3

Glycosides and Tannins

Glycosides are compounds that yield one or more sugars among the products of hydrolysis. The most frequently occurring sugar is β-D-glucose, although rhamnose, digitoxose, cymarose, and other sugars are components of glycosides. When the sugar formed is glucose, the substance may be called a glucoside; however, because other sugars may be developed during the hydrolysis, the term glycoside is applied.

Chemically, the glycosides are acetals in which the hydroxyl of the sugar is condensed with a hydroxyl group of the nonsugar component, and the secondary hydroxyl is condensed within the sugar molecule itself to form an oxide ring. More simply, glycosides may be considered sugar ethers. The nonsugar component is known as the **aglycone;** the sugar component is called the **glycone.** Both *alpha* and *beta* glycosides are possible, depending on the stereoconfiguration of the glycosidic linkage. However, one should note that only *beta* forms occur in plants. It should be noted also that emulsin and most other natural enzymes hydrolyze only the *beta* varieties.

From the biologic viewpoint, glycosides play an important role in the life of the plant and are involved in its regulatory, protective, and sanitary functions. Among such a wide variety of compounds one finds many therapeutically active agents. In fact, the group contributes to almost every therapeutic class. Some of our most valuable cardiac specifics are glycosides from digitalis, strophanthus, squill, convallaria, apocynum, and others (see page 162). Laxative drugs, such as senna, aloe, rhubarb, cascara sagrada, and frangula, contain emodin and other anthraquinone glycosides; sinigrin, a glycoside from black mustard, yields allyl isothiocyanate, a powerful local irritant; and gaultherin from wintergreen yields methyl salicylate, an analgesic.

The classification of glycosides is a difficult matter. If the classification is based on the sugar group, a number of rare sugars are involved, the structures of which are not too well known; if the aglycone group is used as a basis of classification, one encounters groups from probably all classes of plant constituents: tannins, sterols, carotenoids, anthocyanins, and many others, including several whose structures are as yet unknown. A therapeutic classification, although excellent from a pharmaceutic viewpoint, omits many glycosides of pharmacognostic interest.

Some glycosides contain more than one saccharide group, possibly as di- or trisaccharides. Upon proper conditions of hydrolysis, one or more of the saccharide groups can be removed from such compounds, resulting in glycosides of simpler structure (see amygdalin, page 70). The most common sugar present is D-glucose, although the presence of other sugars, such as rhamnose, is quite possible. Occasionally, rare sugars are found as components of glycosides, such as digitoxose, digitalose, and cymarose.

All natural glycosides are hydrolyzed into a sugar and another organic compound by boiling with mineral acids; however, they vary widely in the ease with which this hydrolysis is performed. In most cases, the glycoside is easily hydrolyzed by an enzyme that occurs in the same plant tissue, but in different cells from those that contain the glycoside. Injury to the tissues, the germination process, and perhaps other physiologic activities of the cells bring the enzyme in contact with the glycoside, and the hydrolysis of the latter takes place. A large number of enzymes have been found in plants. Many of these enzymes hydrolyze only a single glycoside; however, 2 enzymes, namely **emulsin** of almond kernels and **myrosin** of black mustard seeds, each hydrolyze a considerable number of glycosides. Glycosides that are derivatives of rhamnose require a special enzyme known as rhamnase for their hydrolysis.

BIOSYNTHESIS OF GLYCOSIDES

Consideration of glycoside (heteroside) biosynthesis necessarily consists of 2 parts. The general reactions couple a sugar residue to an aglycone. Presumably this transfer reaction is similar in all biologic systems. This contrasts with the pathways for biosynthesis of the various types of aglycones, which tend to be diverse and must be considered individually.

Available evidence indicates that the principal pathway of glycoside formation involves the transfer of a uridylyl group from uridine triphosphate to a sugar 1-phosphate. Enzymes catalyzing this reaction are referred to as uridylyl transferases (1) and have been isolated from animal, plant, and microbial sources. Phosphates of pentoses, hexoses, or various sugar derivatives may participate. The subsequent reaction, mediated by glycosyl transferases (2), involves the transfer of the sugar from uridine diphosphate to a suitable acceptor (aglycone), thus forming the glycoside.

$$\text{UTP} + \text{Sugar-1-P} \overset{(1)}{\rightleftharpoons} \text{UDP-Sugar} + \text{PPi}$$

$$\text{UDP-Sugar} + \text{Acceptor} \overset{(2)}{\rightleftharpoons} \underset{\text{(Glycoside)}}{\text{Acceptor-Sugar}} + \text{UDP}$$

Once such a glycoside is formed, other enzymes may transfer another sugar unit to the monosaccharide moiety, converting it to a disaccharide. Enzymes occur in various glycoside-containing plants that are capable of producing tri- and tetrasaccharide moieties of the glycosides by analogous reactions.

To illustrate the biosynthesis of an aglycone moiety and the stereospecificity that can be involved in the glycosyl transferase reaction, the formation of cyanogenic glycosides is an interesting case to note. The process of glycoside formation is shown in Figure 3–1 for prunasin, a cyanogenic glucoside. The amino acid phenylalanine, which arises from the shikimate pathway (see page 112), is the starting precursor. An aldoxime, a nitrile, and a cyanohydrin are involved as intermediates in the pathway. The presence of a chiral center in mandelonitrile provides the opportunity for 2 β-glucosides to occur. In wild cherry, *Prunus serotina,* prunasin (D-mandelonitrile glucoside) is formed. The isomeric sambunigrin (L-mandelonitrile glucoside) is formed in *Sambucus nigra.* Apparently, these compounds do not occur in the same species, further confirming the stereospecificity of the glycosyl transferases that catalyze their formation.

When the chemical nature of the aglycone group is used as a basis of systematization, the classification of the glycoside-containing drugs follows this scheme: (1) cardioactive group (see page 162; (2) anthraquinone group; (3) saponin group; (4) cyanophore group; (5) isothiocyanate group; (6) flavonol group; (7) alcohol

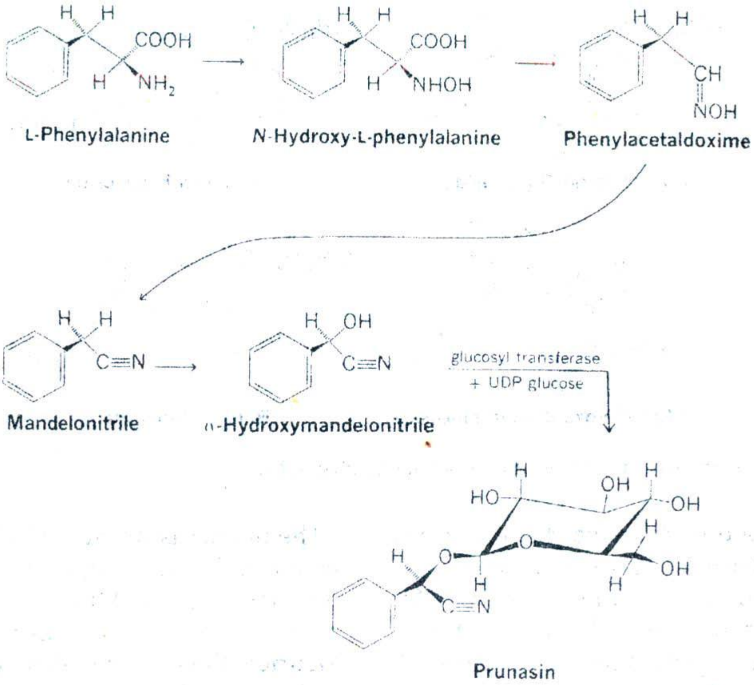


Fig. 3–1. The biosynthetic pathway for the cyanogenic glycoside, prunasin.

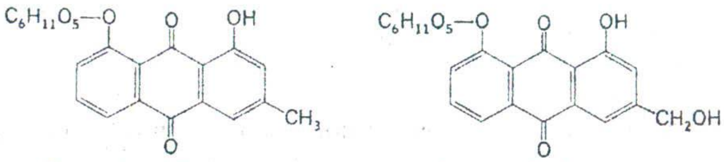
group; (8) aldehyde group; (9) lactone group; (10) phenol group; and (11) tannins.

ANTHRAQUINONE GLYCOSIDES

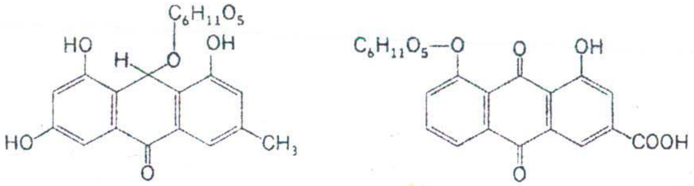
A number of glycosides with aglycones related to anthracene are present in such drugs as cascara sagrada, frangula, aloe, rhubarb, senna, and chrysarobin. With the exception of chrysarobin (which is too irritating), these drugs are employed as cathartics The glycosides, upon hydrolysis, yield aglycones that are di-, tri-, or tetrahydroxyanthraquinones or modifications of these compounds. A typical example is frangulin, which hydrolyzes to form emodin (1,6,8-trihydroxy-3-methylanthraquinone) and rhamnose. The structural formulas of a glycoside yielding emodin and of those yielding chrysophanic acid (1,8-dihydroxy-3-methylanthraquinone), aloe-emodin (1,8-dihydroxy-3-hydroxymethylanthraquinone), and rhein (1,8-dihydroxyanthraquinone-3-carboxylic acid) are shown in Figure 3–2. Glycosides of anthranols and anthrones, reduced derivatives of anthraquinones, also occur in the plant materials, and they make significant contributions to the therapeutic action of these natural products.

