Chapter 3
Secondary Metabolites: Secondary Metabolic Products Consisting of C and H; C, H, and O; N, S, and P Elements; and O/N Heterocycles

Abstract Terpenes and terpenoids, steroids and sterols, volatile oils, miscellaneous isoprenoids, phenols and phenyl propanoids, alkaloids, glycosides, bitter principles, resins, saponins, cardioactive compounds, etc., are important groups of secondary metabolites of plant origin. Terpenes and terpenoids are naturally occurring hydrocarbons, and ~2000 plant species of 60 families produce more than 55,000 terpenes and their derivatives. Terpenes are built from isoprene monomer (C_5H_8), and $(C_5H_8)_n$ is the basic molecular formula. The oxygen-containing terpenes are called terpenoids or isoprenoids while steroids are cyclic terpenoids, and sterols are steroid alcohols. Terpenoids have significant importance in food, pharmaceutical, and cosmetic industry. Terpenoids contribute to plant essential oils (eucalyptus, lavender, thyme, and mint), flavors (cinnamon, cloves, and ginger), color (yellow—sunflowers, red—tomatoes), etc. They protect plant against predators and pests (e.g., from herbivores, insects, fungi, microorganisms, etc.), aid to pollination and dispersal of spores, and in living organisms function range from pigments and fragrances to vitamins and precursors of sex hormones. Plant sterols, including campesterol, inhibit the absorption of cholesterol in the intestines and thereby reduce LDLs or cholesterol level. Phenols or phenolics are a class of chemical compounds with a benzene nucleus supporting a hydroxyl group and range from simple substances like phenolic acids or phenols, cumarines, flavonoids, and quinines to very complex ones such as lignins and tannins. Phenol and its chemical derivatives are used in the production of detergents, phenoxy herbicides, numerous pharmaceutical drugs, and many industrial synthetic goods. Alkaloids are cyclic bitter organic compounds containing nitrogen in a negative state of oxidation having a marked physiological action on man and other animals. A large variety of organisms produce alkaloids, including bacteria, fungi, plants, and animals. Alkaloids like caffeine, ephedrine, codeine, colchicine, nicotine, pilocarpine, opium, quinine, reserpine, cocaine, psilocin morphine, atropine, berberine, vincristine, yohimbine, etc., are some common examples of drugs principles of pharmaceutical importance and often are used as recreational drugs, or in entheogenic rituals. A glycoside is a heteromolecule consisting of a non-sugar (aglycone) and a sugar part (glycone) components. The glycone may be monosaccharide or oligosaccharide, and the aglycone may be an alcohol, anthraquinone derivative,

A. N. M. Alamgir, *Therapeutic Use of Medicinal Plants and their Extracts: Volume 2*, Progress in Drug Research 74,
https://doi.org/10.1007/978-3-319-92387-1_3

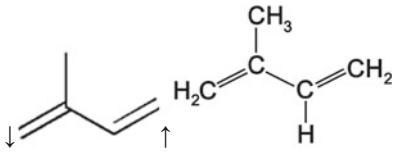
phenol, aldehyde, acid, ester, or another compound. Glycosides play numerous important roles in living organisms, and many such plant glycosides are used as medications, e.g., the active principles of digitalis, strophanthus, cascara, willow, and poplar barks are being among the most valued remedies. The bitter principles are mostly terpenoid, especially the sesquiterpene lactones, monoterpene iridoids, and the secoiridoids. Diterpene bitters are found in columbo root and white horehound, and triterpenoids are the cause of bitterness in Cucurbitaceous plants, which is due to cucurbitacins. Plant lignans are diphenolic compounds (phenylpropanoids dimers) whose structure is the union of two units of phenylpropane. Tannins are non-nitrogenous bitter plant polyphenolic compounds having a molecular weight between 500 and 3000 (gallic acid esters) and up to 20,000 (proanthocyanidins). They are non-crystallisable colloidal compounds and may be (i) hydrolyzable tannins, which consist of gallic acid or related polyhydric compounds esterified with glucose, and they are readily hydrolysed to yield the phenolic acids and the sugar; and (ii) non-hydrolyzable or condensed tannins contain only phenolic nuclei and most of such tannins are formed by the condensation of two or more flavanols, such as catechin. Pharmaceutically, tannins have antibacterial, antiviral, antiparasitic, astringent, and antiseptic properties, and may be used in the treatment of hemorrhages (constrict of blood vessels), burns (cicatrizing), diarrhea, and as an antidote for alkaloid poisoning because of their ability to precipitate alkaloids; effective against 6-hydroxydopamine-induced toxicity and also have anti-inflammatory and antiulcer activity. Quinones are cyclic organic compounds (aromatic diketones) and are found in bacteria, in certain fungi, in various higher plant forms, and in a few animals (e.g., sea urchins, aphids, lac insects, and certain scale insects). It is highly active anti-microbacterial, antifungal agent and highly toxic and fatal if swallowed, inhaled, or absorbed through the skin and widely used in medicine, herbicides, chemical reagents, dyes, and tanning agents. Saponins are amphiphilic glucoside molecules composed of hydrophilic glycoside glycone and lipophilic triterpene or steroid aglycone. Saponins have been used in medicine, foaming agents, in fire extinguishers, and fish poisons. Drugs that influence heart or drugs having an influence on the heart are cardioactive drugs. (i) Beta-adrenoceptor antagonists, (ii) calcium channel blocking drugs, and (iii) cardiac glycosides are three major classes of cardioactive drugs. Cardiac glycosides are also important in the pathogenesis and therapy of different human diseases (e.g., stroke, diabetes, neurological diseases, cancer, etc.). Cardioactive steroids are a class of animal and plant-derived compounds with a steroid nucleus and a specific inotropic, chronotropic, and dromotropic effect. Cardioactive steroids (CAS) became the mainstay of treatment for congestive heart failure and to control the ventricular response rate in atrial tachydysrhythmias. Antibiotics are produced by different groups of microorganisms like bacteria, fungi, and actinomycetes and in many cases by higher plants. Antibiotics in low concentration are capable of inhibiting the growth of microorganisms through an antimetabolic mechanism. They differ from antiseptics and disinfectants in their mode of action, chemical, and physical properties. The development of resistance among the microorganisms on prolonged

contact with the drug is the present-day problems in the field of antibiotics. The microbial and plant sources from the terrestrial and marine environments are now providing natural products with antitumor activity.

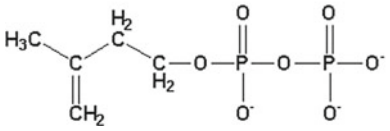
3.1 Secondary Products Consisting of C, H, and O Elements

3.1.1 Terpenes and Terpenoids

Terpenes and terpenoids are naturally occurring hydrocarbons and their derivatives (e.g., alcohols, glycosides, ethers, aldehydes, ketones, carboxylic acids, esters, etc.) all and about 2000 plant species of 60 families including Lamiaceae, Asteraceae, Rutaceae, Myrtaceae, Apiaceae, Pinaceae, etc., produce more than 55,000 terpenes and their derivatives. Buckingham (2004) in a conservative estimate suggests that at least 40,000 different terpenoids produced by a variety of plants, particularly conifers, though also by some insects (termites or swallowtail butterflies), which emit terpenes from their osmeteria. They are often strong smelling, many of which are of plant origin. Terpenes usually contain one or more C=C double bonds and are built from isoprene monomer, a hydrocarbon made up of five carbon atoms (C_5) attached to eight hydrogen atoms (CH_2=C(CH_3)–CH=CH_2=C_5H_8) and they are linked with each other to form linear chains or they may be arranged to form rings. According to isoprene rule or the C_5 rule, the basic molecular formula of terpenes is multiple of isoprene or $(C_5H_8)_n$, nature's common building blocks, and the natural-occurring terpenes and terpenoids obey the isoprene rule (Fig. 3.1). The oxygen-containing terpenes are called terpenoids or isoprenoids. Terpenoids form a large and diverse class of naturally occurring lipid-like chemicals and form the



(Head) Isoprene(Tail) **Isoprene unit (C_5H_8)**



Terpenoid- isopentenyl pyrophosphate(2-methyl-1, 3-butadiene)

Fig. 3.1 Isoprene (C_5H_8)—building block of terpenes and terpenoids

largest class of natural products. The isopropyl part of isoprene (2-methylbutane) is defined as the head, and the ethyl residues the tail. In mono-, sesqui-, di-, and sesterpenes, the isoprene units are linked to each other from head to tail; tri- and tetraterpenes contain one tail-to-tail connection in the center.

Terpenoids have significant importance in food, pharmaceutical, and cosmetic industry. Terpenoids contribute to plant essential oils (eucalyptus, lavender, thyme, mint), flavors (cinnamon, cloves, and ginger), color (yellow—sunflowers, red—tomatoes), etc. They include essential oils, iridoids, lactones, sesquiterpenics, saponins, and cardiotonic heterosides. Citral, menthol, camphor, turpentine, salvinorin A (in *Salvia divinorum*), cannabinoids (in *Cannabis* spp.), ginkgolide and bilobalide (in *Ginkgo biloba*), and the curcuminoids (in *Curcuma longa* and also in *Brassica* spp.) are some of the examples of much known terpenoids of pharmaceutical importance. They protect plant against predators and pests (e.g., from herbivores, insects, fungi, microorganisms, etc.), aid to pollination and dispersal of spores, and in living organisms function range from pigments and fragrances to vitamins and precursors of sex hormones.

Resin and turpentine contain terpenes. Many terpenes are used as major biosynthetic building blocks steroids (derivatives of triterpene squalene), vitamin A (derivatives of tetraterpenoid carotene). Biologically active terpenoids span various orders of magnitude including natural flavor additives for food or fragrances in perfumery and in traditional and alternative medicines as aromatherapy. Application of taxol derivatives, paclitaxel, and docetaxel in cancer chemotherapy is the most comprehensively studied case. In addition to cancer therapies, there are so many important aspects of the pharmacological usage of natural terpenoids including antimicrobial, antifungal, antiviral, antiparasitic, anti-allergenic, antihyperglycemic, anti-inflammatory, antioxidants, antiseptics, expectorants, gastrointestinal disorder, pain relievers, immunomodulatory, and skin permeation enhancer, cholesterolemia, tracheal and bronchial disorders, arthritis, rheumatism, and also to have properties (Wagner and Elmadfa 2003). Epidemiological and experimental studies suggest that monoterpenes may be helpful in the prevention and therapy of several cancers, including mammary, skin, lung, forestomach, colon, pancreatic, and prostate carcinomas (Gould 1997; Crowell 1999). Numerous preclinical efficacy studies have provided extensive evidence that both naturally occurring and synthetic derivatives of triterpenoids possess chemopreventive and therapeutic effects against colon, breast, prostate, and skin cancer (Liby et al. 2007; Rabi and Gupta 2008; Bishayee et al. 2011). A large number of triterpenoids have been shown to suppress the growth of a variety of cancer cells without exerting any toxicity in normal cells (Setzer and Setzer 2003; Petronelli et al. 2009).

Terpenes and terpenoids appear in the leaf, bark, wood, root, rhizome, flower, fruit, and seed of the medicinal and aromatic plants such as bay leaf, cinnamon bark, ginger, sandalwood, nutmeg, thyme, clover, eucalyptus, *Cannabis sativa*, etc. The livers of fishes and other animals are particularly rich in oils that are largely acyclic triterpenoid hydrocarbons, especially squalene. Many of the terpenoid molecules, however, are only found in very low levels in nature. Synthetic biology

and metabolic engineering may provide innovative approaches to increase the production of terpenoids in natural sources. Iridoids are monoterpenic compounds, from a type of Australian ant (*Iridomyrmex* genus), in plants as glycosides, prevalent in the plant root of subclass Asteridae (Ericaceae, Loganiaceae, Gentianaceae, Rubiaceae, Verbenaceae, Lamiaceae, Oleaceae, Plantaginaceae, Scrophulariaceae, Valerianaceae, and Menyanthaceae), harpagosides from the tuberous roots of the harpagophytum, also known as grapple plant, wood spider or devil's claw (*Harpagophytum procumbens* of Pedaliaceae), oleuropeoside in olive leaf (*Olea europaea* of Oleaceae), and genciopicroside in the roots of the genciana (*Gentiana lutea* of Gencianaciae).

Classification

Terpenes may be classified on the basis of the number of isoprene (5C) units in the molecule as (Table 3.1).

Table 3.1 Different classes of terpenes with information about isoprene units, number of carbon atoms, class name, and examples

Classes of terpenes			
Isoprene units	Number of carbonatoms	Classes of terpenes	Examples
1	5	Hemiterpene (2-methylbutane)	Isoprene; prenol, and isovaleric acid are hemiterpenoids
2	10	Monoterpene (2,6-dimethyloctane)	Geraniol, limonene, terpineol
3 (1.5)	15	Sesquiterpene (2,6,10-trimethyldodecane)	Humulene farnesane, farnesol
4	20	Diterpene (2,6,10,14-tetramethylhexadecane)	Cafestol, phytene, kahweol, cembrene, and taxadiene
5 (2.5)	25	Sesterterpene (2,6,10,14,18-pentamethyl icosane)	Manoalide
6	30	Triterpene (2,6,10,15,19,23-hexamethyl tetracosane)	Squalene
7	35	Sesquarterpenes ($C_{35}H_{56}$)	Ferrugicadiol, tetraprenylcurcumene
8	40	Tetraterpene ($C_{40}H_{64}$)	α,β-bicyclic & γ-monocyclic carotenes, acycliclycopene
>8	>40	Polyisoprene$(C_5H_8)_n$ $n > 8$	Rubber with cis and gutta-percha with trans double bonds

3.1.1.1 Hemiterpenes

Hemiterpenes consist of a single isoprene unit (C_5H_8). Isoprene itself is considered the only hemiterpene, but oxygen-containing derivatives such as prenol and isovaleric acids are hemiterpenoids (Fig. 3.2).

Prenol (3-methyl-2-buten-1-ol) is a natural alcohol and a representative of the simplest terpenoids. It is clear colorless oil that is reasonably soluble in water and miscible with most common organic solvents. It has a fruity odor and is used occasionally in perfumery. Prenol occurs naturally in citrus fruits, cranberry, bilberry, currants, grapes, raspberry, blackberry, tomato, white bread, hop oil, coffee, arctic bramble, cloudberry, and passion fruit. Isovaleric acid [$(CH_3)_2CHCH_2COOH$] is a colorless liquid that is sparingly soluble in water, but highly soluble in most common organic solvents. It has a strong pungent cheesy or sweaty smell, but its volatile esters have pleasing scents and are used widely in perfumery. Isovaleric acid is seen as the primary cause of the flavors added to wine caused by Brettanomyces yeasts.

3.1.1.2 Monoterpenes

Monoterpenes consist of two isoprene units ($C_{10}H_{16}$). Monoterpenes may be linear or acyclic and contain rings or cyclic (Fig. 3.3). Besides, biochemical modifications such as oxidation or rearrangement produce the related monoterpenoids acyclic monoterpenes, and monoterpenoids include geraniol, ocimene, myrcenes and their oxidative products citral, citronellal, citronellol, linalool, and many others. Halomon is a halogenated monoterpene found in marine organisms. Classic examples of cyclic monoterpenes are limonene, phellandrenes, terpinolene, carvone, etc. Menthol, thymol, carvacrol, and many others are terpenoids derived from monocyclic terpenes. Bicyclic monoterpenes include pinene, carene, sabinene, camphene, iridoids, and thujene. Camphor, borneol, and eucalyptol are examples of bicyclic monoterpenoids containing ketone, alcohol, and ether functional groups, respectively.

Geraniol is a monoterpenoid alcohol. It is the primary part of rose oil, palmarosa oil, and citronella oil (Java type). It also occurs in small quantities in geranium, lemon, and many other essential oils. Geraniol appears to be an effective

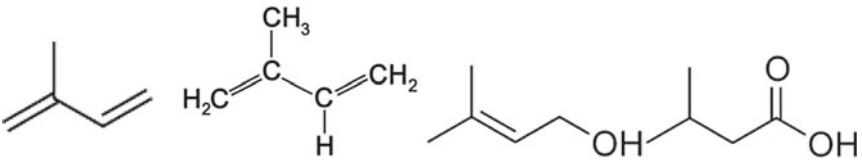


Fig. 3.2 Structure of hemiterpene and hemiterpenoids

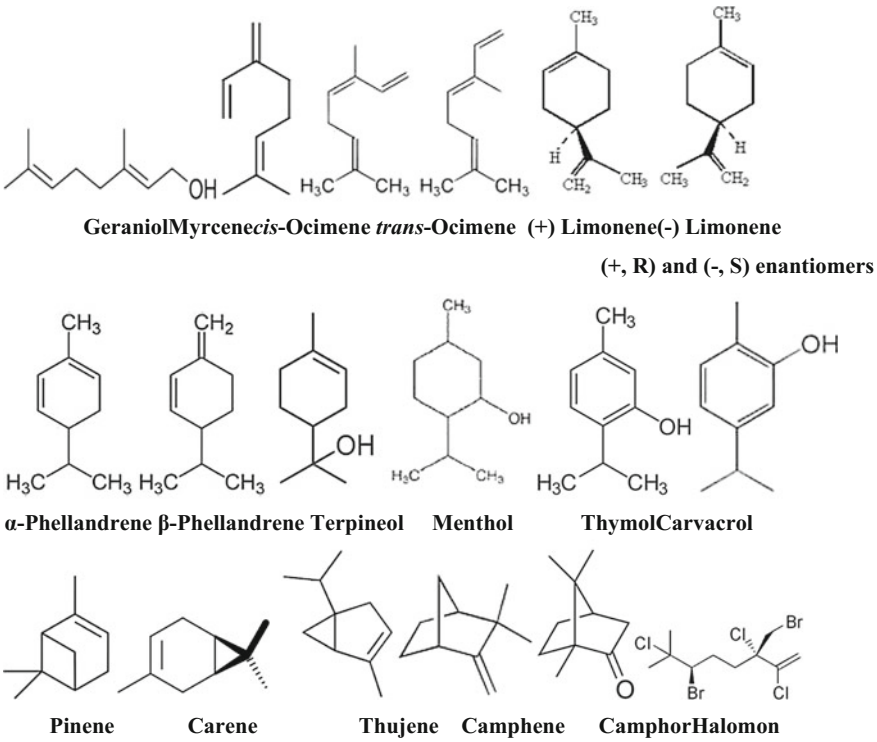


Fig. 3.3 Structure of different monoterpenes and monoterpenoids of plant origin

plant-based mosquito repellent. Limonene is an odor contributing colorless liquid cyclic terpene of the citrus fruits. Limonene is a chiral molecule, and biological sources produce one enantiomer, orange contains D-limonene ((+)-limonene), which is the (R)-enantiomer while lemon contains L-limonene ((−)-limonene), which is the (S)-enantiomer. The symbol R comes from the Latin rectus for right, and S from the Latin sinister for left. The more common D-isomer possesses a strong smell of oranges. Limonene is common in cosmetic products. D-limonene is used in food manufacturing and some medicines, e.g., as a flavoring to mask the bitter taste of alkaloids, and as a fragrant in perfumery, after shave lotions, bath products and other such products that include fragrance to their products; it is also used as botanical insecticide, particularly the (R)-(+)-enantiomer is most active as an insecticide. It is added to cleaning products such as hand cleansers to give a lemon-orange fragrance (see orange oil) and because of its ability to dissolve oils. L-limonene has a piney, turpentine-like odor. In alternative medicine, D-limonene is marketed to relieve gastroesophageal reflux disease and heartburn. Terpineol is a naturally occurring monoterpene alcohol that has been isolated from a variety of sources such as cajunut oil, pine oil, and petitgrain oil. There are four isomers, α-, β-, γ-terpineol, and terpinen-4-ol. Terpineol is usually a mixture of these

isomers with α-terpineol as the major constituent. Terpineol has a pleasant odor similar to lilac and is a common ingredient in perfumes, cosmetics, and flavors. α-terpineol is one of the two most abundant aroma constituents of lapsang souchong tea; the α-terpineol originates in the pine smoke used to dry the tea. Myrcene, or β-myrcene, is an olefinic monoterpene from Myrcia genus of Myrtaceae. It is a component of the essential oil of several plants including bay, cannabis, ylang-ylang, wild thyme, parsley, and hops. Myrcene has an analgesic effect and is likely to be responsible for the medicinal properties of lemongrass tea. It has anti-inflammatory properties through Prostaglandin E2.

