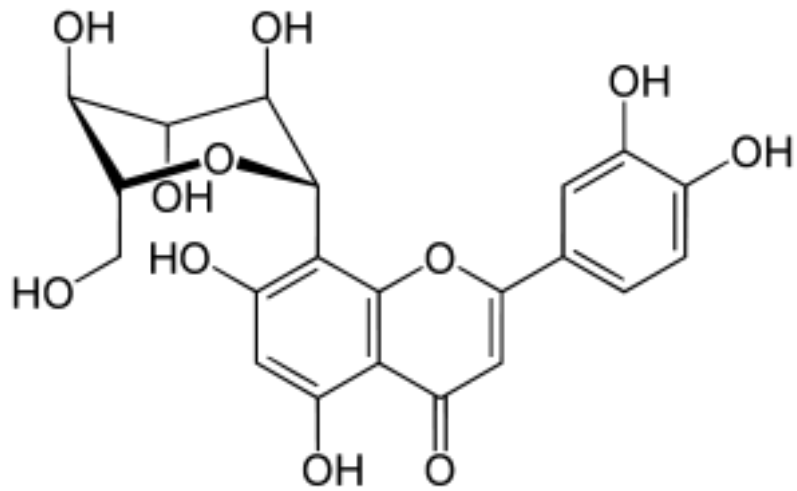
Hawthorn consists of the leaves with flowers and/or unripe fruits (berries) of *Crataegus monogyna* or *C. oxyacantha* = *Crataegus laevigata* (Fam. Rosaceae). *Crataegus* spp. are thorny shrubs or small tree up to 10 m tall common in the temperature areas of the northern hemisphere.

The leaves are broader than long and have 3-5 lobes. The dark red, false fruits are oval and contain a small kernel which is the true fruit.

Crataegus monogyna also grows wildly in Turkey and Cyprus. The other *Crataegus* species growing in Cyprus is *C. azarolus*. In Turkey, about 25 *Crataegus* species grow wildy, some of them are endemic plants.

Chemical Composition : Along with pentacyclic triterpenoid acids, the drugs contain aromatic amines, a trace of essential oil, phenolic acids, 1-2& flavonoids,and 2-3% proanthocyanidins. The chief flavonoid constituent is hyperin (hyperoside = quercetin 3-galactoside), the drugs also contain Flavone C-glycosides : vitexin, orientin, 2’’-O-rhamnosylvitexin (= vitexin 2’’-rhamnoside).
The composition of the proanthocyanidoid fraction is characteristic: the dimeric procyanidin B-2 (epicatechin 4β→8) epicatechin), and the trimeric procyanidin C-1 (epicatechin 4β→8) epicatechin (4β→8) epicatechin) are the chief constituents.





Orientin

Pharmacological Properties :

The activity of hawthorn is attributed to flavonoids anthocyanidins and proanthocyanidins (also known as biflavans or procyanidins). Experimental studies have shown that hawthorn possesses many pharmacological effects which are beneficial for the cardiovascular system. It inhibits arrhythmia, dilates coronary blood vessels, reduces serum cholesterol and triglyceride levels, reduces symptoms of angina and CHF and has a hypotensive action due to peripheral dilation of blood vessels. Cardiac improvement is mainly due to inhibition of cyclic AMP phosphodiesterase which leads to a positive inotropic effect. An effect on β-adrenergic receptors has been also observed. Hawthorn drugs have positive inotropic actions on the heart and thus are potentially useful for the treatment of CHF.

Clinical efficacy

Hawthorn has been extensively studied. At least 15 clinical studies involving a total of about 1000 patients have been reported in the literature.

Most patients were in Stage II heart failure. Almost all the studies showed therapeutic efficacy of hawthorn, particularly in the subjective symptoms of congestive heart failure such as rapid fatigability, exertional dyspnea, lethargy, exertional cough, decreased exercise tolerance. German Commission E states that hawthorn leaves and flowers are indicated "for declining cardiac performance consistent with stage II failure according to NYHA".