The free anthraquinone aglycones exhibit little therapeutic activity. The sugar residue facilitates absorption and translocation of the aglycone to the site of action. The anthraquinone and related glycosides are stimulant cathartics and exert their action by increasing the tone of the smooth muscle in the wall of the large intestine. Glycosides of anthranols and anthrones elicit a more drastic action than do the corresponding anthraquinone glycosides, and a preponderance of the former constituents in the glycosidic mixture can cause discomforting griping action.

BIOSYNTHESIS OF ANTHRAQUINONE GLYCOSIDES. Much of our knowledge of the biosynthesis of anthraquinones has been obtained from studies of microorganisms. Feedings of labeled acetate to *Penicillium islandicum*, a species that produces several



Chrysophanol-8-glucoside **Aloe-emodin-8-glucoside**



(±)-Emodin-oxanthrone glucoside **Rhein-8-glucoside**

Fig. 3–2. Representative structures of anthraquinone glycosides.

anthraquinone derivatives, have revealed that the distribution of radioactivity in these compounds is consistent with formation via a head-to-tail condensation of acetate units. A poly-β-ketomethylene acid intermediate is probably first produced and then gives rise to the various oxygenated aromatic compounds following intramolecular condensations. Anthranols and anthrones are likely intermediates in the formation of anthraquinones. Presumably, the emodin-like anthraquinones are formed in higher plants by a similar pathway. The transglycosylation reaction, which creates a glycoside, probably occurs at a late stage in the pathway after the anthraquinone nucleus has been formed.

CASCARA SAGRADA

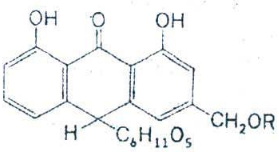
Cascara sagrada or rhamnus purshiana is the dried bark of *Rhamnus purshianus* DeCandolle (Fam. Rhamnaceae). The species epithet was formerly spelled *purshiana,* and that form is retained in one of the titles applied to the drug. It should be aged for at least 1 year prior to use in medicinal preparations. Reduced forms of the emodin-type glycosides are present in the fresh bark; during the minimum 1-year storage period, these glycosides are converted to monomeric oxidized glycosides, which exhibit a milder cathartic activity.

The name cascara sagrada is Spanish for sacred bark; *Rhamnus* is the ancient classical name for buckthorn; *purshianus* was given in honor of the German botanist, Friedrich Pursh. The plant is a tree that attains a height of 10 meters and is indigenous to the Pacific Coast of North America. Most of the present-day market supply comes from Oregon, Washington, and southern British Columbia. Collections are made during the summer, beginning at the end of May and continuing until the rainy season starts. The wild trees are scattered in the native forests on the mountains. The bark is stripped from the tree by making longitudinal incisions (see Fig. 3–3) and peeling off sections that tend to roll into large quills. The trees are often felled and the bark is removed from the larger branches. The bark is sacked and conveyed to suitable places, often sawmill platforms, for sun drying. The inner surface is not exposed to the sun, however, in order to retain the yellow color. After the large quills are dried, they are run through a "breaker" and broken into small transversely curved pieces.

Two types of anthracene compounds have been reported: normal *O*-glycosides (based on emodin), about 10 to 20%, and aloinlike C-glycosides, representing about 80 to 90% of the total. About a dozen such compounds have been identified. Two of

Fig. 3–3. Collecting cascara bark in Oregon forest. (Courtesy of S.B. Penick and Company.)

the C-glycosides are barbaloin and deoxybarbaloin (chrysaloin). Four additional compounds of this type are designated as cascarosides A, B, C, and D. Cascarosides A and B are based on optical isomers of barbaloin and cascarosides C and D on optical isomers of chrysaloin. All 4 of the cascarosides, being primary glycosides of barbaloin and chrysaloin, are actually both O- and C-glycosides. The remaining 4 to 6 anthracene derivatives identified in the drug are normal O-glycosides, based mostly on emodin. Dried, medicinal quality cascara bark yields not less than 7% of total hydroxyanthracene derivatives, calculated as cascaroside A. Hydrolysis of the total glycosides yields rhamnose and glucose in an approximate ratio of 1:1.



R = H, (±)-Barbaloin
R = $C_6H_{11}O_5$, Cascaroside A/B

USE AND DOSE. Cascara sagrada is a cathartic. Its principal use is in the correction of habitual constipation, where it not only acts as a laxative but restores natural tone to the colon. The bitter taste and the activity are considerably reduced by treating cascara sagrada extracts with alkaline earths or magnesium oxide. The usual dose of cascara sagrada fluidextract (bitter cascara) is 1 ml; of aromatic cascara sagrada fluidextract (sweet cascara), 5 ml; of cascara sagrada extract, 300 mg.

SPECIALTY PRODUCTS. Cascara sagrada is the active ingredient in Cas-Evac® and a number of generic products.

Many preparations containing cascara sagrada have appeared on the market. The extract has been combined with such laxative ingredients as (1) phenolphthalein—Caroid®, (2) aloe—Nature's Remedy®, (3) psyllium husks and prune powder—Casyllium®, (4) chondrus and mineral oil—Kondremul® with Cascara, and (5) docusate sodium—Stimulax®.

Casanthranol is a purified mixture of the anthranol glycosides extracted from cascara sagrada. It is marketed as Lane's Pills®. Casanthranol is also combined with surfactant drugs and/or hydrocolloids; such formulations include Afko-Lube Lax®, Comfolax Plus®, Constiban®, Dialose Plus®, Diothron®, Disanthrol®, Dioslan Forte®, and Peri-Colace®.

Frangula or buckthorn bark is the dried bark of *Rhamnus frangula* Linné. This plant is a shrub that grows in Europe and western Asia. The composition and activity of frangula bark correspond to those of cascara sagrada, and it finds a comparable use in Europe and the Near East. Products from the dried, ripe fruits of *R. catharticus* Linné are also used in these areas for their cathartic action. Other *Rhamnus* species contain anthraquinone glycosides but are not employed in medicine.

Movicol® contains frangula and karaya gum.

Aloe

Aloe or aloes is the dried latex (juice) of the leaves of *Aloe barbadensis* Miller (*A. vera* Linné), known in commerce as Curaçao aloe (Fig. 3–4), or of *A. ferox* Miller and hybrids of this species with *A. africana* Miller and *A. spicata* Baker, known in commerce as Cape aloe (Fam. Liliaceae).

Aloe yields not less than 50% of water-soluble extractive.

Aloe is from the Arabic *alloeh* or the Hebrew *halal,* meaning a shining, bitter substance; *vera* is from the Latin *verus,* meaning true. *Barbadensis* refers to the Barbados Islands; *ferox* is from the Latin meaning wild or ferocious; *africana* refers to the habitat of the plant, southern Africa; and *spicata* refers to the flowers in spikes.

About 300 species of *Aloe* are known, most of which are indigenous to Africa. Many have been introduced into the West Indies and Europe. The aloes are typical xerophytic plants that have fleshy leaves, usually have spines at the margins, and resemble to some extent the agave or century plant (*Agave americana* Linné, Fam. Amaryllidaceae).

Aloe barbadensis is a native of northern Africa but was introduced into the Barbados Islands in the 17th century. *A. chinensis,* a variety of *A. barbadensis (A. vera),* was introduced into Curaçao from China in 1817. The drug was cultivated to a considerable extent in Barbados until the middle of the 19th century, but since that time the industry apparently has died out. Curaçao aloe, which is often called Barbados aloe, comes from the Dutch islands of Aruba and Bonaire. The leaves are cut in March and April and placed cut-end down on a V-shaped trough. The latter is inclined so that the latex that is contained in specialized cells just beneath the epidermis of the leaf can be led into a vessel. The latex is evaporated in a copper kettle and, when of the proper consistency, is poured into metal containers and allowed to harden. At the present time, the principal areas of production are Aruba, Bonaire, Haiti, Venezuela, and South Africa. Curaçao aloe is the most important form occurring in the United States.

Aloe occurs on the market as opaque masses that range from reddish black to brownish black to dark brown in color. The taste of each variety of aloe is nauseating and bitter. The characteristic odor is disagreeable.