Pinene ($C_{10}H_{16}$) is a bicyclic monoterpene chemical compound. There are two structural isomers of pinene found in nature: α-pinene and β-pinene. As the name suggests, both forms are important constituents of pine resin; they are also found in the resins of many other conifers, as well as in non-coniferous plants such as big sagebrush (*Artemisia tridentata*). Carene is a bicyclic monoterpene which occurs naturally as a constituent of turpentine, with a content as high as 42% depending on the source. Carene has a sweet and pungent odor, not soluble in water, but miscible with fats and oils. Natural sources of carene include turpentine, rosemary, and cedar. In higher concentrations, carene can be a skin irritant or central nervous system depressant. Thujene is a natural organic compound classified as a monoterpene. It is found in the essential oils of a variety of plants and contributes pungency to the flavor of some herbs such as Summer savory. Camphene is a bicyclic monoterpene. It is nearly insoluble in water, but very soluble in common organic solvents. It volatilizes readily at room temperature and has a pungent smell. It is a minor constituent of many essential oils such as turpentine, cypress oil, camphor oil, citronella oil, neroli, ginger oil, and valerian. It is produced industrially by catalytic isomerization of the more common alpha-pinene. Camphene is used in the preparation of fragrances and as a food additive for flavoring. Camphor is a terpenoid with the chemical formula $C_{10}H_{16}O$. It is a waxy, flammable, white or transparent solid with a strong aromatic odor found in the wood of the camphor laurel—*Cinnamomum camphora*, *Ocotea usambarensis*, *Rosmarinus officinalis*, etc. It can also be synthetically produced from oil of turpentine. It is used for its scent, as an ingredient in cooking (mainly in India), as an embalming fluid, for medicinal purposes, and in religious ceremonies. Camphor is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol, and acts as slight local anesthetic and antimicrobial substance. There are anti-itch gels and cooling gels with camphor as the active ingredient. Camphor is an active ingredient (along with menthol) in vapor-steam products, such as Vicks VapoRub. Camphor may also be administered orally in small quantities (50 mg) for minor heart symptoms and fatigue. Halomon is a polyhalogenated monoterpene first isolated from the marine red algae Portieria hornemannii. Halomon has attracted research interest because of its promising profile of selective cytotoxicity that suggests its potential use as an antitumor agent.

3.1.1.3 Sesquiterpenes

Sesquiterpenes consist of three isoprene units ($C_{15}H_{24}$). Sesquiterpenes and sesquiterpenoids include farnesol and farnesenes (acyclic); zingiberene, humulene, and bisabolol, (monocyclic), β-caryophyllene (bicyclic); artemisinin, longifolene, copaene, and alcohol patchoulol (tricyclic) (Fig. 3.4). Zingiberene, a monocyclic sesquiterpene, is the predominant constituent of the oil of ginger, and caryophyllene, a natural bicyclic sesquiterpene, is a constituent of many essential oils, especially clove oil, the oil from the stems and flowers of *Syzygium aromaticum*, the essential oil of *Cannabis sativa*, rosemary, hops, black pepper, etc. Bisabolol has a weak sweet floral aroma and is used in various fragrances. It has also been used for hundreds of years in cosmetics because of its perceived skin healing properties. Bisabolol, a natural monocyclic sesquiterpene alcohol from *Matricaria recutita* and *Myoporum crassifolium*, is known to have anti-irritant, anti-inflammatory, and antimicrobial properties. Artemisinin, an antimalarial principle from Artemisia annua L., is a cyclic sesquiterpene lactone-containing an unusual peroxide bridge, which is believed to be responsible for the drug's mechanism of action.

Humulene, also known as α-humulene or α-caryophyllene, is a naturally occurring monocyclic sesquiterpene ($C_{15}H_{24}$), which is an 11-membered ring, consisting of three isoprene units containing three nonconjugated C=C double bonds: two of them being triply substituted and one being doubly substituted terpenoid. Humulene is one of the essential oils made in the flowering cone of the hops plant (*Humulus lupulus*) and was first found in the essential oils of hops plant from which it derives its name. Humulene is an isomer of β-caryophyllene, and the two are often found together as a mixture in many aromatic plants. β-caryophyllene is a constituent of many essential oils, especially clove oil (*Syzygium aromaticum*), the essential oil of hemp (*Cannabis sativa*), rosemary (*Rosmarinus officinalis*), and hops. Proven α-humulene emitters into the atmosphere are pine trees, orange orchards, marsh elders, tobacco, and sunflower fields. α-Humulene is contained in

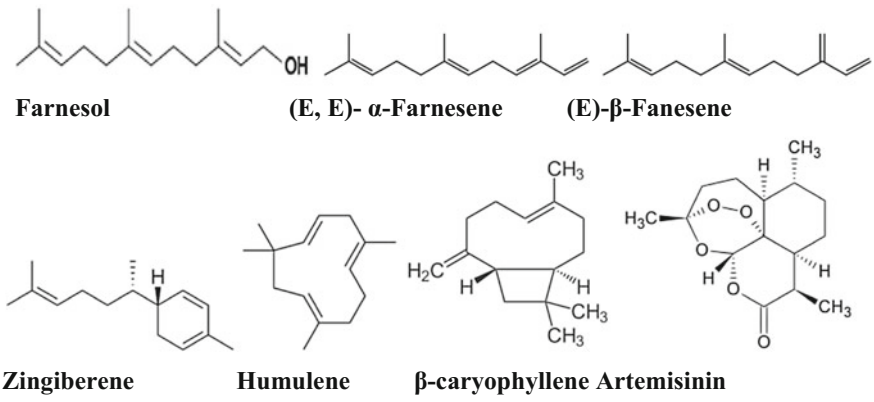


Fig. 3.4 Structure of different sesquiterpenes and sesquiterpenoids

the essential oils of aromatic plants such as common sage, culinary sage (*Salvia officinalis*), Uyaku or Japanese spicebush (*Lindera strychnifolia*), ginseng species (*Panax* spp.), *Mentha spicata*, members of ginger family (Zingiberaceae), Chinese laurel tree (*Litsea mushaensis*), and Brazilian coastal bush erva baleeira (*Cordia verbenacea*). Humulene has been found to produce anti-inflammatory effects in mammals and has potential to be a tool in the management of inflammatory diseases. It produces similar effects to dexamethasone and is found to decrease the edema formation caused by histamine injections. Humulene produced inhibitory effects on tumor necrosis factor-α (TNFα) and interleukin-1 β (IL1β) generation in carrageenan-injected rats.

The term farnesene includes a set of six closely related sesquiterpenes. α-Farnesene and β-farnesene are isomers, differing by the location of one double bond. α-Farnesene is 3,7,11-trimethyl-1,3,6,10-dodecatetraene, and β-farnesene is 7,11-dimethyl-3-methylene-1,6,10-dodecatriene. The alpha form can exist as four while the beta isomer exists as two stereoisomers about the geometry of its central double bond. (E, E)-α-Farnesene is the most common isomer. It is found in the coating of apples, and other fruits, and it is responsible for the characteristic green apple odor. Its oxidation by air gives compounds that are damaging to the fruit. The oxidation products injure cell membranes which eventually causes cell death in the outermost cell layers of the fruit, resulting in a storage disorder known as scald. (E) β-Farnesene has one naturally occurring isomer. The E isomer is a constituent of various essential oils. It is also released by aphids as an alarm pheromone upon death to warn away other aphids. Several plants, including potato species, have been shown to synthesize this pheromone as a natural insect repellent.Farnesol is present in many essential oils such as citronella, neroli, cyclamen, lemongrass, tuberose, rose, musk, balsam, and tolu. It is used in perfumery to emphasize the odors of sweet floral perfumes. Its method of action for enhancing perfume scent is as a co-solvent that regulates the volatility of the odorants. It is especially used in lilac perfumes. Farnesol is a natural pesticide for mites and is a pheromone for several other insects.

Sesquiterpene lactones are found in abundance in the species of Asteraceae, Lauraceae, and Magnoliaceae families, and are responsible for the bitter taste of many drugs; the holy thistle (*Cnicus benedictus*), absinthe (*Artemisia absinthium*), or dandelions (*Taraxacum officinale*). They are antibacterial and antifungal. Some produce dermatitis as they cause the formation of allergens. Artemisinin, an antimalarial sesquiterpenoid pharmaceutical from annual wormwood (*Artemisia annua*) that is being explored for production in metabolically engineered microbial fermentation systems and transgenic plants; taxol, a high-value diterpenoid-derived anticancer drug of limited supply from its initial natural source, the bark of the Pacific yew tree (*Taxus brevifolia*—a conifer of Taxaceae).

3.1.1.4 Diterpenes

Diterpenes composed of four isoprene units ($C_{20}H_{32}$). They derive from geranylgeranyl pyrophosphate. Diterpenes and diterpenoids include cafestol, ginkgolides, kahweol, cembrene, forskolin, aphidicolin, salvinorin A, taxol, phytol and taxadiene (precursor of taxol), and also diterpenes form the basis for biologically important compounds such as retinol, retinal, and phytol (Fig. 3.5).

Retinol is a diterpenoid alcohol. It is one of the animal forms of vitamin A. Retinol is convertible to other forms of vitamin A. Retinyl ester derivative serves as the storage form of the vitamin in animals. Retinaldehyde form of vitamin A is essential for vision, and retinoic acid is essential for skin health, teeth remineralization, and bone growth. These chemical compounds are collectively known as retinoids. Retinoids may be grouped as first-generation retinoids (retinol, retinal, retinoic acid, Retin-A, isotretinoin, alitretinoin); second-generation retinoids (etretinate, acitretin, etc.); and third-generation retinoids (tazarotene, bexarotene, adapalene, etc.).

Structurally, all retinoids also possess a β-ionone ring and a polyunsaturated side chain, with either an alcohol (retinol), aldehyde (retinal), a carboxylic acid group (retinoic acid) or an ester group (retinyl ester). The side chain is composed of four isoprenoid units, with a series of conjugated double bonds which may exist in trans- or cis-configuration (geometric isomerism describing the relative orientation of functional groups within a molecule, cis=on this side and trans="on the other side or" across). Retinol is produced in the body from the hydrolysis of retinyl esters, and from the reduction of retinal. Retinol in turn is ingested in a precursor form; animal sources (liver and eggs) contain retinyl esters, whereas plants (carrots, spinach) contain provitamin A carotenoids. Hydrolysis of retinyl esters results in retinol, while provitamin A carotenoids can be cleaved to produce retinal by carotene dioxygenase in the intestinal mucosa. Retinal (retinaldehyde or vitamin A aldehyde) is one of the many forms of vitamin A (the number of which varies from species to species). Retinal is a polyene chromophore, and bound to proteins called opsins is the chemical basis of animal vision. Bound to proteins called type 1 rhodopsins, retinal allows certain microorganisms to convert light into metabolic energy. Vertebrate animals ingest retinal directly from meat, or produce retinal from one of two carotenes (α-carotene, β-carotene), and also from another type of carotenoid known as β-cryptoxanthin (a type of xanthophyll), these must be obtained from plants or other photosynthetic organisms. No other carotenoids can be converted by animals to retinal, and some carnivores cannot convert any carotenoids at all. The other main forms of vitamin A, retinol, and retinoic acid may be produced from retinal. Retinoids regulate epithelial cell growth and diverse functions throughout the body including vision, cell proliferation and differentiation, growth of bone tissue, immune function, and activation of tumor suppressor genes. Retinoids are used in the treatment of many diverse diseases and are effective in the

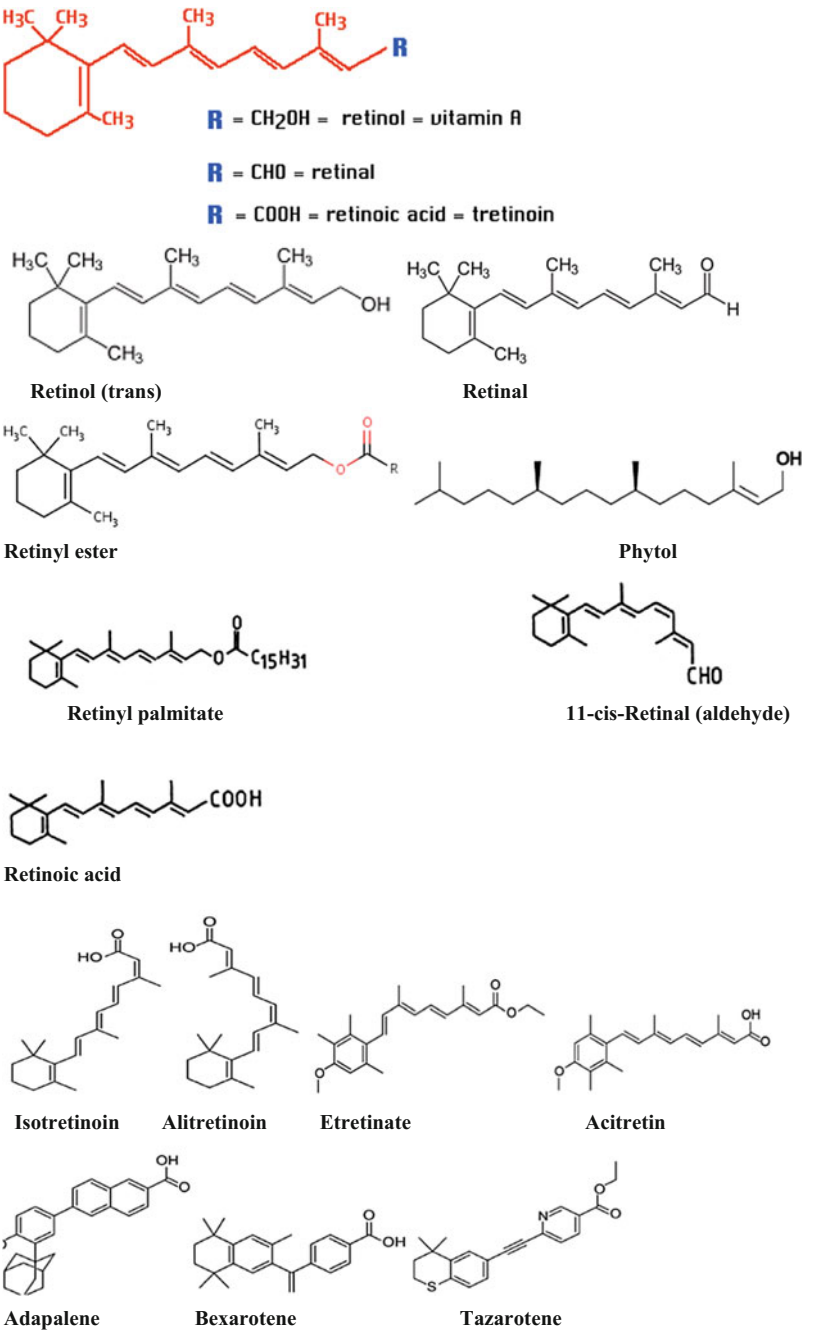
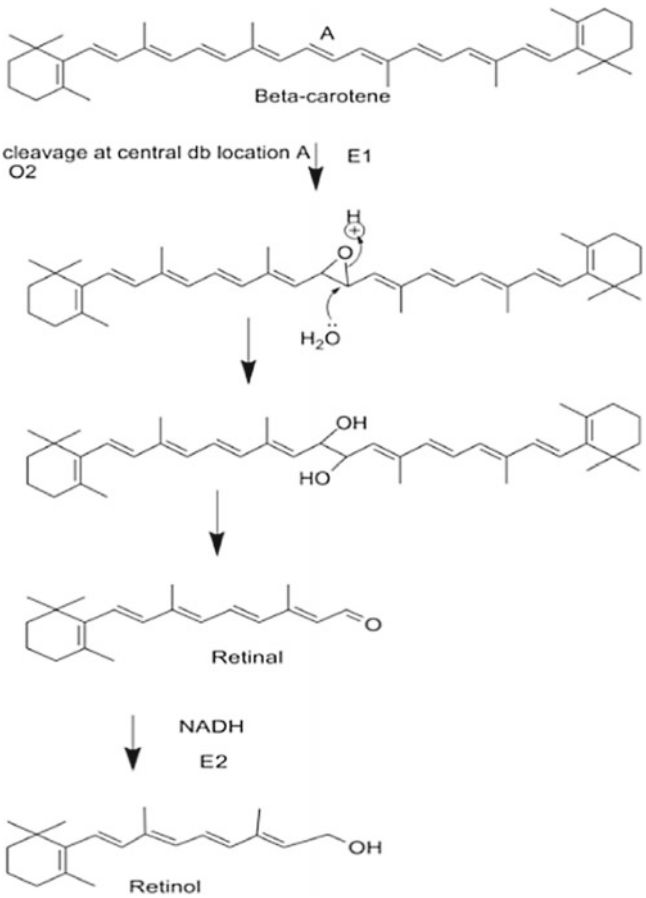


Fig. 3.5 Structure of different diterpenes

treatment of many dermatological conditions such as inflammatory skin disorders, skin cancers, disorders of increased cell turnover (e.g., psoriasis), and photoaging.