A 4- to 8-week course of treatment is necessary to provide significant improvement in subjective complaints and exercise tolerance.

Commission E monograps on the hawthorn recognizes two water- and-alcohol extracts of dried hawthorn leaves with flowers (herbs-to-extract ratio 4-7:1).

Hawthorn drugs are also very convenient for preparing herbal teas.

Adverse events/Contraindications

Hawthorn is devoid of serious adverse effects:

sometimes gastrointestinal complaints, palpitations, vertigo, headache and flushing may occur. In comparison with the inotropic drug digoxin, hawthorn has a reduced arrhythmogenic risk because of its ability to prolong the effective refractory period. The concomitant use of hawthorn and cardiac glycosides can markedly enhance the activity of glycosides. Although hawthorn is available in the United States and other countries without medical prescription, it should not be used unless under the supervision of a physician.

Preparations/Dosage

Flavonoids (calculated as hyperoside) and oligomeric procyanidins (calculated as epicatechin)are the chemical constituents for testing the pharmaceutical quality of hawthorn. The German Commission E recommends a daily dose of 160-900 mg hawthorn extract with 4-30 mg content in flavonoids and 3-160 mg in oligomeric procyanidins. Most clinical studies used alcoholic extracts in the dose ranging from 180 and 900 mg daily.

Crataegus pentagyna

Crataegus orientalis

Crataegus azarolus (grows widespread in Cyprus)

Vitis viniferae folium, Vitis viniferae semen vine

üzüm yaprağı, üzüm çekirdeği

Vitis vinifera Vitaceae

Vine is used in phytotherapy (vine leaf) and in the pharmaceutical industry, which manufactures from grape seeds a purified extract standardized for oligomeric procyanidins. The seeds are also the source of grape seed oil. Experimentally, grape seed procyanidins have an angioprotective activity on several models for alteration of capillary permeability. They are in vitro inhibitors of collagenase, elastase, hyaluronidase, xanthine-oxidase, and angiotensin converting enzyme, as well as free radical scavengers, and they apparently protect collagen and elastin from degradation.

In therapeutics, the procyanidins of grape seed have two indications: treatment of the functional symptoms of venous and lymphatic vessel insuffiency; treatment of the lymphedema of the arm subsequent to breast cancer radiation therapy and chemotherapy. In addition, low-dose formulations are prometed as a treatment for problems involving retinal or choroidal circulation. Like many other free radical scavengers, proanthocyanidins are of interest for the formulation of «dermoprotective» cosmetic products.

Pini maritimae cortex (French maritime pine, çam)

Botany/Key constituents

French maritime pine is the bark of *Pinus pinaster* , subsp. *atlantica* (also named *Pinus maritima*, Fam. Pinaceae), a species of pine tree that is cultivated in the forest of the Landes of Gascogne (South-western France). Chemical identification studies have shown that French maritime pine is primarily composed of procyanidins (e.g. catechin, B-1, B-4) and phenolic acids (i.e. derivatives of benzoic and cinnamic acids).

Pharmacological Properties

French maritime pine possesses a number of pharmacological effects which could contribute to its efficacy in the treatment of chronic venous insufficiency. French maritime pine protects against oxidative stress by increasing the synthesis of anti-oxidative enzymes and by acting as a potent scavenger of free radicals. Anti-inflammatory activity, protection against UV-radiation, anti-allergic and immunostimulant effects, reduction of capillary permeability and beneficial effects on microcirculation have been also described.

Catechu	***Acacia catechu***	**Mimosaceae**

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

Catechu or cutch is an aqueous extract of the heartwood of *Acacia catechu*, concentrated by boiling. Upon cooling crystals separate: this constitute «katha or khat» contains more than 55% catechin. These products are used especially in southeast Asia to tan hides, protect ropes, dye textiles and more.