Aloe contains a number of anthraquinone glycosides, the principal one of which

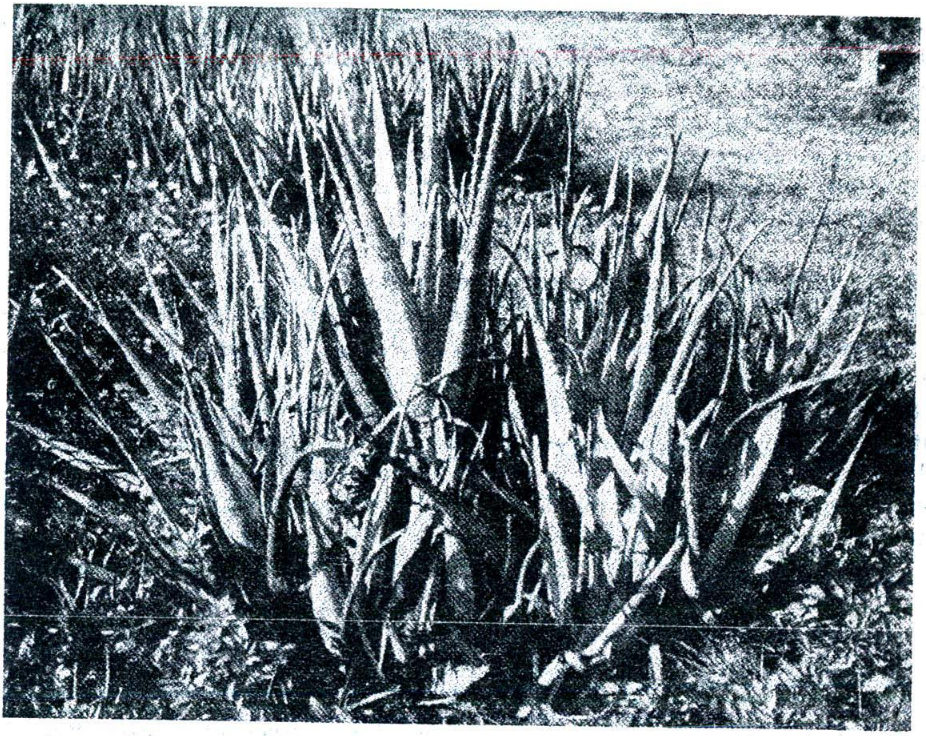


Fig. 3–4. Typical cluster of *Aloe barbadensis (Aloe vera)*, the plant yielding Curaçao aloe. (Photo courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

is barbaloin (aloe-emodin anthrone C-10 glucoside).

O-Glycosides of barbaloin with an additional sugar also have been isolated from certain samples of Cape aloe. These compounds have been designated aloinosides. Free (nonglycosidal) aloe-emodin and a free and combined anthranol are also present. Chrysophanic acid has been detected in certain types of the drug.

The active constituents of aloe vary qualitatively and quantitatively according to the species from which the drug is obtained. Analyses have revealed that Curaçao aloe is superior to Cape aloe because it contains two-and-one-half times as much aloe-emodin. Curaçao aloe also contains an appreciable amount of free and combined chrysophanic acid not present in the other types.

In addition to these physiologically active compounds (10 to 30%), aloe contains inactive ingredients including large amounts (16 to 63%) of a resinous material plus a volatile oil.

USES AND DOSE. Aloe is a pharmaceutic aid for compound benzoin tincture and a cathartic. When used as a cathartic, it acts chiefly on the large intestine. Aloe glycosides elicit a relatively drastic cathartic action, and some authorities advocate a preferential use of other cathartic substances. Aloe is available with cascara sagrada in Nature's Remedy®.

ALOE VERA GEL. The fresh mucilaginous gel contained in the parenchymatous tissue in the center of the leaves of *Aloe barbadensis (A. vera)* has been used for years in the treatment of burns, abrasions, and other skin irritations. In 1935, the juice was recommended in treating third-degree x-ray burns and, more recently, has been advocated for its moisturizing and emollient effects.

Commonly referred to as aloe vera gel, a so-called stabilized product is now prepared from the central leaf tissue by many different proprietary or patented methods, some of which involve expression or solvent extraction under harsh conditions. The resulting product is consequently extremely variable. Thus, while scientific studies have substantiated the cell-proliferative (wound-healing) properties of the fresh gel, they have not verified such activity in the "stabilized" product.

Still, the stabilized product is incorporated into a wide range of preparations for external and internal use, ranging from hand lotion to frozen yogurt, and these are recommended by their producers for alleviating conditions ranging from headache to obesity. In spite of the mystique which, thanks to prolific advertising, surrounds these stabilized aloe gel products today, there is no scientific or clinical evidence to support their therapeutic utility.

Rhubarb

Rhubarb, rheum, or Chinese rhubarb consists of the dried rhizome and root that are deprived of periderm tissues of *Rheum officinale* Baillon (Fig. 3–5), of *R. palmatum* Linné, of other species (except *R. rhaponticum* Linné, the common garden rhubarb plant), or of hybrids of *Rheum* Linné (Fam. Polygonaceae) and are grown in China.

Indian rhubarb or Himalayan rhubarb consists of the dried rhizome and root of *R. emodi* Wallich, of *R. webbianum* Royle, or of some related *Rheum* species that are native to India, Pakistan, or Nepal.

Rheum is from the Latin *Rha*, the name of the Volga River near which species of *Rheum* grow. *Palmatum* refers to the large spreading leaves, *emodi* refers to the emodin content, and *webbianum* refers to an Indian taxonomist.

The principal constituents of medicinal rhubarbs are rhein anthrones. Rhubarb has been used in cathartic preparations; the cathartic action is relatively drastic, and the use of other cathartic substances has largely been adopted.

Senna

Senna or senna leaves consists of the dried leaflet of *Cassia acutifolia* Delile, known in commerce as Alexandria senna, or of *C. angustifolia* Vahl, known in commerce as Tinnevelly senna (Fam. Leguminosae). The name *Senna* is from the Arabic *sena*, the native name of the drug; *Cassia* is from the Hebrew *qetsiah*, meaning to cut off, and refers to the fact that the bark of some of the species was once peeled off and used (the application of the name *cassia* to cinnamon barks should be noted); *acutifolia* is Latin and refers to the sharply pointed leaflets; and *angustifolia* means narrow-leaved (Fig. 3–6). The plants are low-branching shrubs; *C. acutifolia* grows wild near the Nile River from Aswan to Kordofan, and *C. angustifolia* grows wild in Somalia, the Arabian peninsula, and India. Most of the commercial supply of the drug is collected from plants cultivated in southern India (Tinnevelly); some material is also produced in the Jammu district of India and in Northwest Pakistan.

Alexandria senna is harvested in April and in September by cutting off the tops of the plants about 15 cm above the ground and drying them in the sun. Afterward, the stems and pods are separated from the leaflets by using sieves. The portion that passes through the sieves is then "tossed." The leaves work to the surface and the heavier stalk fragments sink to the bottom. The leaves are then graded and baled or packed in bags. This process of collection and separation accounts for the large number of broken leaves in Alexandria senna. This drug was formerly shipped via Alexandria but is now distributed through Port Sudan on the Red Sea.

Tinnevelly senna is gathered by hand and dried in the sun, then carefully baled and shipped primarily from the port of Tuticorin. It is cultivated in nearby areas to which the term "Tinnevelly" is applied.

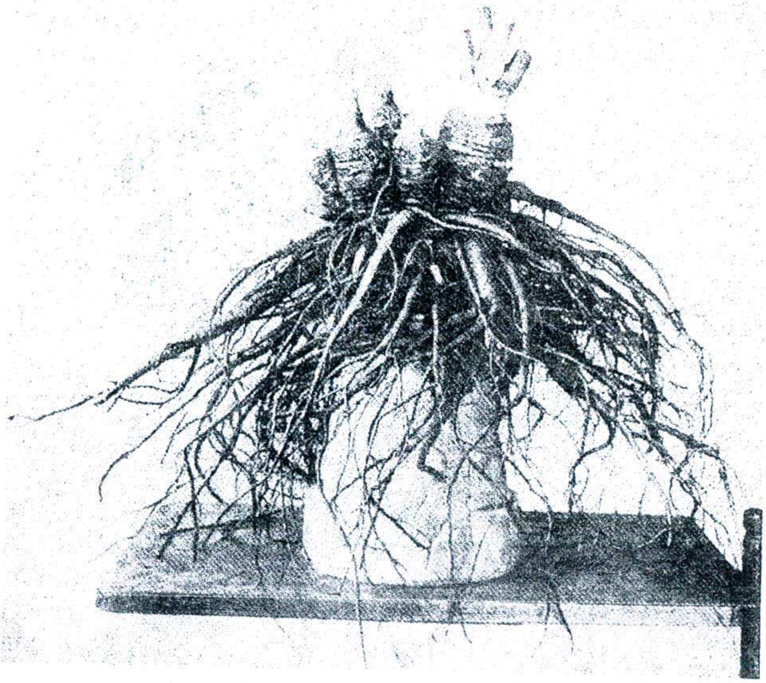
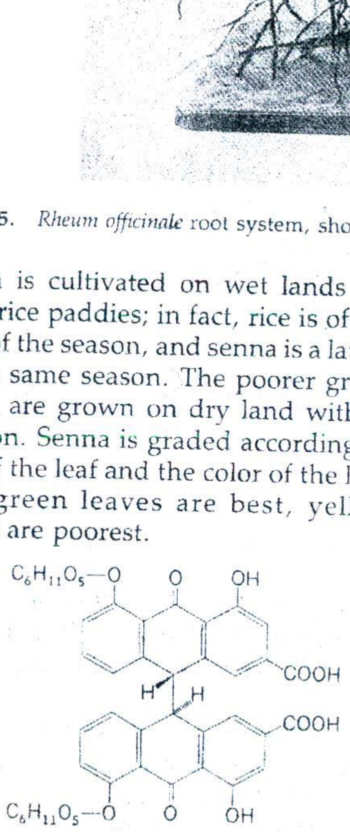


Fig. 3–5. *Rheum officinale* root system, showing large distinctive rhizomes and relatively small roots.

Senna is cultivated on wet lands resembling rice paddies; in fact, rice is often one crop of the season, and senna is a later crop of the same season. The poorer grades of senna are grown on dry land without irrigation. Senna is graded according to the size of the leaf and the color of the leaflets: blue-green leaves are best, yellowish leaves are poorest.