Phytol is an acyclic diterpene alcohol that can be used as a precursor for the manufacture of synthetic forms of vitamin E and vitamin K1. In ruminants, the gut fermentation of ingested plant materials liberates phytol, a constituent of chlorophyll, which is then converted to phytanic acid and stored in fats. Phytol is used in the fragrance industry and used in cosmetics, shampoos, toilet soaps, household cleaners, and detergents. Its worldwide use has been estimated to be approximately 0.1–1.0 metric tons per year. The 11 conjugated double bonds form the chromophore of the β-carotene molecule. On enzymatic hydrolysis and reduction, it produces retinol in the following way (Fig. 3.6).



E1= β-Carotene 15, 15'-monooxygenase; E2= Retinol dehydrogenase

Fig. 3.6 Enzymatic formation of retinol from β-Carotene

3.1.1.5 Sesterterpenes

Sesterterpenes ($C_{25}H_{40}$) are derived from geranylfarnesol pyrophosphate and have five isoprene units or 25 carbon atoms (prefix sester means half to three, i.e., 2.5) and they are rare relative to the other terpenes. Manoalide (**1**), secomanoalide (**2**), (*E*)-neomanoalide (**3**), and (*Z*)-neomanoalide (**4**) are representatives of bioactive sesterterpenes derived from different marine sponges and could lead to potential new drug candidates (Ebada et al. 2010). An example of a sesterterpenoid is geranylfarnesol (Fig. 3.7).

3.1.1.6 Triterpenes

Triterpenes consist of six isoprene units ($C_{30}H_{48}$). Triterpenes are a class of natural products present in all organisms, especially in plants. They include squalene, lanosterol or cycloartenol, sterols, steroids, and lupeol (Fig. 3.8). The triterpene acids (e.g., betulinic, ursolic, oleanolic acids, etc.) exhibit unique and important biological and pharmacological activities like anti-inflammatory, antimicrobial, antiviral, cytotoxic, and cardiovascular effects. The linear triterpene squalene, the major constituent of shark liver oil, is derived from the reductive coupling of two molecules of farnesyl pyrophosphate. From squalene, one may get lanosterol or cycloartenol, the structural precursors to all the steroids, through biosynthetic processes. The pentacyclic triterpenes can be classified into lupane, oleanane or ursane groups. A notable pentacyclic triterpene is boswellic acid. Animals, plants, and fungi, create triterpenes, like, squalene, ambrein, and ganoderic acid. Triterpenoids are thought of as modified triterpenes, such as lanosterol.

Squalene is obtained for commercial purposes primarily from shark liver oil (hence its name). Plant sources (primarily vegetable oils) including amaranth seed, rice bran, wheat germ, and olivesare now used also. It is also found in high concentrations in the stomach oil of birds in the order Procellariiformes. Squalene is produced as a biochemical intermediate in all plants and animals including humans, and it is a vital part of the synthesis of all plant and animal sterols, including

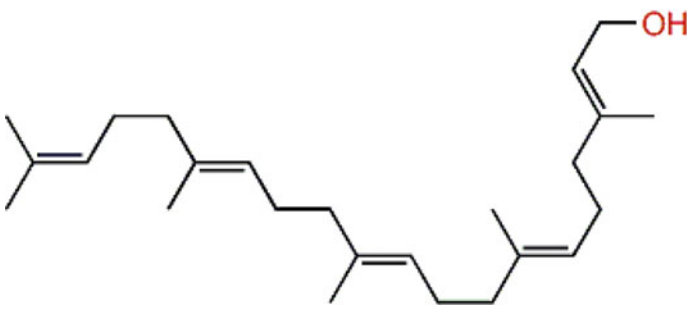


Fig. 3.7 Geranyl farnesol, an acyclic C_{25} isoprenoid alcohol found in insect wax

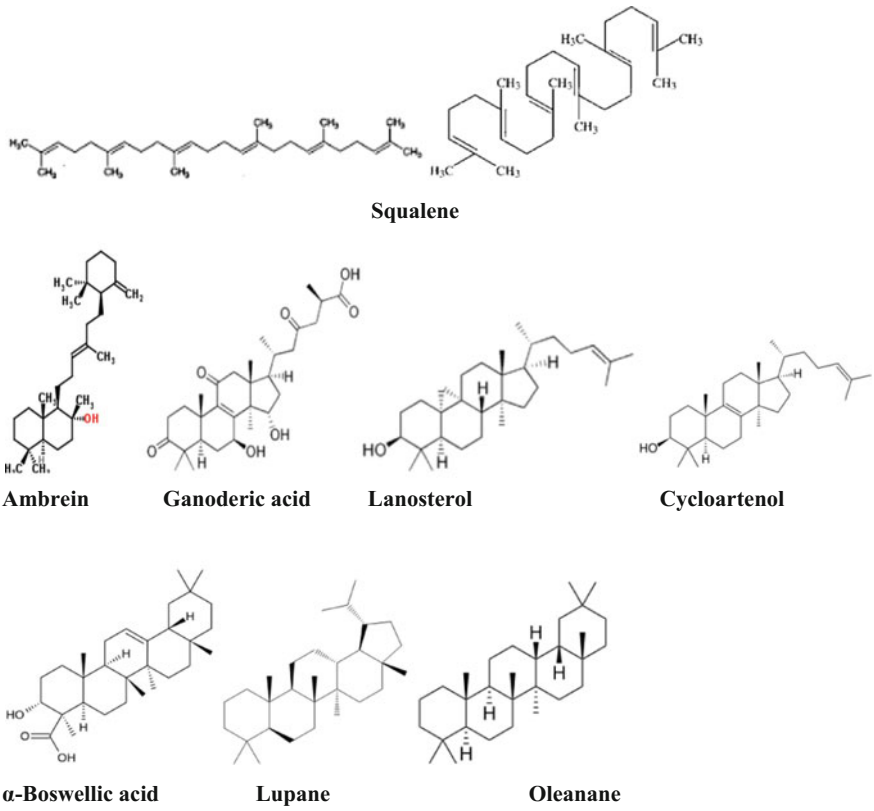


Fig. 3.8 Structure of different triterpenes including squalene, lanosterol or cycloartenol, sterols, steroids, and lupeol

cholesterol, steroid hormones, and vitamin D in the human body. Squalene is used in cosmetics, recently as an immunologic adjuvant in vaccines and as a chemo-preventive substance against cancer. It has been suspected that sharks are resistant to cancer due to high tissue levels of squalene. Ambrein is a triterpene alcohol that is the chief constituent of ambergris, a secretion from the digestive system of the sperm whale, and has been suggested as the possible active component producing the supposed aphrodisiac effects of ambergris. It serves as a biological precursor for a number of aromatic derivatives (ambroxan) and is thought to possess fixative properties for other oderants. It has been shown to act as an analgesic. Ganoderic acids are a class of closely related triterpenoids (derivatives from lanosterol) found in Ganoderma mushrooms. There are dozens of ganoderic acids (ganoderic acid A, B, etc.). Some ganoderic acids have been found to possess biological activities including hepatoprotection, antitumor effects, and 5-alpha reductase inhibition.

Boswellic acids are a series of pentacyclic triterpene molecules that are produced by plants in the genus *Boswellia*. Boswellic acids appear in the resin of the plant

that exudes them and it makes up 30% of the resin of *Boswellia serrata*. A boswellic acid consists of a pentacyclic triterpene, a carboxyl group, and at least one other functional group. α-Boswellic acid and β-boswellic acid both have an additional hydroxyl group; they differ only in their triterpene structure. Acetyl-α-boswellic acid and acetyl-β-boswellic acid, replace the hydroxyl group with an acetyl group. β-Boswellic acid, keto-β-boswellic acid, and acetyl-keto-β-boswellic acid have been indicated in apoptosis of cancer cells, brain tumors, and cells affected by leukemia or colon cancer. Boswellic acids are also thought to decrease the symptoms of asthma.

Oleanane is a natural triterpene. It forms the central core for a wide variety of chemical compounds found in flowering plants which are referred to collectively as oleanane triterpenes. Some oleanane triterpenes have a suppressing effect on insect pests. They are considered a key marker differentiating flowering plants from other life and have been used in the effort to study their evolution, which is as yet poorly documented in the fossil record. Cycloartenol is an important type of stanol found in plants. It is also found in dandelion coffee. The biosynthesis of cycloartenol starts from the triterpenoid squalene. It is the first precursor in the biosynthesis of other stanols and sterols, referred to as phytostanols and phytosterols in photosynthetic organisms and plants.

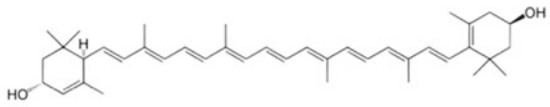
3.1.1.7 Sesquarterpenes

Sesquarterpenes composed of seven isoprene units ($C_{35}H_{56}$). Many sesquarterpenes are typically microbial in their origin. Examples of sesquiterpenoids are ferrugicadiol and tetraprenylcurcumene.

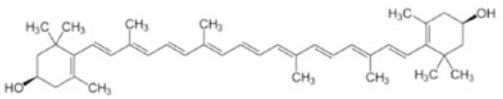
3.1.1.8 Tetraterpenes

Tetraterpenes contain eight isoprene units ($C_{40}H_{64}$) and include carotenoids. Carotenoids containing oxygen such as lutein and zeaxanthin are known as xanthophylls while the oxygen-free carotenoids such as α-carotene, β-carotene, γ-carotene, and lycopene are known as carotenes (Fig. 3.9). The color of this group of pigments, ranging from pale yellow through bright orange to deep red, is directly linked to their structure. Xanthophylls are often yellow, hence their class name. Some of the best sources of xanthophylls are spinach, kale, dandelion, chard, chicory, collards, watercress and parsley, orange-red bell peppers, peas, pumpkin, corn, squash, broccoli, brussels sprouts, chlorella, and spirulina. Vegetables and fruits with yellow and orange pigments and more dark green leafy vegetables are good sources of xanthophylls. The lutein and zeaxanthin in egg yolks is very bioavailable.

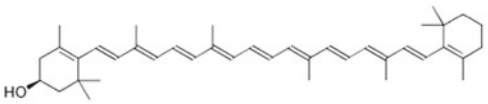
The xanthophylls include astaxanthin, canthaxanthin, cryptoxanthin, lutein, zeaxanthin, etc. They are phytonutrient pigments with many health benefits, e.g., function as powerful antioxidants, and protect body cells from free radicals.



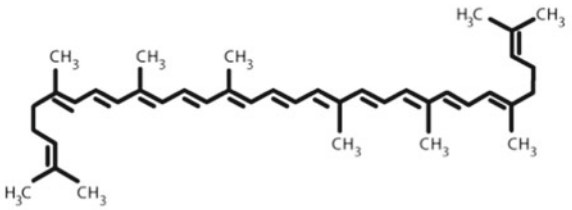
Lutein



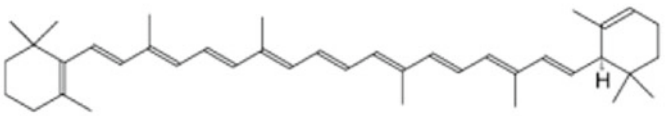
Zeaxanthin



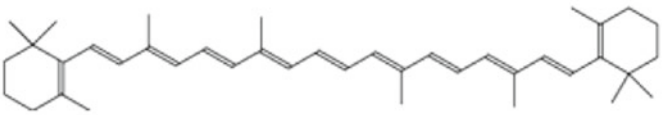
Cryptoxanthin



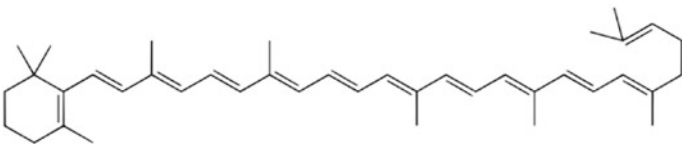
Lycopene (trans-configuration)



α-Carotene



β-Carotene



Monocyclic gamma-carotene

Fig. 3.9 Structure of different tetraterpenes—carotenoids

Cryptoxanthin, a provitamin A, helps to maintain healthy vision and xanthophylls boost up immune system and protect body against a number of disorders. Lutein, zeaxanthin, and cryptoxanthin are major xanthophyll carotenoids in human plasma and reduce the risk of cancers, cardiovascular disease, age-related macular degeneration, and cataract formation. Anyone who spends a lot of time looking at the computer screen could likely benefit from a good intake of lutein and zeaxanthin. Canthaxanthin and astaxanthin also have considerable importance in aquaculture for salmonid and crustacean pigmentation, and are of commercial interest for the pharmaceutical and food industries.

Carotenes and several related unsaturated hydrocarbon substances ($C_{40}H_x$) are synthesized by plants but cannot be made by animals. It is an orange photosynthetic pigment and vegetables and fruits like sweet potatoes, chanterelle, and orange cantaloupe melon contain carotene pigments. Carotenes contribute to photosynthesis by transmitting the light energy they absorb to chlorophyll. They also protect plant tissues by helping to absorb the energy from singlet oxygen, an excited form of the oxygen molecule O_2 which is formed during photosynthesis.

β-Carotene is composed of two retinyl groups and is broken down in the mucosa of the human small intestine by β-carotene 15,15′-monooxygenase to retinal, a form of vitamin A. β-Carotene can be stored in the liver and body fat and converted to retinal as needed, thus making it a form of vitamin A for humans and some other mammals. The carotenes α-carotene and γ-carotene, due to their single retinyl group (β-ionone ring), also have some vitamin A activity (though less than β-carotene), as does the xanthophyll carotenoid β-cryptoxanthin. All other carotenoids, including lycopene, have no beta-ring and thus no vitamin A activity (although they may have antioxidant activity and thus biological activity in other ways)

Lycopene is an acyclic isomer of β-carotene. It is an open chain polyisoprenoid with 11 conjugated double bonds. The structural formula of lycopene is represented in the diagram above. Lycopene is a bright red carotenoid pigment found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons, Vietnamese gac fruit, papayas, pink grapefruits, apricots, pink guavas (in strawberries, red bell peppers, or cherries) as well as in brown beans, parsley, etc., although they are not red. In plants, algae, and other photosynthetic organisms, lycopene is an important intermediate in the biosynthesis of many carotenoids, including beta-carotene, which is responsible for yellow, orange, or red pigmentation, photosynthesis, and photo protection. Lycopene's 11 conjugated double bonds give its deep red color and its antioxidant activity but it has no vitamin A activity. Owing to the strong color and non-toxicity, lycopene is a useful food coloring. Preliminary research has shown that people who consume tomatoes may reduce the risk of prostate, breast, lung, bladder, ovaries, colon, and pancreas cancer, possibly due to lycopene. Consumption of tomato paste may decrease heart disease, atherosclerosis, age-related eye disorders, and sun damage by UV radiation through the action of lycopene. Lycopene is also used for treating human papillomavirus (HPV) infection, which is a major cause of uterine cancer. Some people also use lycopene for cataracts and asthma. All

health-related activities of lycopene are due to its powerful antioxidant activities that may help protect cells from damage.

γ-Carotene is a carotenoid and is a biosynthetic intermediate for cyclized carotenoid synthesis in plants. It is formed from cyclization of lycopene by lycopene cyclase epsilon. Along with several other carotenoids, γ-Carotene is a vitamer of vitamin A in herbivores and omnivores.

α-Carotene is a form of carotene with a β-ionone ring at one end (left end ring) and an α-ionone ring at the opposite end. It is the second most common form of carotene. Vegetables rich in α-carotene include yellow-orange vegetables like carrots sweet potatoes, pumpkin, winter squash, etc., as well as dark green vegetables like broccoli, green beans, green peas, spinach, turnip greens, collards, lettuce, avocado, etc. α-Carotene is a strong antioxidant agent and research findings support the view that blood levels of α-carotene lowers the risk of death from cancer, cardiovascular, and some other diseases. For example, people with 9 μg/dL or more blood levels of α-carotene had a 39% lower risk of premature death than people with 0–1 μg/dL blood levels of α-carotene.

β-Carotene is a strongly colored red-orange pigment abundant in vegetables and fruits like carrots, apricot, pumpkins, sweet potatoes, and also crude palm oil. It is chemically classified as a hydrocarbon, specifically as a terpenoid (isoprenoid), reflecting its derivation from isoprene units. β-carotene is distinguished from others by having beta-rings at both ends of the molecule. Absorption of β-carotene is enhanced if eaten with fats, as carotenes are fat soluble. In nature, β-carotene is a precursor (inactive form) to vitamin A via the action of beta-carotene 15,15′-monooxygenase. β-Carotene is effective in erythropoietic protoporphyria treatment and assumed, but not proved, that it reduces the risk of breast cancer before menopause, age-related cataract and the risk of age-related macular degeneration (AMD). The common side effect of excessive β-carotene consumption is carotenodermia, a physically harmless condition that presents as a conspicuous orange skin tint arising from deposition of the carotenoid in the outermost layer of the epidermis.

3.1.1.9 Polyterpenes

Polyterpenes consist of long chains of many isoprene units. Natural rubber consists of polyisoprene in which the double bonds are cis and some plants produce a polyisoprene with trans double bonds, known as gutta-percha (Fig. 3.10).