Sennoside A

Senna was introduced into European medicine in the 9th or 10th century by the Arabians. Its native use seems to antedate historical record. According to Isaac Judaeus, a native of Egypt who lived about 850 to 900 A.D., senna was brought to Egypt from Mecca.

The principal active constituents of senna are dimeric glycosides whose aglycones are composed of aloe-emodin and/or rhein. Those present in greatest concentration are sennosides A and B, a pair of optical isomers whose aglycones are rhein dianthrone (sennidin A and B). Sennosides C and D are minor constituents having dimeric aglycones composed of 1 molecule of rhein and 1 molecule of aloe-emodin. Small quantities of monomeric glycosides and free anthraquinones are also present. Senna pods also contain useful, active glycosides; some of the primary glycosides in the pods have as many as 10 sugar molecules attached to a rhein dianthrone nucleus.

USE AND DOSE. Senna is a cathartic. The usual dose is 2 g.

PROPRIETARY PRODUCTS. Black Draught®, Dr. Caldwell's Senna Laxative®, Fletcher's Castoria®, Garfields Tea®, Innerclean Herbal Laxative®, Swiss Kriss®.

A concentrate of the active constituents and an isolated mixture of sennosides,

Fig. 3–6. *Cassia acutifolia: E,* fruiting branch; *F,* single leaflet; *G,* pod. *Cassia angustifolia: H,* single leaf; *J,* pod.

which may be prepared from either the leaves or the pods, are used in various products, some of which contain a senna component combined with a hydrocolloid or a surfactant. Such products include Gentlax®, Glysennid®, Nytilax®, Senexon®, Senokap®, Senokot®, and Senolax®.

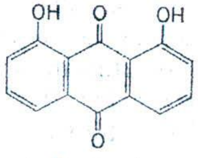
Chrysarobin

Chrysarobin is a mixture of neutral principles obtained from Goa powder. Goa powder takes its name from the former Portuguese colony on the Malabar Coast of India and is obtained from lysogenous cavities in the wood of *Andira araroba* Aguiar (Fam. Leguminosae). Hot benzene is used to extract chrysarobin (50 to 70% yields) from the Goa powder. A representative sample of chrysarobin contains approximately 30 to 40% of chrysophenolanthrone or chrysophenolanthranol, 20% emodinanthrone-monomethyl ether, and 30% of dehydro-emodinanthrone-monomethyl ether.

USES. Chrysarobin is a keratolytic agent and has been employed in the treatment of psoriasis, trichophytosis, and chronic eczema. It is very irritating to mucous membranes and should not be used on the face or scalp. The variable composition of chrysarobin and the lack of adequate standardization procedures have created problems in ensuring reproducible therapeutic effects. Anthralin, a synthetic anthracenetriol, has replaced the use of chrysarobin; prescription products of anthralin include Anthra-Derm®, Dritho-creme®, and Lasan®.

Danthron

Danthron or chrysazin is 1,8-dihydroxyanthraquinone. It occurs as an orange-colored crystalline powder that is practically insoluble in water but soluble in alcohol, ether, benzene, and other solvents.



Danthron

Although 1,8-dihydroxyanthraquinone is a natural constituent in certain drugs, it is difficult to isolate in a pure state; thus, danthron is prepared synthetically from 1,8-anthraquinone potassium disulfonate.

USES AND DOSE. Danthron is a cathartic drug and is an important intermediate in the manufacture of anthralin and of alizarin and indanthrene dyestuffs. The usual dose is 75 to 150 mg.

PROPRIETARY PRODUCTS. Akshun®, Dorbane®, Modane®, Tonelax®. Danthron is also combined with a surfactant in a number of products, including Doctate-P®, Dorbantyl®, Doxan®, Doxidan®, Guarsol®, Pro-Cal-Thron®, and Valax®.

SAPONIN GLYCOSIDES

This group of glycosides is widely distributed in the higher plants. Saponins form colloidal solutions in water that foam upon shaking; they have a bitter, acrid taste, and drugs containing them are usually sternutatory and otherwise irritating to the mucous membrane. They destroy red blood corpuscles by hemolysis and are toxic, especially to cold-blooded animals. Many saponins are used as fish poisons. Upon hydrolysis they yield an aglycone known as a "sapogenin." The sapogenins form readily crystallizable compounds upon acetylization. This process can be used to purify sapogenins. The more poisonous saponins are often called "sapotoxins." Glycyrrhiza and sarsaparilla (see page 68) are among the drugs containing saponins. Plants such as the California soap plant, *Chlorogalum pomeridianum* (DC.) Kunth. (Fam. Liliaceae), which yields amolonin, are sources of saponins that are used extensively for industrial purposes.

Much of the research conducted on the saponin-containing plants was motivated by the attempt to discover precursors for cortisone (see page 174). This substance was originally isolated from the adrenal cortex and later synthesized from certain bile acids of cattle. Because these sources limit the supply of cortisone, academic, industrial, and governmental research agencies have examined many species of plants, particularly those containing steroidal sapogenins.

The determination of the initial desirability of any given steroid compound as a cortisone precursor is based on whether it has hydroxyl groups in the 3- and 11-positions on the molecule or has the ability to be converted readily to this structure. It would appear that the most outstanding plant steroids for cortisone production are:

diosgenin and botogenin from the genus *Dioscorea*
hecogenin, manogenin, and gitogenin from species of *Agave*
sarsasapogenin and smilagenin from the genus *Smilax*
sarmentogenin from the genus *Strophanthus*
sitosterol from crude vegetable oils.

Members of the Liliaceae, Amaryllidaceae, and Dioscoreaceae show the presence of sapogenins among the monocotyledons; however, the genus *Strophanthus* in the Apocynaceae was formerly thought to be the most promising of the dicotyledons. Most of the investigative work for the development of cortisone from plant precursors has centered about the sapogenins in the 3 monocotyledonous families named previously.

Biosynthesis of Saponin Glycosides. Saponin glycosides are divided into 2 types based on the chemical structure of their aglycones (sapogenins). The so-called neutral saponins are derivatives of steroids with spiroketal side chains; the acid saponins possess triterpenoid structures. Biogenesis of the steroid nucleus will be discussed in the chapter on steroids. Less is known about triterpenoid biosynthesis than is known about the steroids, but labeled acetate and mevalonate have been incorporated into such compounds. Therefore, the main pathway leading to both types of sapogenins is similar and involves the head-to-tail coupling of acetate units. However, a branch occurs, probably after the formation of the triterpenoid hydrocarbon, squalene, that leads to steroids in one direction and to cyclic triterpenoids in the other (Fig. 3–7).

Glycyrrhiza

Glycyrrhiza is the dried rhizome and roots of *Glycyrrhiza glabra* Linné, known in commerce as Spanish licorice, or of *G. glabra* Linné var. *glandulifera* Waldstein et Kitaibel, known in commerce as Russian licorice, or of other varieties of *G. glabra* Linné that yield a yellow and sweet wood (Fam. Leguminosae). *Glycyrrhiza* is of Greek origin and means sweet root; *glabra* means smooth and refers to the smooth, podlike fruit of this species. The fruit in the variety *glandulifera* has glandlike swellings. Glycyrrhiza is also called **licorice root.**

Propagation of the variety *typica* is generally done by rhizome cuttings that are planted in rows about 1.3 meters apart. At the end of the third or fourth year, the rhizome and roots are dug, preferably in the autumn and from plants that have not borne fruit, thereby ensuring maximum sweetness of the sap. The washed material is air-dried (4 to 6 months) and packed into bales or cut and tied into short cylindric bundles (see Fig. 3–8). The large thick roots of Russian licorice are peeled before drying. In Turkey, Spain, and Israel, a considerable amount of the crop is extracted with water, the liquid is clarified and evaporated, and the resulting extract is molded into sticks or other forms.

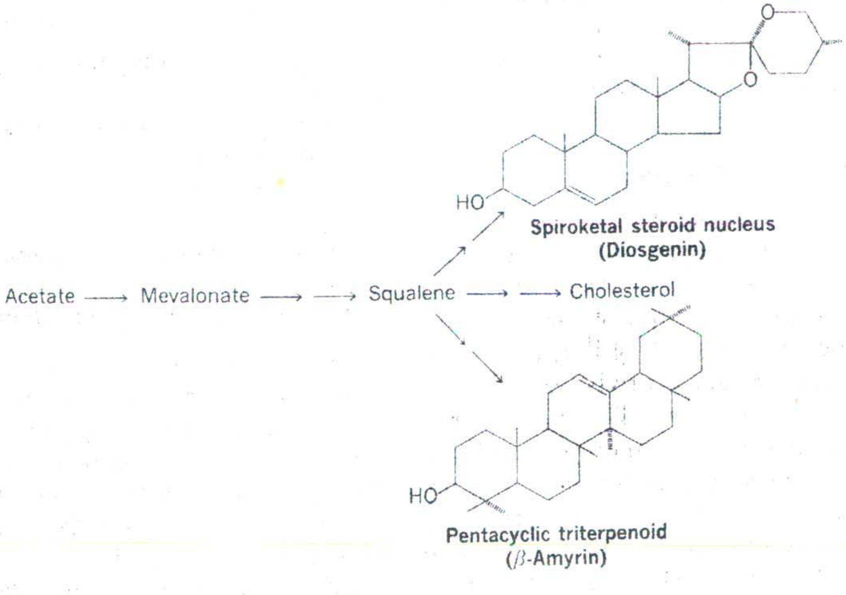


Fig. 3–7. Biosynthesis of sapogenins.