Chemically, gutta-percha is a polyterpene, a polymer of isoprene, or polyisoprene, specifically (trans-1, 4-polyisoprene). The cis structure of polyisoprene is the common latex elastomer or elastic polymers. While latex rubbers are amorphous in molecular structure, gutta-percha (the trans structure) crystallizes, leading to a more rigid material. Gutta-percha latex is biologically inert, resilient, and is a good electrical insulator with a high dielectric strength, an exudate isolated from several species of the tropical tree of the genus *Palaquium* (Sapotaceae), particularly from *Palaquium gutta.* Natural rubber is elastomer of polyisoprene, derived from the

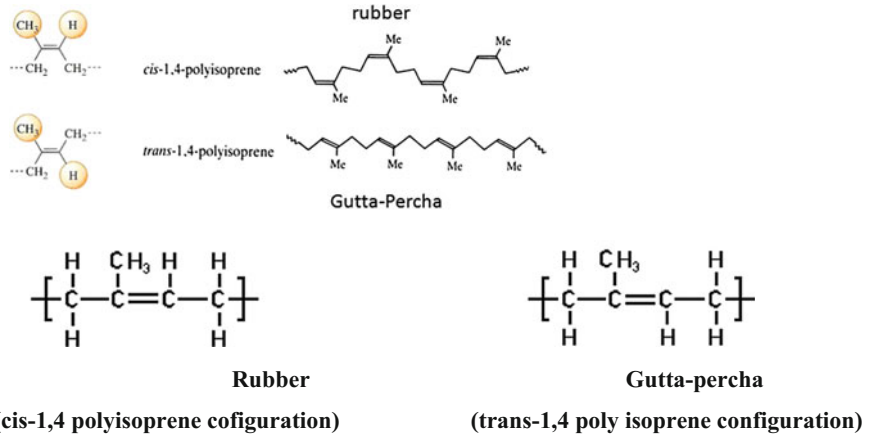


Fig. 3.10 Structure of polyterpenes—rubber and gutta-percha

latex of *Hevea brasiliensis* (Euphorbiaceae). Gutta-percha has been used in Endodontics for over 100 years and is currently the most frequently used core material for permanent obturation of root canals.

3.1.1.10 Norisoprenoids

Norisoprenoids are carotenoid breakdown products, e.g., C_{13}-norisoprenoids 3-oxo-α-ionol, present in Muscat of Alexandria leaves, and 7,8-dihydroionone derivatives, such as megastigmane-3,9-diol and 3-oxo-7,8-dihydro-α-ionol found in leaves of *Vitis vinifera*, can be produced by fungal peroxidases or glycosidases. Norisoprenoids originate in large carotenoid molecules found in grapes, such as β-carotene and lutein. These compounds accumulate during ripening, but break down into smaller compounds as the grapes reach maturity.

Norisoprenoids contribute to the varietal character of many aromatic varieties of wines, e.g., β-damascenone, 1,1,6,-trimethyl-1,2-dihydronaphthalene (TDN), and vitispirane. β-ionone, actinidiol, 3-oxo-α-ionol, and 2,2,6-trimethylcyclohexanone are other members of this class that are found in wine (Fig. 3.11).

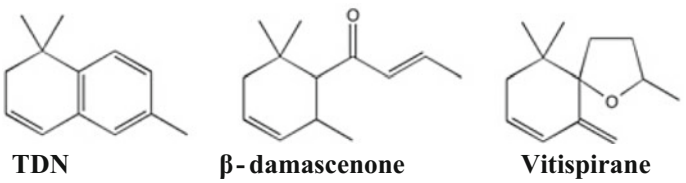


Fig. 3.11 Structures of three major C_{13}—norisoprenoids TDN, β-damascenone, and vitispirane

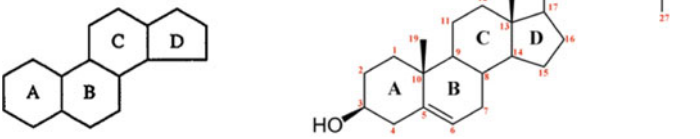
In the vineyard, increased sunlight exposure to the grapes seems to encourage the development of carotenoids, and subsequently increase the levels of norisoprenoids in finished wine. This effect probably occurs because the carotenoids help protect the grape tissue from ultraviolet light. In the laboratory, norisoprenoids are most often measured by gas chromatography–mass spectroscopy.

3.1.2 Steroids and Sterols

Steroids are cyclic terpenoids, and the term simply refers to a chemical molecule of 17 carbon atoms arranged in a fused four-ring structure consisting of three 6-carbon rings (A, B, C) and one 5-carbon ring (D) while sterols are steroid alcohols, with a hydroxyl group at the 3-position of the A-ring. When an eight-carbon side chain is put on carbon 17, the compound becomes typical animal sterol, the cholesterol (Fig. 3.12).

Sterols are amphipathic lipids, the hydroxyl group on the A-ring is polar and the rest aliphatic chain is nonpolar. Sterol is nearly ubiquitous among eukaryotes and almost completely absent in prokaryotes. So far, over 200 phytosterols have been reported, and among them, campesterol, β-sitosterol, stanols, and stigmasterol are most prominent; sterols of animal include cholesterol and steroid hormones like ecdysone, ecdysterone or 20E, cortisone, cortisol, and estradiol (E2) while and ergosterol is fungal origin. Considerable variability in the concentration of free sterols was observed among different oils. While concentrations lower than 100 mg/100 g are found in oils from coconut, palm, olive, and avocado whereas concentrations between 100 and 200 mg/100 g are found in oils from peanut, safflower, soybean, borage, cottonseed, and sunflower, and concentrations between 200 and 400 mg/100 g are found in oils from sesame, canola, rapeseed, corn, and evening primrose (Fig. 3.13).

Campesterol is a phytosterol whose chemical structure is similar to that of cholesterol. It is so named because it was first isolated from the rapeseed (*Brassica campestris*). Many vegetables, fruits, nuts, and seeds contain campesterol, but in low concentrations. Banana, pomegranate, pepper, coffee, grapefruit, cucumber, onion, oat, potato, and lemongrass (citronella) are common sources containing



Four ring structure of steroid **Structure of cholesterol**

Fig. 3.12 Four ring structure of steroid and cholesterol

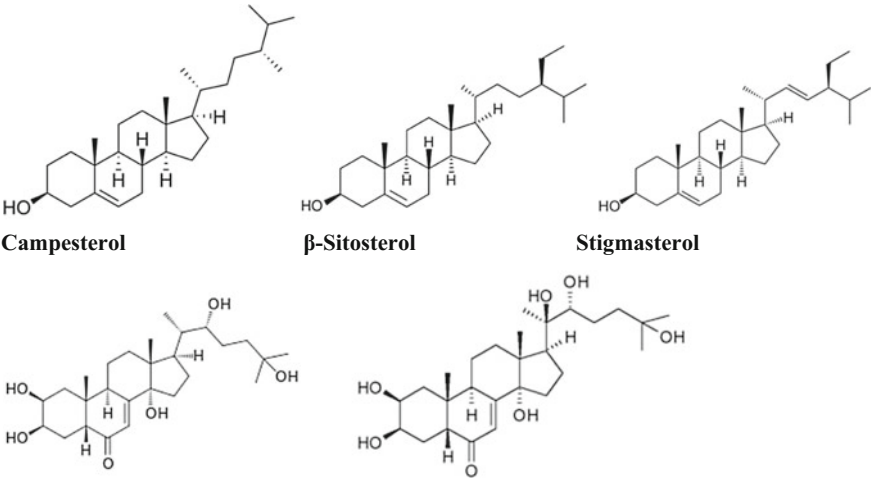


Fig. 3.13 Structure of different sterols—campesterol, β-sitosterol, and stigmasterol; steroid hormones—ecdysone and ecdysterone or 20E

campesterol at ~1–7 mg/100 g of the edible portion. Canola and corn oil contain as much as 16–100 mg/100 g. It is also found in dandelion coffee. It is thought to have anti-inflammatory effects, protects osteoarthritis-induced cartilage degradation. Being a steroid, campesterol is a precursor of anabolic steroid boldenone. Boldenone undecylenate is commonly used in veterinary medicine to induce growth in cattle but it is also one of the most commonly abused anabolic steroids in sports. Plant sterols, including campesterol inhibit the absorption of cholesterol in the intestines and thereby reduce LDLs or cholesterol level. The presence of phytosterols in the blood appears to be beneficial and is thought to reduce the chance of developing cardiovascular disease.

β-Sitosterol is structurally similar to that of cholesterol. Sitosterols are white, waxy powders with a characteristic odor. It is found in pecans, avocados, *Cucurbita pepo* seeds, cashew fruit, rice bran, wheat germ, corn oils, soybeans and dandelion coffee. β-Sitosterol is used for boosting the immune system and for preventing colon cancer, gallstones, common cold and flu (influenza), asthma, bronchitis, HIV and AIDS, rheumatoid arthritis, tuberculosis, psoriasis, allergies, cervical cancer, fibromyalgia, systemic lupus erythematosus (SLE), hair loss, migraine headache and chronic fatigue syndrome and benign prostatic hyperplasia. However, β-sitosterol enriched food should be avoided during pregnancy, and breastfeeding is also not recommended for individuals with sitosterolemia (fat storage disease) as well as β-sitosterol enriched food is not recommended for people suffered from heart attacks.

Stigmasterol (anti-stiffness factor) is chemically like animal cholesterol. Phytosterols are insoluble in water but soluble in most organic solvents and contain one alcohol functional group.Stigmasterol is foundvarious vegetables, legumes,

nuts, seeds, and unpasteurized milk, in the plant fats or oils of soybean, calabar bean, and rape seed, and in a number of medicinal herbs, including the Chinese herbs *Ophiopogon japonicus* and American Ginseng. Stigmasterol is used as a precursor in the manufacture of semisynthetic progesterone, a valuable human hormone that plays an important physiological role in the regulatory and tissue rebuilding mechanisms related to estrogen effects, as well as acting as an intermediate in the biosynthesis of androgens, estrogens, and corticoids. It is also used as the precursor of vitamin D_3. Stigmasterol like other plant sterols inhibits hepatic synthesis and competes with cholesterol for intestinal absorption to limit absorption and lower plasma concentrations of cholesterol. Stanols are a saturated subgroup of sterols. Stanol esters are a heterogeneous group of phytosterol esters with a saturated sterol ring structure known to reduce the level of low-density lipoprotein (LDL) cholesterol in blood when ingested. However, no evidence of any beneficial effect on cardiovascular disease exists. Their main sources are whole-grain foods, mostly wheat and rye. The LDL lowering efficacy of plant stanol ester is dose dependent, but the same effect was not found with plant sterols (Fig. 3.14).

Cholesterol is the principal sterol synthesized by animals. Cholesterol is an essential structural component of animal cell membranes that is required to maintain membrane structural integrity, fluidity and viability. Sterols and related compounds play essential roles in the physiology of organisms as cell membrane component, signaling compounds and as a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D. Sterols may be found either as free sterols (cholestane,cholesterol), acylated (sterol esters), alkylated (steryl alkyl ethers), sulfated (sterol sulfate), or linked to a glycoside moiety (steryl glycosides) which can be itself acylated (acylated sterol glycosides). Major dietary sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish, and shrimp. Human

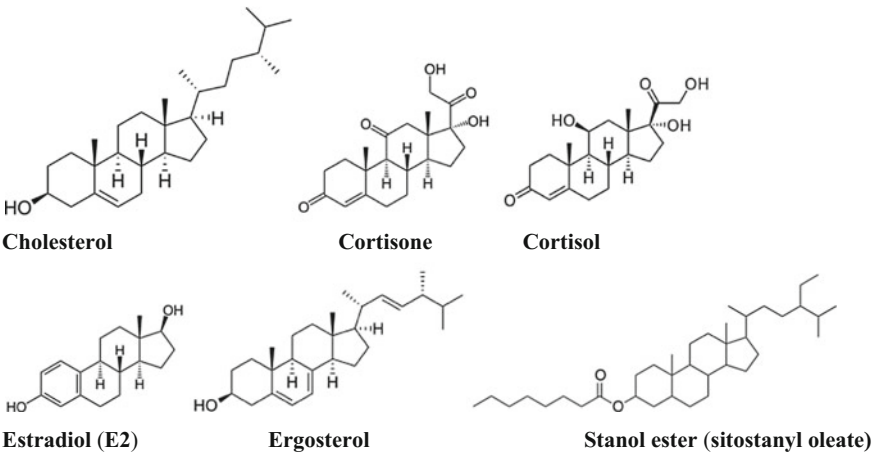


Fig. 3.14 Structure of cholesterol, cortisone, cortisol, estradiol (E2), ergosterol, and stanol ester (sitostanyl oleate)

breast milk also contains significant quantities of cholesterol. From a dietary perspective, cholesterol is not found in significant amounts in plant sources. In addition, plant products such as flax seeds and peanuts contain cholesterol-like compounds called phytosterols, which are believed to compete with cholesterol for absorption in the intestines. Cholesterol also serves All kinds of cells in animals can produce it. In vertebrates, the hepatic cells typically produce greater amounts than other cells. It is almost completely absenting among prokaryotes (bacteria and archaea), although there are some exceptions such as Mycoplasma, which require cholesterol for growth.

Cortisone is a 21-carbon steroid hormone. It is one of the main hormones released by the adrenal gland in response to stress. In chemical structure, it is a corticosteroid closely related to cortisol. It is used to treat a variety of ailments and can be administered intravenously, orally, intra-articularly (into a joint), or transcutaneously. Cortisone suppresses the immune system, thus reducing inflammation and attendant pain, and swelling at the site of the injury. Risks exist, in particular in the long-term use of cortisone. Cortisol is a steroid hormone, more specifically a glucocorticoid, which is produced by the zona fasciculata of the adrenal cortex. It is released in response to stress and a low level of blood glucose. Its functions are to increase blood sugar through gluconeogenesis, to suppress the immune system, and to aid the metabolism of fat, protein, and carbohydrate. It also decreases bone formation. Hydrocortisone is a name for cortisol when it is used as a medication. Hydrocortisone is used to treat people who lack adequate naturally generated cortisol.

Estradiol, or more precisely, 17β-estradiol, is a human sex hormone and steroid, and the primary female sex hormone. It is named for and is important in the regulation of the estrous and menstrual female reproductive cycles. Estradiol is essential for the development and maintenance of female reproductive tissues. Estradiol is found in most vertebrates as well as many crustaceans, insects, fish, and other animal species.

3.2 Volatile Oils

Volatile oils are the odoriferous principles present in various plant organs, e.g., flowers (rose), leaves (mint), fruits (lemon), bark (cinnamon), wood (cedar), root (ginger) or seeds (cardamom), and many resinous exudations as well. They are present in over 60 families, especially in the members of Lauraceae, Myrtaceae, Apiaceae, Lamiaceae, and Asteraceae. They are very complex in chemical nature (>200 components); hydrocarbon terpenes and their oxygenated and sulphured products are two main groups of chemicals. The quantity of oil varies from a very small amount to as much as 1–2%. Volatile oils evaporate when exposed to air at normal temperature and pressure and since they represent the essences or odors of the plant or plant part, they are also called essential oils. Essential oils are also known simply as the oil of the plant from which they were extracted (oil of clove).

Essential oils occur in glandular hairs, modified parenchymatous cells, oil tubes (vittae) and in some special oil ducts and are extracted by water (rose water) or steam distillation (eucalyptus oil), expression (grapefruit oil), solvent extraction (rose absolute and other lipophilic material) and florasol extraction (temperature sensitive material). Volatile oils are mixtures of hydrocarbons and their oxygenated derivatives. The odor and taste of volatile oils are mainly determined by their water soluble oxygenated constituents. This very fact makes it possible to prepare aromatic waters (rose water, orange water) by shaking volatile oils with water.

Volatile oils differ from the fatty or fixed oils both in their chemical composition and physical properties. The principal points of difference between volatile and fixed oils are as follows: (i) volatile oils are hydrocarbon terpenes and their oxygenated derivatives with a pleasant taste and strong aromatic odor and they are mixture of monosesquiterpenes (stereoptenes and oleoptenes) products and not glyceryl esters of fatty acids, (ii) they evaporate or volatilize on contact with the air and do not leave any permanent grease spot on paper, (iii) cannot be saponified with alkalis, (iv) volatile oils are usually extracted from their natural sources by water or steam distillation whereas fixed oils are extracted by hot or cold expression or with organic solvents, (v) volatile oils have high refractive index and optically active while fixed oils have low refractive index and optically inactive, and (vi) volatile oils do not become rancid as do the fixed oils, but instead, on exposure to light and air, they oxidize and resinify.

There are about 100 commercially valuable volatile oils. They are grouped on the basis of their synthetic path ways as (i) terpene derivatives (synthesized via the acetate–mevalonic acid path way), e.g., peppermint oil (menthol), caraway oil (carvone), thyme oil (thymol); (ii) aromatic compounds (synthesized via the shikimic acid–phenylpropanoid pathways), e.g., clove oil (eugenol), anise oil (anethole), cinnamon oil (cinnamaldehyde) and (iii) others (follow some miscellaneous route). Figure 3.15 shows structures of plant essential oil constituents with closely related precursors—menthol, carvone, thymol eugenol, anethole, cinnamaldehyde, vanillin, guaiacol, γ-terpinene, amiodrone, cineole, safrole, myristicin, apiole, and ascaridiole; stereoisomers—L-limonene and D-limonene.

Safrole is a constituent of many volatile oils, the dried dark of the roots of *Sassafras albidum* of *Lauraceae* and in a variety of other plant sources, namely: *Acorus calamus*, *Araceae*; *Angelica polymorpha*, *Apiaceae*; *Cananga odorata*, *Annonaceae*; *Cinnamomum comphora*, *Lauraceae*; *Illicium verum*, *Magnoliaceae*; *Myristica fragrans*, *Myristicaceae*; *Ocimum basilicum*, *Lamiaceae*; *Piper nigrum*, *Piperaceae*; *Theobromacacao*, *Sterculiaceae*. Botanical sources of the aromatic ether myristicin include black pepper (*Piper nigrum*, *Piperaceae*); mace, nutmeg (*Myristica fragrans*, Myristaceae), French parsley (*Petroselinum crispum*, *Apiaceae*); carrots (*Daucus carota*) *and* dill seed (*Anethum graveolens*, *Apiaciae*); sassafras (*Sassafras albidum*, *Lauraceae*). Apiole (a phenylpropene) occurs abundantly in dill oil (*Anethum graveolens*, Apiaceae); parsley seed oil (*Petroselinum crispum*, Apiaceae). Cineole (an essential oil) is the chief constituent of oil of eucalyptus obtained from the leaves of *Eucalyptus globulus* (Myrtaceae) and other species of Eucalyptus. Ascaridiole (a bicyclic monoterpene) is the major constituent (65–70%) in the chenopodium oil, i.e., a volatile oil of *Chenopodium ambrosioides* of Chenopodiaceae.

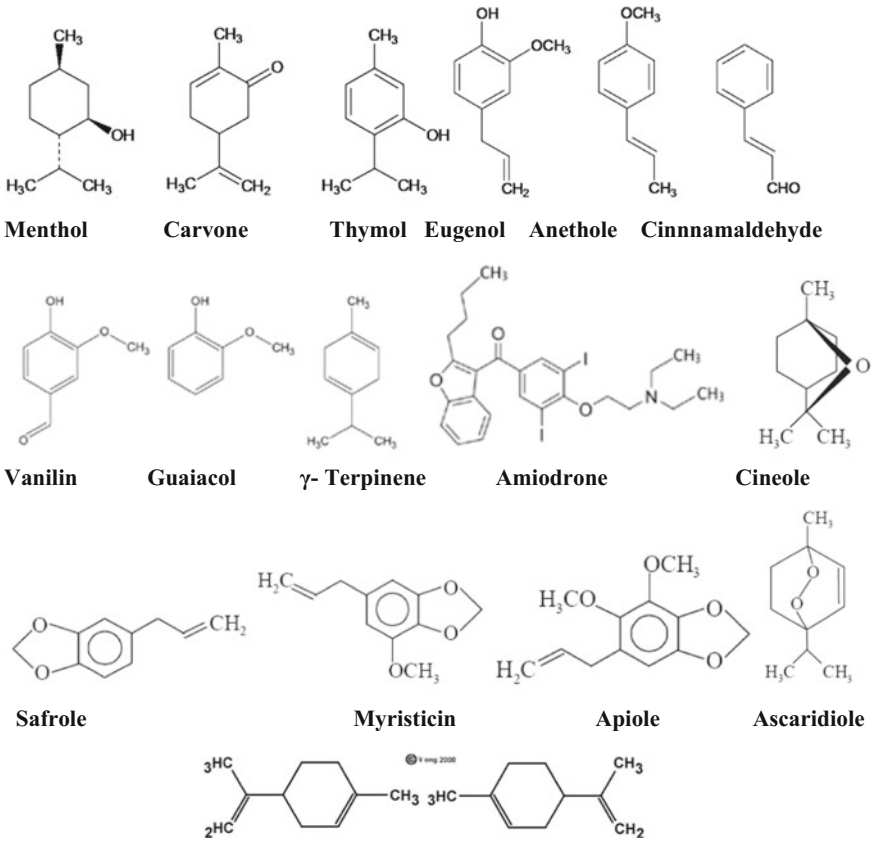


Fig. 3.15 Structures of plant essential oil constituents with closely related precursors—menthol, carvone, thymol eugenol, anethole, cinnamaldehyde, vanillin, guaiacol, γ-terpinene, amiodrone, cineole, safrole, myristicin, apiole, and ascaridiole. Stereoisomers—L-limonene and D-limonene

Volatile oils have no physiological significance to plants; they represent byproducts rather than foods. However, the characteristic aromas have some advantage in attracting insects and other animals for pollination and dispersal of fruits and seeds and in some cases for repelling the herbivore enemies. There is some evidence that they play an even more vital role as hydrogen donors in oxidoreduction reactions, as potential sources of energy, or in affecting transpiration and other physiological processes. The oils may also have some antiseptic and bactericidal value.

Volatile oils are mainly used as flavoring agents in cosmetics (perfumes, soaps and other products), in food products (food and drink), in household cleaning products, and in pharmaceuticals. They possess a carminative action and some of them also have other therapeutic properties like antiseptic and anesthetic properties.

They are commonly used in both modern allopathic and traditional systems of medicine. The important volatile oil-containing drugs of natural origin include Peppermint (*Mentha piperita*), Cinnamon (*Cinnamomum zeylanicum*), Lemon peel (*Citrus limon*), Camphor (*Cinnamomum camphora*), Clove (*Eugenia caryophyllus*), Anise (*Pimpinella anisum*), and Eucalyptus (*Eucalyptus globulus*). Plants grown for their unique essential oils include *Rosa damascena* (Rosaceae), *Jasminum grandiflorum* (Oleaceae), *Pelargonium* spp. (Geraniaceae), *Gardenia* spp. (Rubiaceae), and *Viola odorata* (Violaceae). Lavender comes from the species of *Lavandula* (Lamiaceae). Orange blossom perfume comes from *Citrus aurantium* and bergamot is from the fruit rinds of *C. bergamia* (Rutaceae). In addition to that, they are also utilized for many other industrial and commercial purposes.Volatile oils are used in aromatherapy, a form of alternative medicine that uses essential oils and other aromatic compounds for the purpose of altering one mood, cognitive, psychological or physical wellbeing, through topical application, (general massage, baths, compresses, therapeutic skin care massage), aerial diffusion (environmental fragrancing or aerial disinfection), direct inhalation (respiratory disinfection, decongestion, expectoration as well as psychological effects) or water immersion to stimulate a desired response.

3.3 Miscellaneous Isoprenoids

3.3.1 Resins

Resins are complex viscous exudates (containing essential oils, oxygenated products of terpenes and carboxylic acids) of many plants, particularly in the schizogenous ducts of coniferous trees, resin cells of ginger and glandular hairs of Cannabis. Distribution of resins in Cryptogam is absent (including sea weeds and fungi) and present in a few Phanerogam families like Pinaceae, Araceae, Dracaenaceae, Berberidaceae, Plumbaginaceae, Moraceae, Fabaceae, Dipterocarpaceae, Burseraceae, Apiaceae, Anacardiaceae, Piperaceae, etc. In plants, resins occur in different secretory zones or structures, e.g., in resin cells of ginger, in schizogenous ducts or cavities of pine wood and in glandular hairs of cannabis. Chemically, resins are a complex mixture of many components and the major chemical constituents of resins may be grouped under three heads: of (i) resin acids, (ii) resin esters, i.e., esters of resin alcohols (resinols) and resin phenols (resinotannols), and (iii) chemically inert compounds resenes. Acid resins include colophony (abietic acid), copaiba (copaivic and oxycopaivic acid), sandarac (sandracolic acid), shellac (aleuritic acid), and myrrh (commiphoric acid); ester resins include benzoin (benzyl benzoate), storax (cinnamyl cinnamate), balsam of Peru (peruresinotannol), guaiacum resin (guaic resinol), and gurjun balsam (gurjuresinol); and resene resins include dragon's blood (dracoresene), gutta-percha (fuavil) dammar, mastic, myrrh, and olibanum. Resins may also be grouped as

Coniferous (colophony, sandarac), Berberidaceae (Podophyllum), and Zygophyllaceae (Guaiacum) resins. Aroma pertains to different volatile fluid terpenes while the dissolved nonvolatile solids make resins thick and sticky. Some resins also contain a high proportion of resin acids. The volatile components of resins from Jeffrey Pine and Gray Pine are largely pure *n*-heptane with little or no terpenes. Resins often occur in mixtures with volatile oils (oleoresins) or with gums (gum resins) or with both gum and volatile oils (oleo-gum-resins). Acid resins may be abietane (abietic acid), pimarane (pimaric acid), labdane (communic acid, ozoic acid), kaurane (trachylobanic acid), and clerodane (hardwickiic acid) types having the characteristic acids noted inside the parenthesis. Resins are also grouped as hard resins (copal, damar, mastic, dragon's blood, etc.) and soft resins and balsams (benzoin, styrax, balsams of tolu and Peru, copaiba, elemi, asafetida and galbanum, etc.). Resins are usually hard and transparent or translucent substances, which are insoluble in water but soluble in alcohol and other organic solvents. True balsams are oleoresins, but the resinous mixtures that contain cinnamic or benzoic acid or both or esters of these acids are also known as balsams. Hence, all balsams are oleoresins but not all resins are balsams. Canada balsam (from fir tree, *Abies balsamea*, a widely used Christmas tree), larch balsam (often called larch turpentine is exudate of the *Larix europaea*), and copaiba balsam (from the trunk exudate of South American leguminous trees genus *Copaifera*) are terpenes, containing the characteristic resin in solution, and are not regarded as true balsams. Resins and balsams are used in pharmacy as stiffening agents, purgatives, and cathartics. Important resin-containing drugs of natural origin include Rosin (from *Pinus palustris*), Podophyllum, Jalap (roots of *Exogonium purga*), Cannabis (*Cannabis sativa*) and Ginger (*Zingiber officinale*) Copaiba balsam is medicinally important due to its anti-inflammatory, antitumor, anti-tetanus, antiseptic and antihemorrhagic properties. Galbanum, used in medicine, is a gum resin from the perennial herb *Ferula galbaniflua* of western Asia. Creosote bush resin is obtained from the leaves and small twigs of the greasewood bush, *Larrea tridentata*, or creosote bush, *L. divaricata*, of the desert regions of Mexico and the southwestern United States. It is used in adhesives, insecticides, core binders, insulating compounds, and pharmaceuticals. Okra gum is from the fruits of *Hibiscus esculentus* is edible and is used as a thickening agent in foodstuffs and pharmaceuticals. It has antioxidant properties and acts as a stabilizer and a gelling agent. Okra gum is also used in plating baths as a brightener. Ammoniac is a gum resin from the stems of *Dorema ammoniacum*, a desert perennial plant of Persia and India. It is used in adhesives, in perfumery, and as a stimulant in medicine. Amber and copal are fossil resins from ancient trees, which have been chemically altered by long exposure.

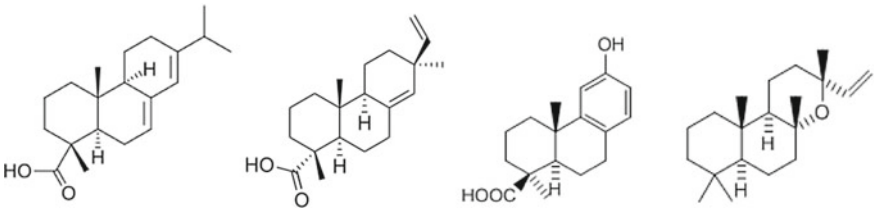
Resin alcohols may occur in free state or esters, e.g., balsam of Peru with peruresinotannol and guaiacum resin with guaic resinol. Resins (colophony, cannabis); oleoresins (copaiba, ginger); oleo-gum-resins (asafetida, myrrh); balsams (balsam of Peru, balsam of tolu); glycoresins (jalap); and resenes (asafetida, colophony are known from different plant sources. The oleo-gum-resin yields about 30% alcohol soluble extract and contains phenolic compounds such as pyrocatechin and protocatechuic acid, and gum is alcohol insoluble and comprised of protein

(18%) and carbohydrate (64%) made up of arabinose, galactose, and glucuronic acid and associated with an oxidase enzyme. Myrrh contains volatile oil (7–17%), resin (20–25%), gum (57–61%). The volatile oil consists of eugenol, m-cresol, and cuminaldehyde. The resin is found to consist of a mixture of α-, β-, and γ-commiphoric acids (resin acids) which ether soluble, and also two ether insoluble phenolic resins α- and β-herrabomyrrhololic acids

Resin acid refers to mixtures of several related carboxylic acids, and basic skeleton is made up of three fused rings (diterpenes composed of four isoprene units) with the empirical formula $C_{19}H_{29}COOH$. Acid resins contain abietic acids, sandracolic acid, commiphoric acid, copaivic acid, etc. A few typical examples of resin acids are shown below (Fig. 3.16).

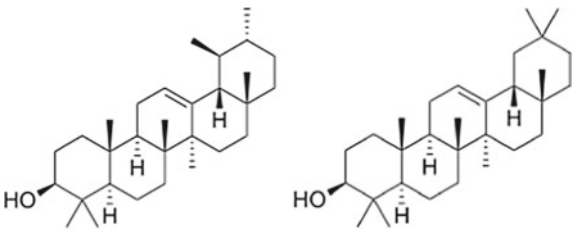
The α- and β-amyrins are commonly found in wood resins and the bark of many trees (Fig. 3.17).

Rosin (also called colophony or resin from the pine trees of Colophon), a semitransparent, yellow to black solid form of resin, is obtained mostly from conifers. It chiefly consists of different resin acids, especially abietic acid. Rosin is an ingredient in printing inks, photocopying and laser printing paper, varnishes, adhesives (glues), soap, paper sizing, soda, soldering fluxes, and sealing wax. Rosin can be used as a glazing agent in medicines and chewing gum, can be used as an emulsifier in soft drinks. In pharmaceuticals, rosin forms an ingredient in several plasters and ointments, also used for tablet film and enteric coating purpose. Rosins have also been used to formulate microcapsules and nanoparticles.



Abietic acid **Pimaric acid** **Podocarpic acid** **Manoyl oxide**

Fig. 3.16 Abietic acid, pimaric acid, podocarpic acid, and manoyl oxide



α-Amyrin **β-Amyrin**

Fig. 3.17 α- and β-amyrins are commonly found in wood resins

3.4 Phenols and Phenylpropanoids

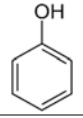
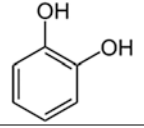
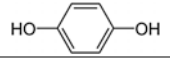
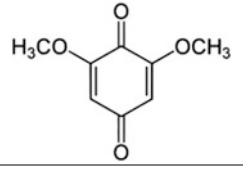
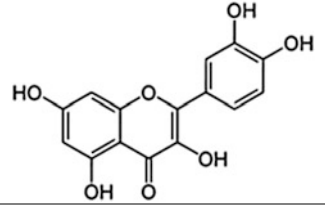
3.4.1 Phenol, Polyphenol, Phenolic Acids and Phenylpropanoids

Phenols or phenolics, are a class of chemical compounds consisting of a hydroxyl group (–OH) bonded directly to an aromatic hydrocarbon group. The simplest of the class is phenol, which is also called carbolic acid C_6H_5OH. Unlike alcohols, phenols can contribute proton in solution since the hydroxyl group is bonded to an unsaturated carbon atom having tight coupling with the oxygen and a relatively loose bond between the oxygen and hydrogen. The acidity of the hydroxyl group in phenols is commonly intermediate between that of aliphatic alcohols and carboxylic acids, and their pKa is usually between 10 and 12. Loss of H^+ from the hydroxyl group of a phenol forms a corresponding negative phenolate ion or phenoxide ion, and the corresponding salts are called phenolates or phenoxides. Phenols are aromatic compounds and are classified as simple phenols or polyphenols based on the number of phenol units in the molecule; occur naturally in many fruits, vegetables and also in some essential oils of plants and show powerful antiseptic and antibacterial properties (Table 3.2). Polyphenols are a structural class of mainly natural organic compounds characterized by the presence of large multiples of phenol structural units while phenols are substances with a benzene nucleus supporting a hydroxile group. They range from very simple substances to very complex ones such as lignins and tannins. The main groups in this category are phenolic acids or phenols, cumarines, flavonoids, lignanes, tannins, and quinines. The historically important chemical class of tannins is a subset of the polyphenols. Phenols are aromatic compounds and these fragrant compounds can act to stimulant nerves and immune system, and can sometimes cause liver damage and skin irritation.

Phenolic acids are aril-carboxilics and contain one or more OH groups in the aril. They have various pharmacological properties and uses: antioxidant, analgesics, choleretic, etc. Eugenol, for example, is an antiseptic and also a local anesthetic used in dentistry.

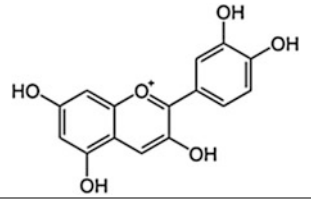
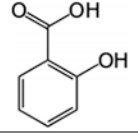
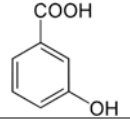
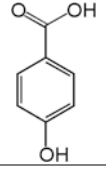
Phenolics are compounds possessing one or more aromatic rings with one or more hydroxyl groups. Phenolic compounds are classified as simple phenols or polyphenols based on the number of phenol units in the molecule. Phenol (carbolic acid) is an aromatic organic compound with the molecular formula C_6H_5OH. It is a white crystalline solid but volatile. It is mildly acidicand may cause chemical burns. The molecule consists of a phenyl group ($–C_6H_5$) bonded to a hydroxyl group (–OH). Similar to alcohols but unlike alcohols the hydroxyl group in phenol is attached to an unsaturated aromatic hydrocarbon ring and phenols can donate H^+ insolution to produce conjugate base. Loss of H^+ from the hydroxyl group of a phenol forms a corresponding phenoxide ion, and the corresponding salts are called phenolates or phenoxides. Phenols with two or more hydroxyl groups bonded to one or several aromatic ring or rings of the same molecule are called polyphenols (quercetin). The simplest examples are the three benzenediols, each having two

Table 3.2 Classification of phenol, polyphenol, and phenolic acids with their structure, source, and function

Phenol, polyphenol, and phenolic acids					
Classes	Name	Moleculr formula	Structure	Source	Function
1. Simple- and poly-phenols	Carbolic acid	C_6H_6O		Berries, tea, cocoa, coffee, fruits,spices, and vegetables	Antioxidant, precursors of aspirin, herbicides and pharmaceutical drugs, and antiseptic
	Catechol	$C_6H_4(OH)_2$		*Mimosa catechu*	Precursor to pesticides, flavors, and fragrances
	Hydroquinone	$C_6H_4(OH)_2$		Active toxin in *Agaricus hondensis* mushrooms	Reducing agent, a potential carcinogen suspect
	2,6-dimethoxybenzoquinone	$C_8H_8O_4$		*Rauvolfia vomitoria*, *Tibouchina pulchra*	Mutagenic, cytotoxic, genotoxic, and hepatotoxic
	Quercetin, a flavonol.				