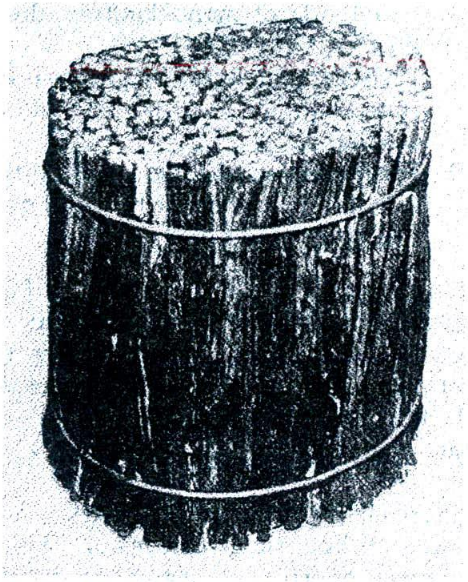


Fig. 3–8. A bundle of Spanish licorice root.

Glycyrrhiza contains a saponinlike glycoside, glycyrrhizin (glycyrrhizic acid), which is 50 times as sweet as sugar. Upon hydrolysis, the glycoside loses its sweet taste and is converted to the aglycone glycyrrhetic acid plus 2 molecules of glucuronic acid. Glycyrrhetic acid is a pentacyclic triterpene derivative of the β-amyrin type. Other constituents include flavonoid glycosides (liquiritin, isoliquiritin, liquiritoside, isoliquiritoside, rhamnoliquiritin, and rhamnoisoliquiritin), coumarin derivatives (herniarin and umbelliferone), asparagine, 22,23-dihydrostigmasterol, glucose, mannitol, and about 20% of starch. Reports of estrogens in the plant appear to be based on low-level estrogenlike activity of other constituents.

Glycyrrhiza is considered to possess demulcent and expectorant properties. It is used considerably as a flavoring agent and is frequently employed to mask the taste of bitter drugs such as aloe, ammonium chloride, quinine, and others; the surfactant property of the saponins may also facilitate absorption of poorly absorbed drugs, such as the anthraquinone glycosides. Commercially, licorice is added to chewing gums, chocolate candy, cigarettes, smoking mixtures, chewing tobacco, and snuff; when it is added to beer, it increases the foaminess; when it is added to root beer, stout, and porter, it imparts a bitter taste.

Pharmacologic studies of licorice have been extensive in recent years, particularly in Europe. As a result, glycyrrhetic acid is utilized there in dermatologic practice for its anti-inflammatory properties, and licorice root extract is employed in the treatment of peptic ulcer and of Addison's disease (chronic adrenocortical insufficiency). Licorice is an ingredient in Lydia E. Pinkham® Tablets and Vegetable Compound Liquid® for menstrual problems.

Glycyrrhizin increases fluid and sodium retention and promotes potassium depletion. Persons with cardiac problems and hypertension should avoid consumption of significant quantities of licorice.

Pure glycyrrhiza extract or pure licorice root extract is prepared from glycyrrhiza and is a black pilular mass having a characteristic sweet taste. It is an ingredient in aromatic cascara sagrada fluidextract.

Glycyrrhiza fluidextract is prepared by extracting coarsely ground licorice root with warm water, rendering the extractive alkaline with ammonium hydroxide, concentrating, and bringing it to final volume with alcohol and water. It is a pharmaceutic aid.

Dioscorea

Yam is a popular name for several of the edible species of *Dioscorea* and is sometimes incorrectly applied to certain varieties of the sweet potato. Various species of *Dioscorea* known as Mexican yams represent rich sources of the principles used as cortisone precursors. Botogenin and diosgenin are obtained from the root of *Dioscorea spiculiflora,* a cultivated species. The steroid nucleus of botogenin was altered by transferring an oxygen atom from the 12- to the 11-position of the polycyclic molecule before it could be utilized as an intermediate in the production of cortisone. Diosgenin, obtained upon hydrolysis of dioscin, is now the major precursor of glucocorticosteroids, which are prepared by processes that involve microbial transformation (see page 178).

A Mexican yam derived from *D. floribunda* is considered by the U.S. Department of Agriculture as the best source of steroids.

CYANOPHORE GLYCOSIDES

Several glycosides yielding hydrocyanic acid as one of the products of hydrolysis are commonly found in rosaceous plants. They are sometimes designated as cyanogenic glycosides. Perhaps the most widely distributed of these is amygdalin. (Note that another of the hydrolytic products is benzaldehyde; thus, amygdalin-containing drugs may also be classified in the aldehyde glycoside group.)

The common cyanophore glycosides are derivatives of mandelonitrile (benzaldehyde-cyanohydrin). 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, and also by prunasin, which occurs in *Prunus serotina*. Both amygdalin and prunasin yield D-mandelonitrile as the aglycone. Sambunigrin from *Sambucus nigra* liberates L-mandelonitrile as its aglycone.

When amygdalin is hydrolyzed, it forms 2 molecules of glucose (Fig. 3–9). Although these are usually written as linked in apparent disaccharide form, one should note that a disaccharide sugar has never been broken off from the molecule by any known means of hydrolysis. Amygdalin is therefore a true glucoside rather than a maltoside. The hydrolysis of amygdalin takes place in 3 steps, which briefly are as follows:

1. The molecule is hydrolyzed initially to liberate 1 molecule of glucose and 1 molecule of mandelonitrile glucoside.
2. The second molecule of glucose is liberated with the formation of mandelonitrile.
3. The mandelonitrile then breaks down with the formation of benzaldehyde and hydrocyanic acid.

The enzyme emulsin, as obtained from almond kernels, consists of a mixture of 2 enzymes: amygdalase, which causes the first step in the hydrolysis, and prunase, which causes the second step. (It is said that emulsion consists of at least 4 enzymes.)

Preparations from plant materials containing cyanogenic glycosides are widely employed as flavoring agents. Anticancer claims have also been made for an amygdalin-containing preparation known as laetrile or vitamin B_{17}, and the possibility for control of sickle cell anemia with cyanogenic glycosides has been noted. The FDA has not recognized the efficacy of laetrile for treatment of cancer, although some states have legalized its sale (see page 460).

Wild Cherry

Wild cherry is the carefully dried stem bark of *Prunus serotina* Ehrhart (Fam. Rosaceae). *Prunus* is the classic name of the plum tree; *serotina* means late or backward, referring to the time of flowering and fruiting of the species. Wild cherry is known as **prunus virginiana** and as **wild black cherry tree.**

The plant is a tree that grows to a height of 30 meters or more in the eastern United States and Canada. The commercial supplies of the drug come chiefly from Tennessee, Mississippi, Virginia, and North Carolina (Fig. 3–10).

Wild cherry bark was used by the Indians, and no doubt the early settlers learned its use from them. It has long enjoyed popular usage in domestic medicine.

Wild cherry bark contains a cyanogenic glycoside, prunasin (D-mandelonitrile glu-

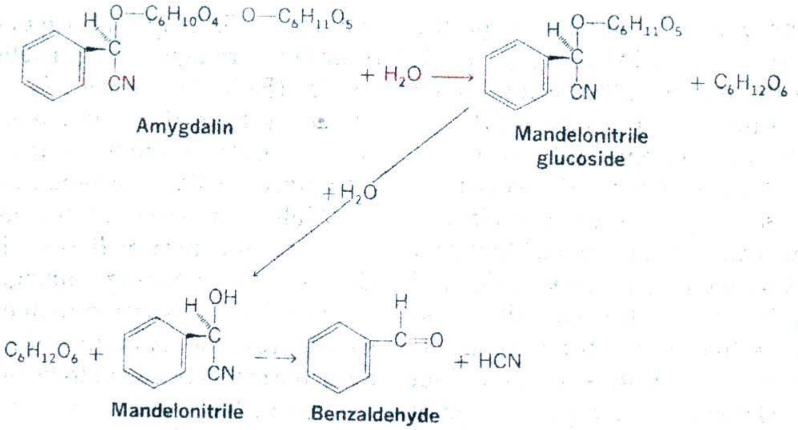


Fig. 3–9. Hydrolysis of amygdalin.

Fig. 3–10. Photograph of the trunk of a wild cherry tree showing the characteristic transverse lenticels of the bark. (Photo courtesy of Dr. Jerry L. McLaughlin.)

coside), a compound formed by the partial hydrolysis of amygdalin (see Fig. 3–9). Other constituents include the hydrolytic enzyme, prunase, *p*-coumaric acid, trimethyl gallic acid, starch, and traces of a volatile oil. A resin that yields scopoletin on hydrolysis is also present. The yield of hydrocyanic acid varies from 0.23 to 0.32% in inner bark, 0.03% in trunk bark, and varies even in bark of the same thickness from the same tree. When the exposure is such that the chloroplastids are abundant in the cells of the bark, the percentage of the D-mandelonitrile glucoside is higher. When the exposure is such that the cells do not take an active part in photosynthesis, the percentage of the glucoside is lower. In the latter case the bark is yellowish brown.

Wild cherry, in the syrup form, is employed as a flavored vehicle, especially in cough remedies. It has been considered a sedative expectorant.

ISOTHIOCYANATE GLYCOSIDES

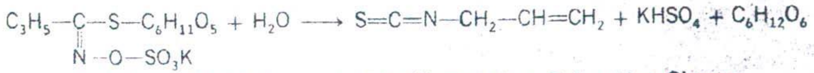
The seeds of several cruciferous plants contain glycosides, the aglycones of which are isothiocyanates. These aglycones may be either aliphatic or aromatic derivatives. Principal among these glycosides are sinigrin from black mustard, sinalbin from white mustard, and gluconapin from rape seed. When hydrolyzed by the enzyme myrosin, they yield the mustard oils. Although the fixed oil content of these seeds exceeds the amount of the volatile oil developed on hydrolysis, the activity is caused by the latter.

Mustard

Black mustard, sinapis nigra, or brown mustard is the dried ripe seed of varieties of *Brassica nigra* (Linné) Koch or of *B. juncea* (Linné) Czerniaew or of varieties of these species (Fam. Cruciferae). The term, Cruciferae, is from the Latin, meaning cross bearing, and refers to the shape of the flowers whose petals are arranged in the form of a Maltese cross; *sinapis* is from the Celtic *nap,* meaning turnip; *Brassica* is from the Celtic *bresic,* meaning cabbage; *juncea* is from the Latin, meaning rush or reed; and *nigra* is from the Latin, meaning black. The term *mustard* is believed to be derived from the use of the seeds as a condiment. The sweet *must* of old wine was mixed with crushed seeds to form a paste called "mustum ardens" (hot must) hence the name "mustard."

The plants are annual herbs that have slender erect stems, yellow flowers, pinnatifid leaves, and somewhat four-sided siliques with short stalks. They are native to Europe and southwestern Asia but are naturalized and cultivated in temperate climates in many countries and show considerable variations in form. *B. nigra* is cultivated in England and on the continent, and *B. juncea* is cultivated in India. Black mustard is mentioned in an edict of Diocletian (301 A.D.) as a condiment, and both Theophrastus and Pliny mention its use in medicine. During the Middle Ages it was an accompaniment to salted meats. The popularity of mustard as a condiment has by no means diminished.

Although black mustard contains fixed oil (30 to 35%), its principal constituent is the glycoside, sinigrin (potassium myronate), which is accompanied (probably in adjacent cells) by the enzyme, myrosin. Upon the addition of water to the crushed or powdered seeds, the myrosin effects the hydrolysis of the sinigrin, as shown below.



$$C_3H_5-\underset{\underset{N-O-SO_3K}{\|}}{C}-S-C_6H_{11}O_5 + H_2O \longrightarrow S{=}C{=}N-CH_2-CH{=}CH_2 + KHSO_4 + C_6H_{12}O_6$$

Sinigrin + (Myrosin) ⟶ Allyl isothiocyanate + Pot. acid + Glucose
(Mustard oil) sulfate

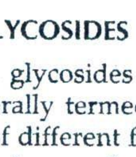
The allyl isothiocyanate produced is volatile; it is commonly called volatile mustard oil.

Black mustard is a local irritant and an emetic. Externally, the drug is a rubefacient and vesicant. Commercially, it is used as a condiment.

PROPRIETARY PRODUCTS. Mustard oil is an ingredient in Act-On Rub® and Musterole®.

White mustard or sinapis alba consists of the dried, ripe seeds of *Brassica alba* (Linné) Hooker filius (Fam. Cruciferae). White mustard is as commercially important as black mustard. The plant resembles that of *B. nigra* but is usually considerably shorter, and its siliques are more rounded and tapered. Like black mustard, it is cultivated in temperate climates all over the world.

White mustard contains the enzyme, myrosin, and a glucoside, sinalbin, which, upon hydrolysis, yield acrinyl isothiocyanate, a pungent-tasting but almost odorless oil that is much less volatile than allyl isothiocyanate. It also contains 20 to 25% of fixed oil.

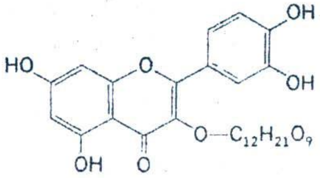


Acrinyl isothiocyanate
(Parahydroxybenzyl isothiocyanate)

FLAVONOL GLYCOSIDES

The flavonol glycosides and their aglycones are generally termed flavonoids. A large number of different flavonoids occur in nature, and these yellow pigments are widely distributed throughout the higher plants. Rutin, quercitrin, and the citrus bioflavonoids (including hesperidin, hesperetin, diosmin, and naringen) are among the best-known flavonoid constituents.

Rutin and hesperidin have been called vitamin P or permeability factors. They have been used in the treatment of various conditions characterized by capillary bleeding and increased capillary fragility. Claims have also been advanced for the value of citrus bioflavonoids in treating symptoms of the common cold. Evidence for the therapeutic efficacy of rutin, citrus bioflavonoids, and related compounds is not conclusive, and products containing them are no longer marketed for medicinal purposes in the United States. They are included in some preparations as dietary supplements.

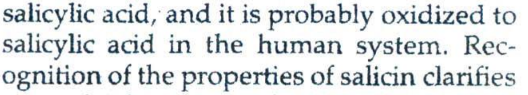


Rutin

ALCOHOL GLYCOSIDES

Salicin

Salicin is a glycoside obtained from several species of *Salix* and *Populus*. Most willow and poplar barks yield salicin, but the principal sources are *Salix purpurea* and *S. fragilis*. The glycoside, populin (benzoyl salicin), is also associated with salicin in the barks of the Salicaceae.



Salicin Saligenin

Salicin is hydrolyzed into D-glucose and saligenin (salicyl alcohol) by emulsin. Salicin has antirheumatic properties (1-g dose). Its action closely resembles that of salicylic acid, and it is probably oxidized to salicylic acid in the human system. Recognition of the properties of salicin clarifies many folkloric uses of poplar and willow barks.

ALDEHYDE GLYCOSIDES

Vanilla is a drug that has an aldehydic aglycone as its chief constituent. **Vanillin** is the aglycone developed during the curing of vanilla beans. Vanillin is methylprotocatechuic aldehyde.

Vanilla

Vanilla or vanilla bean is the cured, full-grown, unripe fruit of *Vanilla planifolia* Andrews, often known in commerce as Mexican or Bourbon vanilla, or of *V. tahitensis* J. W. Moore, known in commerce as Tahiti vanilla (Fam. Orchidaceae). *Vanilla* is from the Spanish *vania*, a sheathlike pod, and *illa*, meaning small; *planifolia* is from the Latin *planus*, meaning flat, and *folium*, meaning leaf; *tahitensis* refers to Tahiti, its adopted home.

The plants are perennial, climbing, dioecious epiphytes attached to the trunks of trees by means of aerial rootlets. The plant is native to the woods of eastern Mexico but is cultivated in tropical countries where the temperature does not fall below 18°C and where the humidity is high.

The plant is usually propagated by means of cuttings and, after 2 or 3 years, reaches the flowering stage. It continues to bear fruit for 30 or 40 years. The flowers, approximately 30 on each plant, are hand pollinated, thus producing larger and better fruits. The fruits are collected as they ripen to a yellow color, 6 to 10 months after pollination, and are cured by dipping in warm water and repeated sweating between woolen blankets in the sun during the day and packing in wool-covered boxes at night. This requires about 2 months, during which the pods lose from 70 to 80% of their original weight and take on the characteristic color and odor of the commercial drug. The pods are then graded, tied into bundles of about 50 to 75, and sealed in tin containers for shipment.

The Spaniards found that the Aztecs of Mexico used vanilla as a flavor for cocoa and consequently introduced its use into Europe. Cultivation began in Réunion and Madagascar (now the Malagasy Republic) in 1839, and shortly after, other countries adopted this practice.

Green vanilla contains two glycosides, glucovanillin (avenein) and glucovanillic alcohol. Glucovanillin is hydrolyzed by 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). Vanillin is the principal flavoring constituent. Vanilla also contains about 10% of sugar, 10% of fixed oil, and calcium oxalate.

USES. Vanilla, in the form of vanilla tincture, is used as a flavoring agent and as a pharmaceutic aid. It is a source of vanillin.

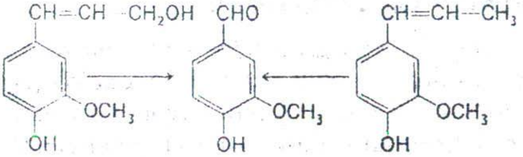
COMMERCIAL VARIETIES:

Mexican or Vera Cruz vanilla is the best grade on the market; the pods frequently attain a length of 30 to 35 cm. The supply is largely consumed in Mexico and the United States.

Bourbon vanilla is produced on the island of Réunion and shipped from the Malagasy Republic. It resembles the Mexican variety but is about two thirds as long, blacker in color, usually covered with a sublimate of needle-shaped vanillin crystals, and possesses a coumarinlike odor.

Tahiti vanilla, grown in Tahiti and Hawaii, is reddish brown in color and about as long as the Mexican variety but sharply attenuated and twisted in the lower portion. The odor is somewhat unpleasant, and the variety is less suitable for flavoring.

Vanilla splits and cuts represent the more mature fruits in which dehiscence has taken place. They are cut into short lengths.