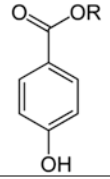
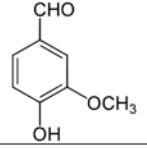
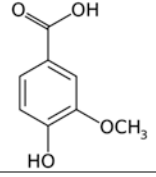
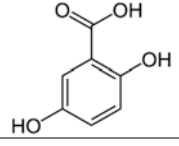
(continued)

Table 3.2 (continued)

Phenol, polyphenol, and phenolic acids					
Classes	Name	Moleculr formula	Structure	Source	Function
	Cyanidin, an anthocyanidin				
2. Derivatives of benzoic acid: a. Mono hydroxy benzoic acids	Salicylic acid	$C_7H_6O_3$		*Salix alba*	Ease aches, pains, and reduce fevers
	3-hydroxybenzoic acid	$C_7H_6O_3$		*Citrus paradise*, *Olea europaea*, *Mespilus germanica*, and *Castor canadensis*	Shows antifungal, antimutagenic, antisickling, and estrogenic antimicrobial activities
	4-hydroxybenzoic acid	$C_7H_6O_3$		*Vitex. agnus-castus*, *V. negundo*, and *Hypericum perforatum*	Used as intermediate for pesticide, antiseptics, and pharmaceuticals

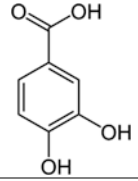
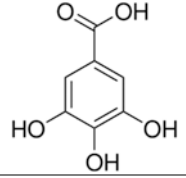
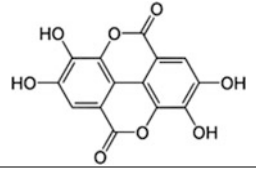
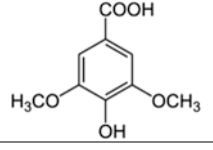
(continued)

Table 3.2 (continued)

Phenol, polyphenol, and phenolic acids					
Classes	Name	Moleculr formula	Structure	Source	Function
	Paraben (methyl propyl parabens)	Ester of 4/ para-hydroxybenzoate, R=an alkyl group—methyl, propyl		Commercial parabens are synthetic; methylparaben is found inblueberries	Antimicrobial agent; used as food additives, as preservatives by cosmetic and pharmaceutical industries, breast cancer suspect
b. Dihydroxy benzoic acids	Vanillin, phenolic aldehyde	$C_8H_8O_3$		*Vanilla planifolia* orchid bean seed	Flavoring foods, icecream, baked goods, and medicines
	Vanillic acid, an oxidizedform of vanillin	$C_8H_8O_4$		*Angelica sinensis*, a Chinese herb	Used as a flavoring agent
	Gentisic acid, a dihydroxybenzoic acid	$C_7H_6O_4$		African tree *Alchornea cordifolia*	Used as an antioxidant excipient in pharmaceutical preparations

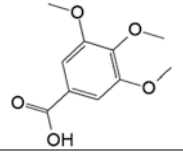
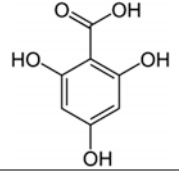
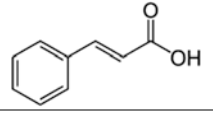
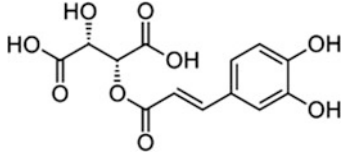
(continued)

Table 3.2 (continued)

Phenol, polyphenol, and phenolic acids					
Classes	Name	Moleculr formula	Structure	Source	Function
	Protocatechuic acid, a dihydroxybenzoic acid	$C_7H_6O_4$		*Hibiscus sabdariffa*, green tea	Antioxidant and anti-inflammatory agent
c. Trihy droxybenzoic acids	Gallic acid	$C_7H_6O_5$		In gallnuts, sumac, witchhazel, tea leaves, oak bark	Antifungal, antiviral, antioxidant, and anticarcenogenic
	Ellagic acid	$C_{14}H_6O_8$		Blackberries, cranberries, pecans, pomegranates, raspberries, strawberries, walnuts, wolfberries, grapes, Quercus alba	Antiproliferative and antioxidant
	Syringic acid	$C_9H_{10}O_5$		*Ardisia elliptica*, *Euterpe oleracea*	

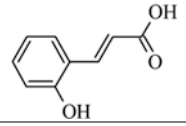
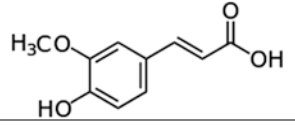
(continued)

Table 3.2 (continued)

Phenol, polyphenol, and phenolic acids					
Classes	Name	Moleculr formula	Structure	Source	Function
	Eudesmic acid	$C_{10}H_{12}O_5$		*Eucalyptus* spp.	
	Phloroglucinol carboxylic acid	$C_7H_6O_5$		Produced by Pseudomonasfluorescen, *Acinetobactercalcoaceticus*	
3. Derivatives of cinnamic acid	Cinnamic acid				
	Caffeic acid				

(continued)

Table 3.2 (continued)

Phenol, polyphenol, and phenolic acids					
Classes	Name	Moleculr formula	Structure	Source	Function
	Coumaric acid				
	Ferulic acid				

hydroxyl groups on a benzene ring. Phenol and its chemical derivatives are used in the production of detergents, phenoxy herbicides, numerous pharmaceutical drugs and many industrial synthetic goods.

Phenolic acids are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants (>8000 phenolic structures currently known) ranging from simple molecules (phenolic acids) to highly polymerized substances (tannins). Phenolic acids or phenolcarboxylic acids are types of aromatic acid compound containing a phenolic ring and an organic carboxylic acid function (C_6–C_1 skeleton). Phenolic acids can be divided into two classes, e.g., derivatives of benzoic acid (gallic acid), and derivatives of cinnamic acid (coumaric, caffeic and ferulic acid). The benzoic acid derivatives of phenolic acids include mono-hydroxybenzoic acids (salicylic acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid and also esters of this group like paraben, methyl paraben, propyl paraben, etc.); dihydroxybenzoic acids (vanillin, vanillic acid, gentisic acid, protocatechuic acid, etc.); and trihydroxybenzoic acids (gallic acid, ellagic acid, syringic acid, eudesmic acid, phloroglucinol carboxylic acid). Phenolic acids can be found in many plant species. Natural phenols in horse grams (*Macrotyloma uniflorum*) are mostly phenolic acids (3,4-dihydroxybenzoic, *p*-hydroxybenzoic, vanillic, caffeic, *p* coumaric, ferulic, syringic, and sinapinic acids). Phenolic acids can be found in mushroom, in humic substances of soil humus and also in human urine. The diverse classes of phenolic compounds made by plants are known to play multifunctional roles in rhizospheric plant–microbe interactions. Phenolic acids are the main polyphenols made by plants. Phenolic compounds act as signaling molecules in the initiation of legume rhizobia symbioses, establishment of arbuscular mycorrhizal symbioses and can act as agents in plant defense. Caffeic acid is the most abundant phenolic acid in many fruits and vegetables, most often esterified with quinic acid as in chlorogenic acid, which is the major phenolic compound in coffee. Another common phenolic acid is ferulic acid, which is present in cereals and is esterified to hemicelluloses in the cell wall.

The phenylpropanoids, the name indicates a phenyl ring and a propene tail (C_6–C_3), include a diverse group of organic compounds they are synthesized in plants from the phenylalanine and tyrosine (Fig. 3.18). Phenylpropanoids are found throughout the plant kingdom and serve as essential components of a number of structural polymers, provide protection from ultraviolet light, defend against herbivore and pathogen predators, and attract pollinators as floral pigments and scent compounds. Concentrations of phenylpropanoids within plants are also altered by changes in resource availability (Davey et al. 2004). Plant-derived phenylpropanoids (PPPs) are parent molecules for biosynthesis of numerous structurally and functionally diverse plant polyphenols, E.G, phenolic acids and esters, glycosylated derivatives of primary PPPs, flavonoids, isoflavonoids, stilbenes, coumarins, curcuminoids, lignans, etc., and play multiple essential roles in plant physiology.

Phenylpropanoids have been identified as potential radiotherapeutic agents due to their anticancer activity and relatively safe levels of cytotoxicity and based on experimental findings, it is expected that these compounds could not only sensitize

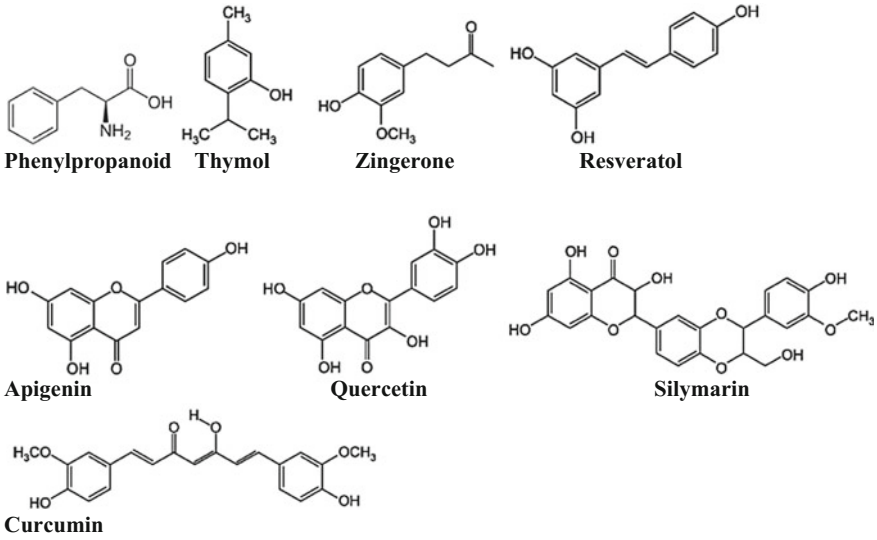


Fig. 3.18 Structure phenylpropanoid and examples of several other phenylpropanoids with radioregulation properties

cancer cells to radiation resulting in inhibition of growth and cell death but also protect normal cells against radiation-induced damage. Radiosensitizing properties of phenylpropanoids include inhibition of inflammatory response, antiapoptopic activity, ROS regulation, inhibition of NF-kB activation, ERK activation, inhibition of AKT activation, cell cycle arrest, etc. (Kim et al. 2011).

3.5 Alkaloids

Alkaloids include a vast and diverse group of chemical arsenals of secondary metabolic origin with alkali-like reaction. A clear-cut boundary between alkaloids and naturally occurring complex amines is absent and also a precise definition of alkaloids. However, alkaloids (alkali-like) may be defined as basic nitrogenous heterocyclic compounds with bitter taste, plant origin and possess a marked physiological action on man and other animals. Exceptions to this definition are known, e.g., (i) several alkaloids like colchine, piperine, and quaternary alkaloids (tubercurarine) are not basic and in some others basicity may be weak base (caffeine), strong base (atropine), amphoteric (morphine, narceine, theobromine and theophylline) or neutral (colchicine); (ii) nitrogen in ephedrine, colchine, hordenine and mescaline is not in a heterocyclic ring; and (iii) alkaloids are not confined to plant kingdom only, some alkaloids are also found in bacteria, fungi, frogs, insects and other animals. Considering all these exceptions, now alkaloids are defined as

cyclic organic compounds containing nitrogen in a negative state of oxidation with limited distribution among living organisms.

Alkaloids may be solid crystalline (majority), amorphous (emetine), volatile liquid (nicotine, coniine) or nonvolatile (pilocarpine, hyoscine). Alkaloids may contain other elements (oxygen, sulfur and more rarely chlorine, bromine, and phosphorus) in the molecule in addition to CHN and oxygen-containing (majority) alkaloids are usually colorless crystals at ambient conditions while oxygen-free alkaloids (e.g., nicotine, coniine, spartine, etc.) are typically volatile, colorless, oily liquids. Some alkaloids may be yellow (berberine, colchicine), brown (nicotine), orange (betanidine, sanguinarine) or copper red (salts of sanguinarine), etc.

Alkaloids may occur as free bases, salts with organic acids (oxalic, acetic acids), inorganic acids (HCl, H_2SO_4), salts with special acids (maconic acid in opium, quinic acid in Cinchona), glycosides (solanine in Solanum), etc. Alkaloid bases are generally soluble in most organic solvents (alcohol, diethyl ether, chloroform or 1,2-dichloroethane) and sparingly soluble or insoluble in water. However, bases like caffeine, ephedrine, codeine, colchicine, nicotine, pilocarpine, etc., are moderately water soluble, whereas morphine and yohimbine are highly water soluble. Some bases are insoluble or sparingly soluble in organic solvents like ether (morphine) and benzene (theobromine, theophylline). Salts are usually soluble in water including quinine sulfate and lobeline salts are soluble in organic solvent like chloroform. Alkaloids give a precipitate with metal or heavy metal iodides (iodine in potassium iodide of Wagner's, potassiomercuric iodide of Mayer's, potassium bismuth iodide of Dragendorff's and potassium cadmium iodide of Marme's reagents as well as noniodide reagents like picric acid (Hager's reagent), phosphomolybdenic acid (Sonnenschein's reagent), gold chloride, mercuric chloride, tannic acid except caffeine, which does not precipitate like most alkaloids, form salts with acids, may exist in the free state, salts or as N-oxides, occur in a limited number of plants.

The boundary between alkaloids and other nitrogen-containing non-alkaloid natural compounds like amino acid peptides, proteins, nucleotides, nucleic acid, amines, and antibiotics is not clear-cut. Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually attributed to amines rather than alkaloids. Some authors, however, consider alkaloids a special case of amines. A large variety of organisms produces alkaloids, including bacteria, fungi, plants, and animals, and are part of the group of many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals. Examples are the local anesthetic and stimulant cocaine, the psychedelic psilocin, the stimulant caffeine, nicotine, the analgesic morphine, the antibacterial berberine, the anticancer compound vincristine, the antihypertension agent reserpine, the cholinomimetic galantamine, the anticholinergic agent atropine, the vasodilator vincamine, the antiarrhythmia compound quinidine, the antiasthma therapeutic ephedrine, and the antimalarial drug quinine. There is no unique method of naming alkaloids. In Trivial system, names are formed by adding the suffix "ine" to botanical genus (atropine from *Atropa belladonna*, strychnine from *Strychnos nux-vomica*), species

(cocaine from *Erythroxylon coca*), common name of the drug (ergotamine fron ergot), name of the discoverer (pelletierine from the discoverer Pelletier), after the name of physical action (emetine that acts as emetic, morphine that acts as narcotic), prominent physical character (hygrine from hygroscopic character), etc. If several alkaloids are extracted from one plant then their names often contain suffixes idine, anine, aline, inine, etc. There are at least 86 alkaloids containing the roots of *Catharanthus roseus*. Suffixes "dine" designates isomerism (quinidine, cinchonidine), "ine" indicates a lower pharmacological activity (ergotaminine is less potent than ergotamine), etc. Prefix "Nor" designates *N*-demethylation or *N*-demethoxylation (norpseudoephedrine, nornicotine), "Apo" designates dehydration (apomorphine) while "iso-, pseudo-, neo-, epi-" indicate different types of isomers. Alkaloids may be of primary-($R–NH_2$, morphine), secondary-($R_2–NH$, ephedrine), tertiary-($R_3–N$, atropine) amines and quaternary ammonium salts ($R_4–N$, D-tubocurarine) and their basicity may be graded as $R_2–NH > R–NH_2 > R_3–N$. Saturated heterocyclic amines are more basic than aromatic amines.

The role of alkaloids for living organisms that produce them is still not clear. Alkaloids may act as protective against pathogen, insects and herbivores due to their bitter principles and toxicity (e.g., liriodenine protects tulip tree from parasitic mushrooms, pyrrolizidine alkaloids render larvae and adult ornate moths unpalatable to their natural enemies like coccinellid beetles, green lacewings, insectivorous hemiptera, and insectivorous bats). Recent research has proved that they are not toxic to the organisms that produce them. Biotoxicity is directed only towards foreign organisms or cells and it is selective. Some animals are adapted to alkaloids and even use them in their own metabolism (serotonin, dopamine and histamine are important neurotransmitters). Alkaloids were the final products of detoxification (waste products) products of nitrogen metabolism in plants as urea in mammals, but this hypothesis is refuted because alkaloid concentrations in plants varies over time. They play a very important role in the immune systems of animals and plants, they are, in certain cases, source of nitrogen in case of nitrogen deficiency; sometimes, they act as growth regulators in certain metabolic systems, show allelopathic activity, and they may be utilized as a source of energy in case of deficiency in CO_2 assimilation. They are biologically significant as active stimulators, inhibitors and terminators of growth, a part of an endogenous security and regulation mechanism. Although the physiological role of alkaloids in the organisms that produce them is obscure but their therapeutic and pharmacological activities are highly significant. Some alkaloids have remarkable structural similarities with neurotransmitters (e.g., dopamine, serotonin, acetylcholine, etc.), some possess analgesic, hallucinogenic effects and some create serious addictions. Most of the natural drugs are obtained from the alkaloid-containing plants and alkaloids always play important role in herbal, allopathic and homeopathy systems of medicine as well as they play role as biopesticides.

Alkaloid-containing plants have been used by humans since antiquity for therapeutic and recreational purposes. Studies on alkaloids began in the early part of nineteenth century that led the discovery of xanthine (1817), strychnine (1818), atropine (1819), caffeine (1820), quinine (1820), coniine (1827), nicotine (1828),

colchicine (1833), sparteine (1851), and cocaine (1860) and up to now more than 12,000 alkaloids have been identified. Raffauf (1996) earlier, however, wrote about the discovery of >10,000 different alkaloids in plant species from over 300 plant families. Medical use of alkaloids has a long history and when the first alkaloids were isolated in the nineteenth century, they immediately found application in clinical practice. Many alkaloids such as ajmaline (antiarrhythmic), atropine, scopolamine, hyoscyamine (anticholinergic), caffeine(stimulant, adenosine receptor antagonist), codeine (cough medicine, analgesic), colchicine (remedy for gout), emetine (antiprotozoal agent), ergot alkaloids (sympathomimetic, vasodilator, antihypertensive), morphine (analgesic), nicotine (stimulant, nicotinic acetylcholine receptor agonist), physostigmine (inhibitor of acetylcholinesterase), quinidine (antiarrhythmic), quinine (antipyretics, antimalarial), reserpine (antihypertensive), tubocurarine (muscle relaxant), vinblastine, vincristine (antitumor), vincamine (vasodilating, antihypertensive), and yohimbine (stimulant, aphrodisiac) are still used in medicine, usually in the form of salts. Cocaine, caffeine, and cathinone are stimulants of the central nervous system. Mescaline and many of indole alkaloids (such as psilocybin, dimethyltryptamine and ibogaine) have hallucinogenic effect. Morphine and codeine are strong narcotic pain killers. All these are used as psychoactive drugs. Many synthetic and semisynthetic drugs are structural modifications of the alkaloids, designed to enhance or change the primary effect of the drug and reduce unwanted side effects (thebaine of opium modified to naloxone, an opioid receptor antagonist). Ephedrine and pseudoephedrine are used to produce methcathinone and methamphetamine and thebaine is used in the synthesis of oxycodone for enhancing their effects. Salts of nicotine and anabasine are insecticides in agriculture but their use is limited by their high toxicity to humans.