Coniferyl alcohol Vanillin Isoeugenol

Vanillin is 4-hydroxy-3-methoxybenzaldehyde or methylprotocatechuic aldehyde. It may be obtained from vanilla or prepared synthetically from other sources: (1) coniferin, a glycoside present in the cambium sap of pine trees; (2) eugenol, a phenol present in clove oil; and (3) lignin, a by-product of the pulp industry. Most of the vanillin in commerce is made from lignin.

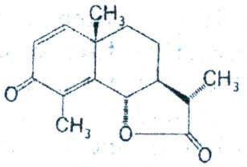
Vanillin consists of fine, white to slightly yellow, needlelike crystals that have an odor and a taste resembling vanilla. It is slightly soluble in water and glycerin and is freely soluble in alcohol, chloroform, and ether. Vanillin is employed as a flavoring agent.

Ethyl vanillin, a synthetic analog of vanillin, is also used as a flavoring agent.

LACTONE GLYCOSIDES

Although **coumarin** is widely distributed in plants, glycosides containing coumarin as such are rare. Several glycosides of hydroxylated coumarin derivatives, however, occur in plant materials; these glycosides include skimmin in Japanese star anise, aesculin in various parts of the horse chestnut tree, daphnin in mezereum, fraxin in ash bark, scopolin in belladonna, and limettin in citrus trees. None of the hydroxycoumarin glycosides is of particular medicinal importance.

Some use has been made of natural, nonglycosidic coumarin and other lactone substances. Coumarin and **tonka beans,** coumarin-containing seeds of *Dipteryx odorata* (Aublet) Willdenow and *D. oppositifolia* (Aublet) Willdenow, (Fam. Leguminosae), were formerly used pharmaceutically as flavoring agents. Some coumarin derivatives still find application for their anticoagulant properties. The antispasmodic activity of the barks of *Viburnum prunifolium* Linné (blackhaw) and *V. opulus* Linné (true cramp bark) (Fam. Caprifoliaceae) has been attributed to scopoletin (6-methoxy-7-hydroxy-coumarin) and other coumarins. Preparations of these plant drugs were used at one time as uterine sedatives. Other lactone-containing natural products include **cantharidin and methoxsalen** which are used for dermatologic purposes, and **santonin,** which is obtained from the unexpanded flowerheads of *Artemisia cina* Berg, *A. maritima* Linné and several other *Artemisia* species (Fam. Compositae). Santonin was formerly used as an anthelmintic, but its use has been discontinued in the United States because of its potential toxicity.



Santonin

Coumarin

Coumarin is the lactone of *o*-hydroxycinnamic acid. It occurs as colorless, prismatic crystals and has a characteristic fragrant odor and a bitter, aromatic, burning taste. It is soluble in alcohol. Coumarin can be synthesized readily.

Coumarin is rather widely distributed in nature. In addition to its occurrence in tonka beans (1 to 3%), it has been isolated from sweet vernal grass (*Anthoxanthum odoratum* Linné, Fam. Gramineae), sweet clover [*Melilotus albus* Medicus and *M. officinalis* (Linné) Lamarck, Fam. Leguminosae], sweet-scented bedstraw (*Galium triflorum* Michaux, Fam. Rubiaceae), and red clover (*Trifolium pratense* Linné, Fam. Leguminosae).

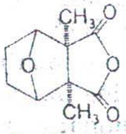
Coumarin and extracts of tonka beans were formerly used as flavoring agents. However, coumarin-drug interactions occur with a number of therapeutic substances, and the FDA has banned the use of coumarin and coumarin-containing materials for flavoring purposes.

Bishydroxycoumarin or dicumarol is a drug related to coumarin. It was obtained originally from improperly cured leaves and flowering tops of *Melilotus officinalis* (Linné) Lamarck (Fam. Leguminosae), but it is now prepared synthetically.

Dicumarol is an anticoagulant. The usual dose is 200 to 300 mg initially, then 25 to 200 mg once a day, as indicated by prothrombin-time determinations. A number of synthetic analogs of bishydroxycoumarin also are used in anticoagulant therapy; these include warfarin salts (Athrombin-K®, Coumadin®, Panwarfin®) and phenprocoumon (Liquamar®).

Cantharides

Cantharides, Spanish flies, Russian flies, or blistering flies consists of the dried insect, *Cantharis vesicatoria* (Linné) De Geer (Fam. Meloidae). *Cantharis* is Greek and means beetle, and *vesicatoria* is from the Latin *vesica*, meaning a bladder, and refers to the blistering qualities. This insect is found on certain shrubs of the Caprifoliaceae and Oleaceae that grow in southern and central Europe. The mature insects, which are brilliant green with a metallic luster, usually appear in June or July. In the early morning, when the insects are still sluggish from the cold night air, the shrubs are shaken or beaten with poles, and the insects are collected on cloths spread on the ground. They are killed by plunging them into dilute vinegar, by exposure to the fumes of hot vinegar, ammonia, or sulfur dioxide, or by means of chloroform, ether, or similar drugs. After the insects are killed, they are carefully dried at a temperature not higher than 40°C. The drug should be stored in tight containers, and a few drops of chloroform or carbon tetrachloride should be added occasionally to preserve the drug from attack by other insects.



Cantharidin

Cantharides contains as its chief constituent the vesicating principle, cantharidin (0.6 to 1.0%), which is the lactone or anhydride of cantharidic acid. In addition, about 12% of a fat is associated with the cantharidin in the soft body tissues of the insect.

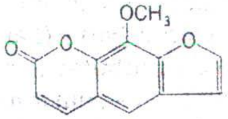
USES. Cantharides is an irritant, a vesicant, and rubefacient. If taken internally, it is excreted by the kidney, irritates the urinary tract, and can result in priapism. This accounts for the drug's popular reputation as an aphrodisiac. Internal administration of cantharides is potentially dangerous, however, and deaths have been reported. Topical application of a solution of cantharidin is effective in the removal of certain types of warts; preparations containing 0.7% cantharidin in collodion (Cantharone® and Verr-Canth®) are available for this purpose.

Psoralens

Psoralens are photosensitizing furocoumarins that occur in a number of plant families, including the Umbelliferae, where they are a common cause of phototoxicity. **Methoxsalen, 8-methoxypsoralen, or xanthotoxin,** a constituent of the cremocarps of *Ammi majus* Linné (Fam. Umbelliferae), is used to facilitate repigmentation in idiopathic vitiligo (leukoderma) and for symptomatic control of severe, disabling psoriasis. Methoxsalen may be applied topically or taken orally. Therapeutic regimens require cautious patient exposure to ultraviolet radiation (sunlight); repigmentation therapy usually involves extended periods of time. Risks inherent in therapy with methoxsalen, including carcinogenesis, cataract development, and actinic degeneration of the skin, restrict its use to specialists.

PRESCRIPTION PRODUCT. Oxsoralen®.

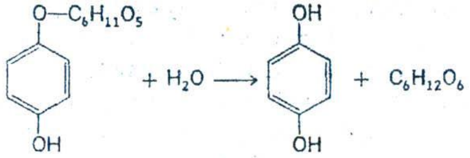
Trioxsalen (Trisoralen®), a synthetic furocoumarin, is also available for use in the treatment of vitiligo.



Methoxsalen

PHENOL GLYCOSIDES

The aglycone groups of many of the naturally occurring glycosides are phenolic in character. Thus, arbutin, found in uva ursi, chimaphila, and other ericaceous drugs, yields hydroquinone and glucose upon hydrolysis. Hesperidin, which occurs in various citrus fruits (page 73) and is included with the flavonol group, may be classified as a phenol glycoside. Phloridzin, found in the root bark of rosaceous plants, baptisin from baptisia, and iridin from *Iris* species are additional examples of phenol glycosides.



Arbutin **Hydroquinone** **Glucose**

Uva Ursi

Uva ursi or bearberry is the dried leaf of *Arctostaphylos uva-ursi* (Linné) Sprengel or its varieties *coactylis* or *adenotricha* Fernald and MacBride (Fam. Ericaceae). The plant is a procumbent evergreen shrub indigenous to Europe, Asia, and the northern United States and Canada.

In addition to the glycoside, arbutin, the leaves contain corilagin, pyroside, several esters of arbutin, quercitin, gallic acid, elagic acid, and ursolic acid.

Uva ursi has a long history of use for its diuretic and astringent properties. Extract of uva ursi was formerly an ingredient in some proprietary formulations, but its use in prescription medications has been replaced by more effective diuretic agents. The inclusion of uva ursi and other diuretic materials in various products intended for weight reduction is without recognized merit.

TANNINS

Tannins comprise a large group of complex substances that are widely distributed in the plant kingdom; almost every plant family embodies species that contain tannins. When tannins occur in appreciable quantities, they are usually localized in specific plant parts, such as leaves, fruits, barks, or stems.

Chemically, tannins are complex substances; they usually occur as mixtures of polyphenols that are difficult to separate because they do not crystallize. Some authors prefer to use the term "tannin extracts" rather than "tannins." Recently, the use of chromatographic methods has enabled research workers not only to confirm the complicated nature of tannin extracts but also to identify the simple polyphenols present in small amounts in such mixtures. Determination of the latter is important because complex tannins are generally considered to have arisen from simple polyphenols by polymerization. Many condensed tannins have never been isolated or characterized; thus, their biogenetic development is not positively known.