Distribution

Alkaloids, especially true alkaloids are of rare occurrence in lower plants, in fungi, the psilocybin in the genus *Psilocybe*, the lysergic acid derivatives and the sulfur-containing alkaloids (gliotoxins) are the best known and in animals—bufotenin in the skin of toad—*Bufo alvarius.* About 300 alkaloids under 24 classes are known to occur in the skins of amphibians including the potent neurotoxic alkaloids of frogs—*Phyllobates*, which are among some of the most poisonous substances known. Other reptilian alkaloids are strongly antimicrobial. Alkaloids derived from mammals include ones of indole and isoquinoline classes. Many marine organisms also contain alkaloids. Estimates for the distribution of alkaloids in vascular plants have been placed as high as 15–20%, although this figure appears somewhat high with respect to data derived from several extensive phytochemical screening programs, 9–10% seems to be the more logical estimate representing alkaloids yielding plant species.

Alkaloids appear to have a restricted and uneven distribution in the plant kingdom; approximately 5000 alkaloids are known to occur in 15% of all land plants under about 150 families of angiosperm. Among the pteridophytes and gymnosperms, the lycopodium, ephedra, and Taxus alkaloids have medicinal interest. Alkaloid distribution in the angiosperms is uneven, about 10–25% of

higher plants contain alkaloids and dicots are richer than monocots. Apocynaceae, Berberidaceae, Boraginaceae, Campanulaceae, Chenopodiaceae, Convolvulaceae, Lauraceae, Loganiaceae, Magnoliaceae, Menispermaceae, Ranunculaceae Rubiaceae, Rutaceae, Solanaceae, Papilionaceae, Papaveraceae, Fumariaceae, etc., families of dicotyledons are rich in alkaloids. Amaryllidaceae and Liliaceae of monocotyledons are rich in alkaloids. The Lamiaceae and Rosaceae are almost free from alkaloids, and the monocotyledons (except Amaryllidaceae and Liliaceae) and gymnosperms (except Taxaceae) are poor in alkaloids. A specific alkaloid is usually confined to a specific plant family (e.g., hyoscyamine in Solanaceae, colchicine in Liliaceae) except caffeine, berberine and nicotine, which are found in a number of widely scattered plant families.

Alkaloids may be distributed in all plant parts (*Datura metel*), leaves (*Nicotiana tabacum*), underground stem (sanguinaria), roots (*Aconitum napellus*, *Rauwolfia serpentina*), rhizomes (ipecac, hydrastis), bark (*Cinchonaofficinalis*), fruits (*Piper nigrum*), seeds (*Strychnos nux-vomica*), and latex (*Papaver somniferum*). Furthermore, different tissues of the same plants may contain different alkaloids. Factors influencing the alkaloid distribution in plants include age, climate, habitat, season, time of harvest, chemical races of plants, etc. For example, broad leaf form of *Geijera salicifolia* (Rutaceae) gives better alkaloid tests than narrow leaf form even they grow side by side in the field.

Classification

Alkaloids are characterized by a great structural diversity and presence of nitrogen in the molecule is the only unifying character for various classes of alkaloids. There is no uniform classification of alkaloids and they are classified in various ways on the basis of their (a) biogenic precursors like nonamino acid (e.g., purine) or amino acids (e.g., phenylalanine, ornithine, lysine, tyrosine, tryptophan, histidine, anthranilic acid), etc.; (b) biosynthetic carbon skeleton (e.g., indole-, isoquinoline-, and pyridine-trigonelline); (c) the presence of the basic heterocyclic nucleus, the chemical entity (e.g., pyridine—trigonelline; pyrrolidine alkaloids—hygrine, nicotine, stachydrine; pyridine—arecoline, ricinine, trigonelline; piperidine alkaloids—connine, lobeline, pelletierine; pyrrolizidine alkaloids—senecionine; tropane alkaloids—atropine, cocaine, hyoscyamine; quinoline alkaloids—quinine, quinidine, cuspareine; isoquinoline alkaloids—papaverine, berberine, emetine, corydaline, tubocurarine, narcine, berberine; aporphine alkaloids—boldine; indole alkaloids—strychnine, reserpine, ergometrine); phenanthrene group—morphine, codeine; phenethylamine group—ephedrine, hordenine, capsaicin, mescaline, narceine; purine group—caffeine; steroidal alkaloids—conicine, withanine. (d) pharmacological characteristics (e.g., morphine as narcotic analgesic; quinine as antimalarial; strychnine as reflex excitability; lobeline as respiratory stimulant; boldine as choleretics and laxatives; aconitine as neuralgia); (e) taxonomic category (e.g., Cannabinaceous alkaloids—*Cannabis sativa* Linn.—hemp, marijuana; Rubiaceous alkaloids—*Cinchona* sp.,—quinine, *Mitragyna speciosa* Korth—katum, kratum, kutum, *Pausinystalia johimbe*—yohimbe; Solanaceous alkaloids—*Atropa belladonna* L.—belladonna), etc., and on many more number of modes and means.

However, they require compromises in borderline cases; for example, nicotine contains a pyridine fragment from nicotinamide and pyrrolidine part from ornithine and therefore can be assigned to both classes.

(a) Classification based on biogenic precursors

Based on biogenesis, alkaloids are classified into true alkaloids and pseudo alkaloids. The true alkaloids are derived from α-amino acid precursors; and true alkaloids without nitrogen heterocyclic ring in the molecule are called proto alkaloids. Pseudo alkaloids are derived from nonamino acid precursors such as terpenes, steroids, etc. The classification based on biogenic precursors is shown in the Fig. 3.19.

(i) Protoalkaloids originate firm amino acids but do not possess heterocyclic ring the molecule, they acquire their nitrogen atom through transamination and not from their originating amino acid, e.g., hordenine, ephedrine, colchicine, mescaline, adrenaline, cathinone, tyramine, pseudoephedrine, catecholamines, etc. (Fig. 3.20).

Hordenine (*N*,*N*-dimethyltyramine) occurs naturally in a variety of plants and its name came from the genus *Hordeum*. It is a stimulant of the central nervous system and can promote weight loss by enhancing metabolism but these are proved scientifically. Ephedrine is an alkaloid with a phenethylamine skeleton found in various plants in the genus *Ephedra*. The Chinese herb *Ephedra sinica* contains

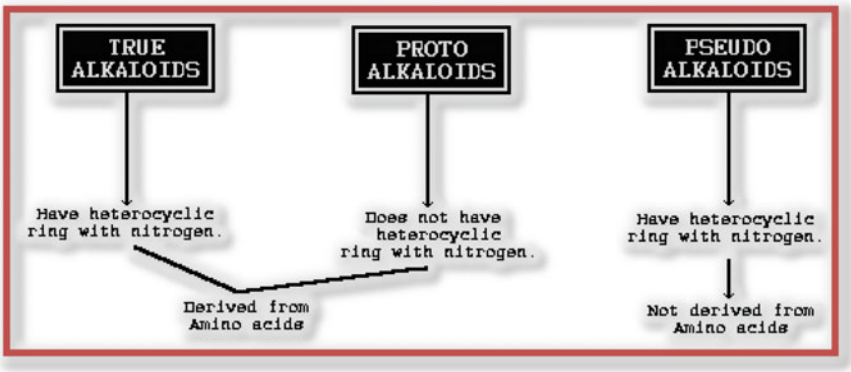


Fig. 3.19 Classification of alkaloids based on biogenic precursors

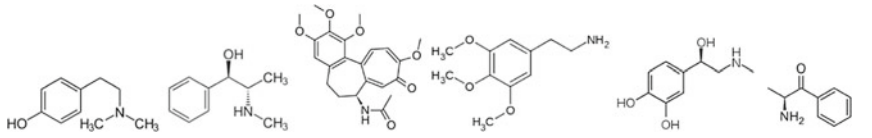


Fig. 3.20 Structure of different protoalkaloids—hordenine, ephedrine, colchicine, mescaline, adrenaline, and cathinone

ephedrine and pseudoephedrine as its principal active constituents. It is a sympathomimetic amine commonly used as a stimulant, concentration aid, decongestant, appetite suppressant, and to treat hypotension associated with anesthesia. Cathinone is a monoamine alkaloid found in the shrub *Catha edulis* and is chemically similar to ephedrine, cathine, methcathinone, and other amphetamines. Cathinone has stimulant and euphoriant effects and may be used to treat obesity and prevent hunger in are as with meager food supplies. Colchicine is a toxic natural product, originally extracted from plants of the genus *Colchicum.* It is used to treat gout, familial Mediterranean fever, pericarditis, and Behçet's disease. Adverse effects are primarily gastrointestinal upset at high doses. Mescaline (3,4,5-trimethoxyphenethylamine) is a naturally occurring psychedelic alkaloid and is known for its hallucinogenic effects similar to those of psilocybin. It occurs naturally in different members of the Cactaceae including *Lophophora williamsii*, *Echinopsis pachanoi*, *Echinopsis peruviana*, and also in small amounts *Acacia berlandieri*. Adrenaline (β, 3,4-trihydroxy-*N*-methylphenethylamine) is made in the adrenal gland of the kidney. Its biological name is epinephrine, from the Greek nephros for kidney. It works as hormone and neurotransmitter. Adrenaline is used to treat a number of conditions including cardiac arrest, anaphylaxis, and superficial bleeding.

(ii) True alkaloids are derived from the amino acids and have nitrogen in a heterocyclic ring, e.g., atropine, nicotine, morphine, ergotamine, coniine, coniceine, etc. (Fig. 3.21). Some members of this group may contain terpene (e.g., evonine) or peptide fragments (e.g., ergotamine) in addition to nitrogen heterocycle, and also includes coniine and coniceine alkaloids although they do not originate from amino acids, get N through transamination reaction. Alkaloids are derived from amino acid precursors include ornithine (pyrrolidine—cuscohygrine, hygrine, hygroline, stachydrine; tropane—atropine, scopolamine, hyoscyamine and also cocaine, ecgonine; pyrrolizidine alkaloids—retronecine, heliotridine, laburnine, indicine,

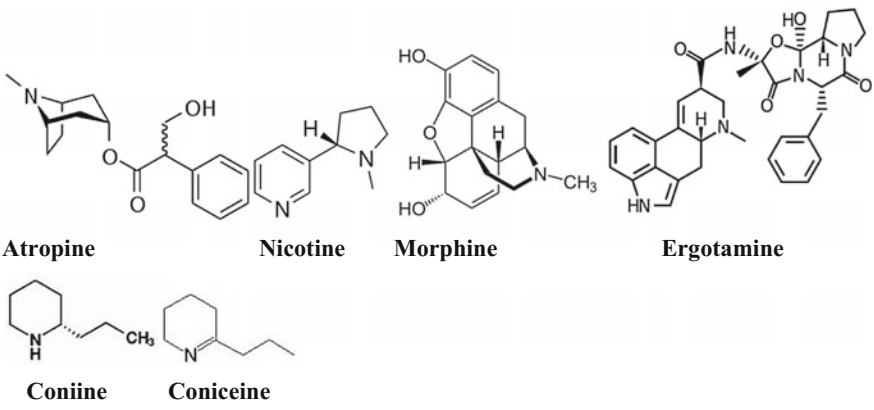


Fig. 3.21 Structure of different true alkaloids—atropine, nicotine, morphine, ergotamine, coniine, and coniceine

lindelophin, sarracine, platyphylline, trichodesmine, loline, *N*-formylloline, and *N*-acetylloline); lysine (piperidine—sedamine, lobeline, anaferine, piperine, coniine, coniceine; quinolizidine—lupinine, nupharidin, cytosine, sparteine, lupanine, anahygrine, matrine, oxymatrine, allomatridine, ormosanine, piptantine; and indolizidine alkaloids—swainsonine, castanospermine); nicotinic acid (pyridine alkaloids—trigonelline, ricinine, arecoline, nicotine, nornicotine, anabasine, anatabine, actinidine, gentianine, pediculinine, evonine, hippocrateine, triptonine); tyrosine (phenylethylamines, isoquinoline—salsoline, lophocerine, papaverine, laudanosine, sendaverine, cularine, yagonine, berberine, canadine, ophiocarpine, mecambridine, corydaline, morphine, codeine, thebaine, sinomenine; tetrahydroisoquinoline alkaloids; Amaryllidaceae includes *Amaryllis*, *Narcissus*, and *Galanthus*, and the alkaloid content of bulbs from most members makes these toxic, alkaloids—lycorine, galanthamine, crinine, etc.); tryptophan (simple indole-serotonin, psilocybin, dimethyltryptamine, bufotenin; β-carboline-harmane, harmine, harmaline, eleagnine; terpenoid indole-ergotamine, ergobasine, ergosine, ajmalicine, sarpagine, vobasine, ajmaline, yohimbine, reserpine, mitragynine, strychnine and strychnine brucine, aquamicine, vomicine, ibogamine, ibogaine, voacangine, vincamine, vinca alkaloids, vincotine, aspidospermine; quinolone; pyrroloindole—physostigmine (eserine), etheramine, physovenine, eptastigmine; and ergot alkaloids); phenylalanine—L-phenylalanine is usually contributes only carbon atoms, e.g., C_6C_3, C_6C_2, or C_6C_1 units, without providing a nitrogen atom from its amino group, e.g., ephedrine, norpseudoephedrine (cathine), capsaicin, colchicine, lobeline, etc.; anthranilic acid is a key intermediate in the biosynthesis of L-tryptophan and so contributes to the elaboration of indole alkaloids (quinazoline, quinolone and acridine alkaloids, while histidine gives imidazole derivatives (histamine, pilocarpine, isopilocarpine, pilosene, stevensine, etc.).

Atropine, a naturally occurring tropane alkaloid, may be obtained from *Atropa belladonna*, *Datura stramonium*, *Mandragora officinarum,* and other members of Solanaceae. It serves as a drug with a wide variety of effects. Atropine dilates the pupils, increases heart rate, and reduces salivation and other secretions. Nicotine is named after the tobacco plant *Nicotiana tabacum*. It is made in the roots of and accumulates in the leaves. It constitutes approximately 0.6–3.0% of the dry weight of tobacco and is present in the range of 2–7 μg/kg of various edible plants. It functions as an antiherbivore chemical; consequently, nicotine was widely used as an insecticide in the past. In lesser doses (an average cigarette yields about 1 mg of absorbed nicotine), the substance acts as a stimulant in mammals, while high amounts (50–100 mg) can be harmful. Morphine is an analgesic and psychoactive drugfound in opium *Papaver somniferum.* In clinical medicine, morphine is regarded as the gold standard of analgesics used to relieve intense pain, morphine acts directly on the central nervous system (CNS) to relieve pain. Ergotamine is an ergot fungus alkaloid. It has been used to prevent postpartum hemorrhage (bleeding after childbirth). Coniine is a poisonous alkaloid found in hemlock (*Conium maculatum*) and yellow pitcher plant (*Sarracenia flava*) as a mixture of the R-(−)- and S-(+)-enantiomers with thepredominance of S-enantiomer. It is a neurotoxin, disrupts the peripheral nervous system, and causes death by respiratory paralysis.

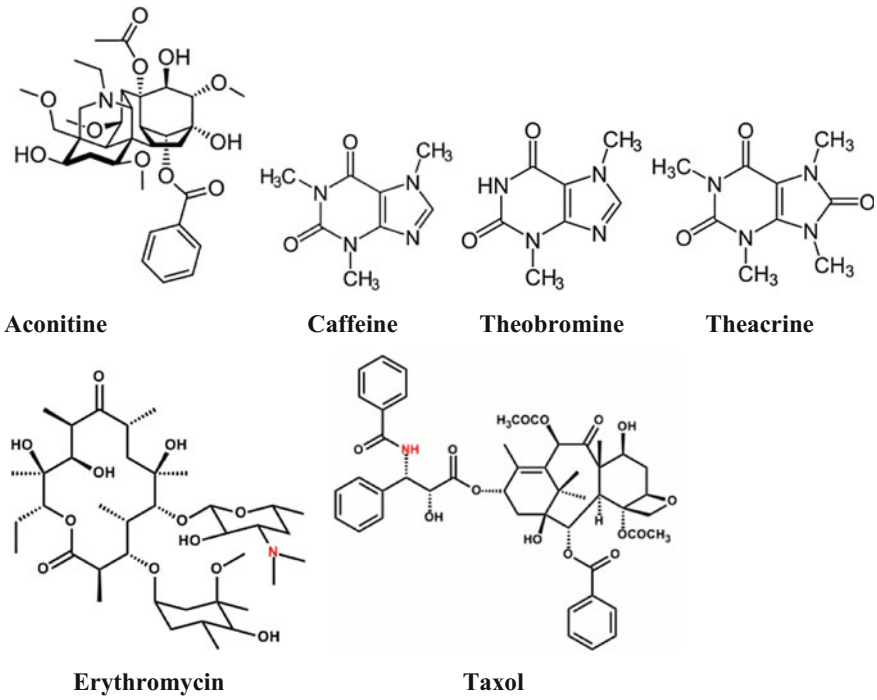


Fig. 3.22 Structure of different pseudo alkaloids—aconitine, caffeine, theobromine, theacrine, erythromycin, and taxol

Socrates was put to death by means of this poison in 399 BC. Coniceine is also found in hemlock.

(iii) Pseudo alkaloids are not derived from amino acids but have nitrogen in a heterocyclic ring, e.g., caffeine, colchicines, aconitine, etc. This group includes terpene alkaloids—aconitine, delphinine; steroid alkaloids—solasodine, solanidine, veralkamine, batrachotoxin as well as purine-like alkaloids such as caffeine, theobromine, theacrine and theophylline (Fig. 3.22). Some authors include ephedrine and cathinone in pseudalkaloids although they originate from the amino acid phenylalanine but acquire their nitrogen not from the amino acid but through transamination.