Tannins are customarily divided into 2 chemical classes, based on the identity of the phenolic nuclei involved and on the way they are joined. Members of the first class consist of gallic acid or related polyhydric compounds esterified with glucose Because such esters are readily hydrolyzed to yield the phenolic acids and the suga they are referred to as **hydrolyzable tannins.**

Nonhydrolyzable or condensed tannins compose the second class. Basically, these tannins contain only phenolic nuclei but frequently are linked to carbohydrates or proteins. Most such tannins result from the condensation of 2 or more flavan-3-ols, such as catechin, or of flavan-3,4-diols, such as leucocyanidin. When treated with hydrolytic agents, these tannins tend to polymerize, yielding insoluble, usually red-colored products known as phlobaphenes.

Both classes of tannins are widely distributed in nature. It must be emphasized that, in many species, both types are present, although one type generally tends to predominate in any particular plant part.

Tannins are noncrystallizable compounds that, with water, form colloidal solutions possessing an acid reaction and a sharp "puckering" taste. They cause precipitation of solutions of gelatin as well as of alkaloids, they form dark blue or greenish black soluble compounds with ferric salts, they produce a deep red color with potassium ferricyanide and ammonia, and they are precipitated by salts of copper, lead, and tin and by strong aqueous potassium dichromate (or 1% chromic acid) solutions. In alkaline solutions, many of their derivatives readily absorb oxygen.

Tannins precipitate proteins from solution and can combine with proteins, rendering them resistant to proteolytic enzymes. When applied to living tissues, this action is known as an "astringent" action and forms the basis for therapeutic application of tannins. Tannin-bearing drugs, such as hamamelis and nutgall, as well as partially purified tannins (tannic acid) and their derivatives (acetyltannic acid), are employed in medicine as astringents in the gastrointestinal tract and on skin abrasions. In the treatment of burns, the proteins of the exposed tissues are precipitated and form a mildly antiseptic, protective coat under which the regeneration of new tissues may take place.

Considerable epidemiologic and experimental evidence suggests that prolonged utilization of certain tannin-rich plant materials may be hazardous owing to their carcinogenic potential. The habitual chewing of betel nut *(Areca catechu)*, an alkaloid-containing drug that is also rich in condensed catechin tannin, has been linked to high rates of oral and esophageal cancer in India and South Africa. Even the drinking of ordinary tea (leaves of *Camellia sinensis*) has been implicated. Apparently, the British, who add milk to their tea, thereby binding the tannin, have a much lower incidence of esophageal "obstruction" than do the Dutch, who formerly drank large quantities of tea without milk. Experimentally, the subcutaneous injection into rats of aqueous extracts of tannin-rich *Areca catechu* and *Rhus copallina* produced a significant number of malignant mesenchymal tumors.

The ability of tannins to precipitate proteins is also utilized in the process of vegetable tanning, which converts animal hides to leather. The tannin not only affects the pliancy and toughness of the leather but also acts as a preservative because of its antiseptic qualities. Various types of tannins produce a variety of leathers; thus, certain hydrolyzable types form a "bloom," whereas the nonhydrolyzable types produce the "tanner's red." The deeply colored compounds obtained with iron salts have been used on a commercial scale in the manufacture of inks. Because of their precipitating qualities, solutions of tannins are utilized in the laboratory as reagents for the detection of gelatin, proteins, and alkaloids. In the antidotal treatment of alkaloidal poisoning, tannin solutions are extremely valuable for inactivating the alkaloid by the formation of insoluble tannate.

TANNIN-CONTAINING PLANT MATERIALS

Hamamelis Leaf

Hamamelis leaf or witch hazel leaves is the dried leaf of *Hamamelis virginiana* Linné (Fam. Hamamelidaceae).

Hamamelis is from the Greek *hama*, meaning at the same time, and *melis*, meaning a fruit; *virginiana* indicates that the plant is found in Virginia, although the actual habitat ranges from New Brunswick to Minnesota and extends southward to Florida and Texas. The plant is a shrub or small tree that attains a height of 8 meters and is found particularly in low, damp woods. The flowers appear in the fall as the fruits of the previous year ripen (Fig. 3–11). The leaves are collected throughout the summer and are dried in the open air, preferably under shade to preserve the green color. The commercial supply comes from the Blue Ridge Mountain region, chiefly

Fig. 3–11. Witch hazel branches with foliage, flowers, and fruit. (Photo courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

from Virginia, North Carolina, and Tennessee. The decoction or infusion of witch hazel leaves has been commonly used since the days of the early colonists who learned of the drug from the American Indians.

CONSTITUENTS. Hamamelis leaf contains hamamelitannin and a second tannin that appears to be derived from gallic acid; a hexose sugar, a volatile oil, a bitter principle, gallic acid, and calcium oxalate. Hamamelis leaf possesses astringent and hemostatic properties.

Hamamelis Water or Distilled Witch Hazel Extract is prepared by steam distillation of the recently cut and partially dried dormant twigs of *Hamamelis virginiana*. Essentially, it is a hydroalcoholic solution of the volatile oil of that plant.

Analyses of the volatile oil reveal that it contains 2-hexen-1-al (9.7%), acetaldehyde (3.2%), α-ionone (3.5%), β-ionone (1.0%), and safrole (0.2%).

USES. Although tannins are not carried over in the distillation process, hamamelis water is nevertheless widely utilized for its so-called astringent properties. It is incorporated in hemorrhoidal products, preparations for treating insect bites and stings, and even teething preparations. The contained volatile oil does confer a pleasant fragrance to such products.

PROPRIETARY PRODUCTS. Hamamelis water is an ingredient in Dr. Hands Teething Gel and Lotion®, Gentz Wipes®, Mediconet®, Perifoam®, Preparation H Cleansing Pads®, and Tucks®.

Nutgall

Nutgall is the excrescence obtained from the young twigs of *Quercus infectoria* Olivier and allied species of *Quercus* (Fam. Fagaceae). The galls are obtained principally from Aleppo in Asiatic Turkey.

The excrescence (gall) is caused by the puncture of a hymenopterous insect, *Cynips tinctoria*, and the presence of the deposited ovum. Several stages in the development of the gall correspond to the development of the insect:

1. When the larva begins to develop and the gall begins to enlarge, the cells of the outer and central zones contain numerous small starch grains.
2. When the chrysalis stage is reached, the starch near the middle of the gall is replaced in part by gallic acid, but the peripheral and central cells contain masses of tannic acid.
3. As the winged insect develops, nearly all of the cells contain masses of tannic acid with a slight amount of adhering gallic acid.
4. When the insect emerges from the gall, a hole to the central cavity is formed. Thus, the tannic acid, owing to the presence of moisture and air, may be oxidized in part into an insoluble product, and the gall becomes more porous, thereby constituting the so-called **white gall** of commerce.

The technical and medicinal use of galls was known to the ancient Greeks (450 B.C.). Since the Crusades, great quantities of galls have been exported from Asia Minor.

CONSTITUENTS. The principal constituent is tannic acid, which is found to the extent of 50 to 70%; the drug also contains gallic acid, 2 to 4%; ellagic acid; starch; and resin.

Nutgall, the chief source of tannic acid, is used in the tanning and dyeing industry and, formerly, in the manufacture of ink. Medicinally, it has astringent properties.

ALLIED PRODUCTS. **Japanese and Chinese galls** are formed on *Rhus chinensis* Mill. (Fam. Anacardiaceae) as a result of the stings of certain plant lice *(Aphis)*. These galls are rich in tannin and, as they contain less coloring matter than the oak galls, are used in the manufacture of gallic acid.

Tannic Acid

Tannic acid, gallotannic acid, or tannin is a tannin usually obtained from nutgall. The powdered galls are extracted with a mixture of ether, alcohol, and water and the liquid separates into 2 layers. The aqueous layer contains gallotannin and the ethereal layer contains the free gallic acid present in the gall. After separation, the solution of gallotannin is evaporated and the tannin is purified in various ways.

COMPOSITION. Tannic acid is not a single homogeneous compound but is a mixture of esters of gallic acid with glucose, whose exact composition varies according to its source. The tannin from Chinese galls analyzes entirely as octa- or nonagalloyl-glucose and yields, on hydrolysis, methyl gallate and 1,2,3,4,6-pentagalloylglucose. Turkish tannin, which is a mixture of hexa- or heptagalloylglucoses, hydrolyzes to form methyl gallate and a mixture of 1,2,3,6- and 1,3,4,6-tetragalloylglucose. On milder treatment, both types of tannic acid yield methyl *m*-digallate, indicating the presence of a *m*-trigalloyl group in each.

DESCRIPTION. Tannic acid occurs as an amorphous powder, glistening scales, or spongy masses that are light brown to yellowish white. The odor is faint and the taste is strongly astringent. Tannic acid is soluble in water, alcohol, and acetone and insoluble in ether, chloroform, and benzin.

USES AND DOSES. Tannic acid is an astringent. It was formerly used in the treatment of burns, but this application has been discontinued. Its topical use is now restricted to the treatment of bed sores, minor ulcerations, and the like. As an alkaloidal precipitant, it has been employed in cases of alkaloidal poisoning.

PROPRIETARY PRODUCTS. Preparations that incorporate tannic acid as an astringent include Amertan®, Hemocaine®, Kankex®, Tanac®, and Tannic Spray®.

Gallic acid is 3,4,5-trihydroxybenzoic acid that crystallizes with 1 molecule of water. It occurs in nutgall and can be prepared from tannic acid by hydrolysis with dilute acids. Bismuth subgallate is used by ostomates to help control odors.

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