Aconitine is a toxic alkaloid produced by the *Aconitum* plant. It has antipyretic and analgesic effects and has some limited application in herbal medicine In China, aconitine is used as a herbal medicine against pain. Caffeine is a bitter, white crystalline trimethyl xanthine (purine base) alkaloid found in various seeds, leaves, nuts, and berries. Common sources of caffeine are coffee, tea, soft drinks and energy drinks, caffeine supplements, and chocolate derived from cocoa beans. Also include the yerba mate, guarana and ilex guayusa plants. Caffeine is a CNS and metabolic stimulant and widely consumed legal psychoactive drug. It produces increased wakefulness, faster and clearer flow of thought, increased focus, and

better general body coordination. Theobromine is a crystalline bitter dimethyl xanthine (purine base) alkaloid. It is similar to caffeine but differs in degree of methylation. It is found in chocolate, tea, and the cola nut. It has a similar to caffeine in the effect on human nervous system but in lesser extent making it a lesser homologue. Theobromine is an isomer of theophylline and paraxanthine. Theacrine is an purine alkaloid found in *Theobroma grandiflorum* and in *Camellia assamica* var. kucha). It shows anti-inflammatory and analgesic activities. Erythromycin is an antibiotic from *Streptomyces erythreus*, jurubin, a steroid with 3-amino group from *Solanum paniculatum*, and taxol, a modified diterpene pseudo alkaloid from *Taxus brevifolia* (Taxaceae) is used in the treatment of ovarian cancer, breast cancer and non-small cell lung cancer, pachysandrine A, a steroid with *N*-containing C-17 side chain from *Pachysandra terminalis* (Buxaceae).

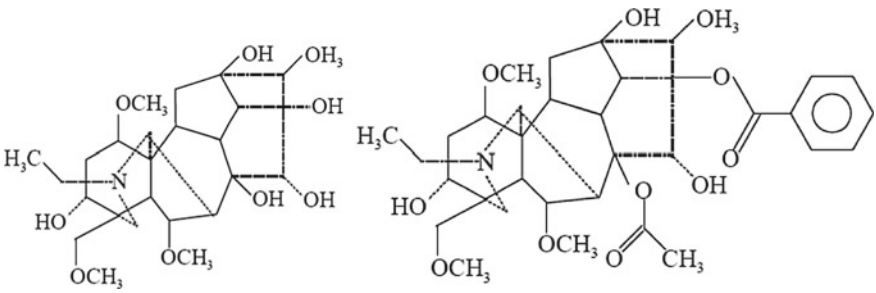
Terpenoid alkaloids

Terpenoid alkaloids based on mono-, sesqui-, di-, and tri-terpenoid skeletons are known. It has been observed that the monoterpene alkaloids are derived from the structurally related iridoid materials, wherein the O-atom in the heterocyclic ring is replaced by an N-containing ring. Typical examples of the terpenoid alkaloids are aconine and actinitine (Fig. 3.23).

Aconine is used in the treatment of neuralgia, sciatica, rheumatism, and inflammation. It is employed occasionally as analgesic and cardiac depressant. Aconitine is exclusively used in producing heart arrythmia in experimental animals. It has also been used topically in neuralgia.

Steroidal alkaloids

Steroidal alkaloids represent an important class of alkaloids that essentially afford a close structural relationship to sterols (they contain a perhydro-1,2-cyclopentanophenanthrene nucleus) and occur in the plant kingdom as glycosidal combination with carbohydrate moieties, e.g., solasonine is a glycoside of solasodine with carbohydrate moieties such as L-rhamnose, D-galactose, D-glucose; α-tomatine consists of two D-glucose units, a D-galactose unit, and a D-xylose unit (Fig. 3.24). The solanum and veratrum alkaloids are two major groups of steroidal alkaloids.



Aconine **Actinitine**

Fig. 3.23 Structure of terpenoid alkaloids—aconine and actinitine

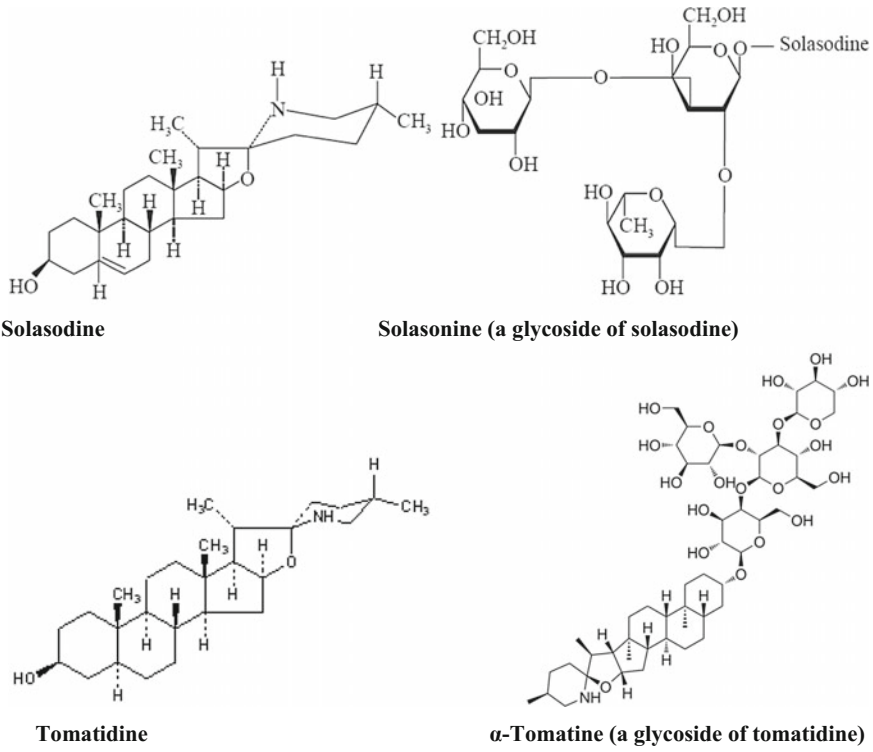
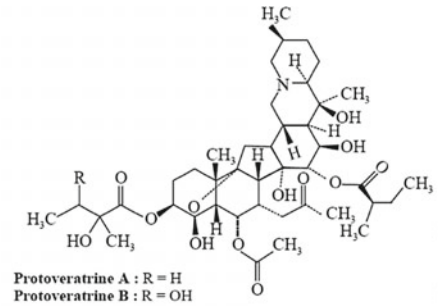


Fig. 3.24 Structure of steroidal alkaloids—solasodine and tomatidine and their glycosides

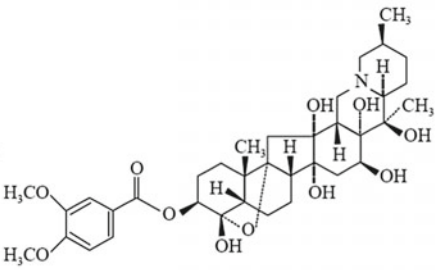
Several steroidal alkaloids are based on a C_{27} cholestane skeleton, e.g., solasodine, tomatidine, solanidine and occur in a wide variety of the genus *Solanum* (*S. laciniatum*, *S. dulcamara*, *S. nigrum*, *S. torvum*, *S. tuberosum*, *S. aviculare*, *Lycopersicon exculentum*, etc.). Solasodine is invariably used as a starting material for steroidal drugs.

The veratrum alkaloids represent the most important and medicinally significant class of steroidal alkaloids obtained from the rhizomes of *Viratrum viride*, *V. grandiflorum* and *V. eschscholtzii* (Liliaceae). The basic ring systems present in the veratrum alkaloids, however, are not quite the same as seen in the usual steroidal nucleus as present either in the cholesterol or in the aglycone residues of the cardiac glycosides. In veratrum alkaloids, the ring 'C' is a five-membered ring while ring 'D' is a six-membered, ring (B) is just the reverse of the pattern in the regular steroidal nucleus. Cevaratrum alkaloids (protoveratrines, veratridine, cevadine, germine, etc.) and jeveratrum alkaloids (veratramine, jervine and pseudojervine, etc.) are two major categories of veratrum alkaloids (Fig. 3.25).

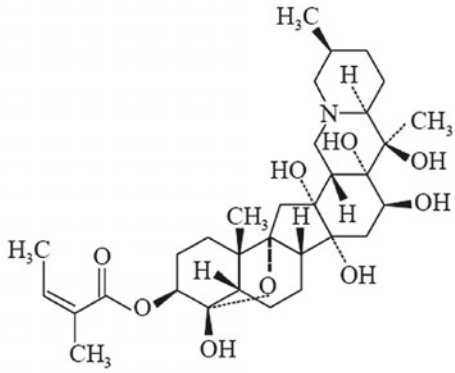
Protoveratrines is used as an antihypertensive agent which exerts its action through reflex inhibition of pressor receptors in the heart and carotid sinus. It also possesses emetic action. It is used in the treatment of toxemia of pregnancy.



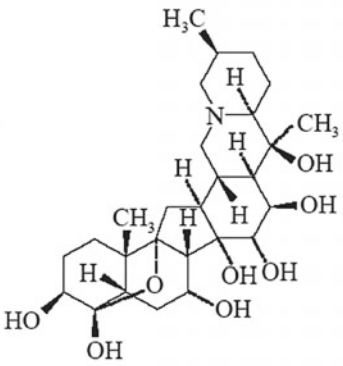
Protoveratrines (Protoveratrine A, Protoveratrine B)



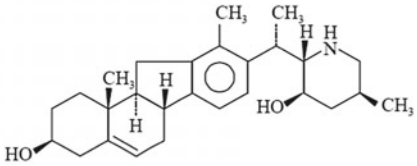
Veratridine



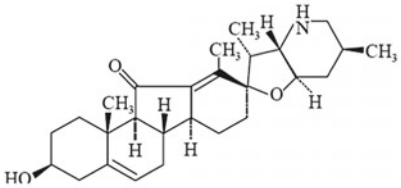
Cevadine



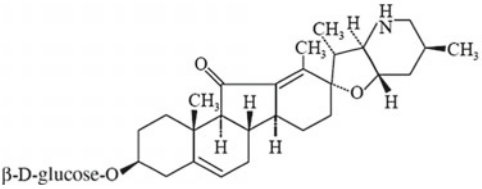
Germine



Veratramine



Jervine



Pseudojervine

Fig. 3.25 Structure of steroidal veratrum alkaloids—cevaratrum alkaloids, e.g., protoveratrines, veratridine, cevadine, germine, etc., and Jeveratrum alkaloids, e.g., veratramine, jervine and pseudojervine, etc.

(vi) False alkaloids are a variety of compounds that give false-positive alkaloid reactions with Dragendorff's reagent. The most frequent false-positive reactions have been attributed to the presence of proteins which precipitate on the addition of heavy metal containing reagents. Included in this category are ptomaine's, certain glycosides, carbohydrate, betaine, choline, purines, methylated amines, tannins, ammonium salts, etc. The false-positive alkaloid tests in *Piper methysticum* Forst. (Piperaceae) has been reported to be due to certain non-nitrogenous α-pyrone compounds.

(b) Classification based on biosynthetic carbon skeleton

In this instance, the significance solely lies to the precursor from which the alkaloids in question are produced in the plant biosynthetically. Therefore, it is quite convenient and also logical to group together all alkaloids having been derived from the same precursor but possessing different taxonomic distribution and pharmacological activities. Examples include:

(i) Alkaloids derived from ornithine include pyrrolidine (hygrine, cuscohygrine, hygroline, stachydrine); tropane (atropine, scopolamine, hyoscyamine and also cocaine, ecgonine) and pyrrolizidine (retronecine, heliotridine, laburnine, indicine, lindelophin, sarracine, platy, phylline, trichodesmine, loline, *N*-formylloline, *N*-acetylloline) alkaloids.

About 80 pyrrolidine alkaloids are known. The three glaring examples of pyrrolidine alkaloids are hygrine, cuscohygrine and stachydrine (Fig. 3.26).

Pyrrolidine is a saturated heterocycle. Hygrine is a pyrrolidine alkaloid, found mainly in Erythroxylon coca leaves (0.2%) accompanying and in *Withania somniferum* roots. Hygrine is extracted as thick yellow oil, having a pungent taste and odor. It basically stimulates the salivary gland. The drug is broadly used as a sedative, hypnotic laxative and diuretic. Cuscohygrine is a pyrrolidine alkaloid found in coca, *Atropa belladonna*, *Datura inoxia* and *D. stramonium*. Cuscohygrine usually comes with other, more potent alkaloids like atropine or cocaine. Stachydrine is a Betony alkaloid. Stachydrine is also present also in Yarrow, Motherwort, Alfalfa, Chrysanthemum and Citrus plants. It is an osmoprotectant capable of helping organisms to survive extreme osmotic stress. Motherwort contains lionurine and stachydrine alkaloids that help lower blood

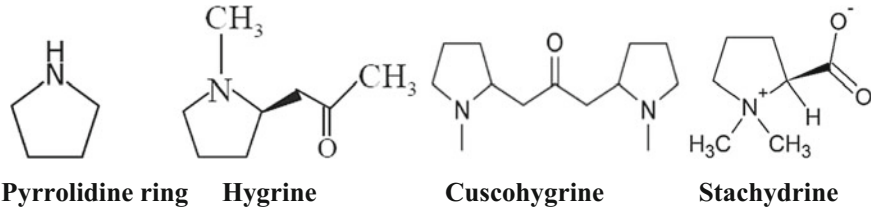


Fig. 3.26 Structure of alkaloids derived from pyrrolidine—hygrine, cuscohygrine, and stachydrine

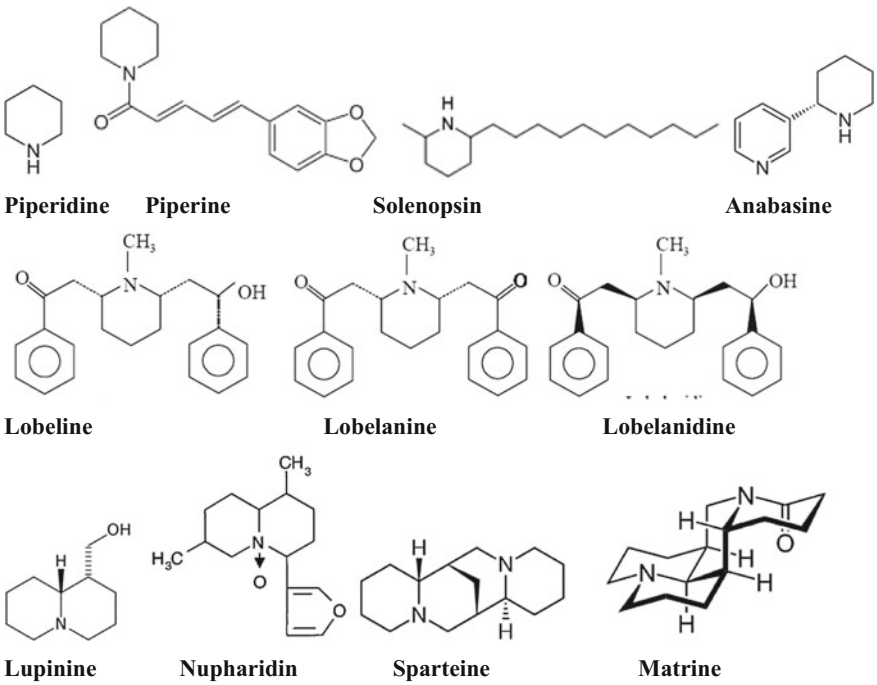


Fig. 3.27 Structure of alkaloids derived from lysine—piperine, solenopsin, anabasine, lobeline, lobelanine, lobelanidine, lupinine, nupharidin, sparteine, and matrine

pressure and have a sedating effect on the central nervous system, which supports motherwort's traditional use as a treatment for depression anxiety.

Tropane alkaloids include atropine, scopolamine, hyoscyamine and also cocaine, ecgonine, etc. Pyrrolizidine alkaloids are retronecine, heliotridine, laburnine, indicine, lindelophin, sarracine, platy, phylline, trichodesmine, loline, *N*-formylloline and *N*-acetylloline.

(ii) Alkaloids derived from lysine are piperidine (sedamine, lobeline, anaferine, piperine, coniine, coniceine); quinolizidine (lupinine, nupharidin, cytosine, sparteine, lupanine, anahygrine, matrine, oxymatrine, allomatridine, ormosanine, piptantine); and indolizidine alkaloids (swainsonine, castanospermine) (Fig. 3.27). Piperidine alkaloids are identified by their saturated heterocyclic ring, i.e., piperidine nucleus. This heterocyclic amine consists of a six-membered ring containing five methylene bridges (–CH_2–) and one amine bridge (–NH–). It is a colorless fuming liquid with an odor described as ammoniacal, pepper-like, or semen-like; the name comes from the genus name Piper, which is the Latin word for pepper.

Piperidine itself has been obtained from *Piper nigram*, from *Psilocaulon absimile* and in *Petrosimonia monandra*. The piperidine structural motif is present in numerous natural alkaloids. These include piperine, which gives black pepper its spicy taste. Other examples are the fire ant toxin solenopsin, the nicotine analog

anabasine of the Nicotiana glauca, lobeline, lobelanine of *N. tabacum*, and the toxic alkaloid coniine from poison hemlock. Piperinehas been used in some forms of traditional medicine and as an insecticide. It has shown 'antidepression like activity', and cognitive enhancing effects in rats. Piperine has shown anti-inflammatory and anti-arthritic effects in human interleukin-1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models. Piperine also possesses antiangiogenic activities. Solenopsin inhibits angiogenesis via the phosphoinositol-3 kinase (PI3-K) signaling pathway, contributes to the toxic effect of fire ant venom and has cytotoxic, hemolytic, necrotic, insecticidal, antibacterial, antifungal, and anti-HIV properties. Principal industrial use of anabasine is as an insecticide.

Quinolizidine alkaloids are lupinine, nupharidin, sparteine, lupanine, anahygrine, matrine, oxymatrine, allomatridine, ormosanine and piptantine. Lupinine is a bitter tasting quinolizidine alkaloid present in Lupinus species (lupins), plants of the family Fabaceae.Sparteine is the predominant alkaloid in *Lupinus mutabilis*. It is an antiarrhythmic agent and a sodium channel blocker but FDA did not approve it for human use as an antiarrhythmic agent. Matrine is found in plants from the *Sophora* genus. It has anticancer effects, and action as a kappa opioid receptor and μ-receptor agonist. Matrine possesses strong antitumor activities in vitro and in vivo. Inhibition of cell proliferation and induction of apoptosis are the likely mechanisms responsible for matrine's antitumor activities. Matrine is a component of the traditional Chinese medical herb *Sophora flavescens*.

Phenylethylamines, isoquinoline alkaloids are salsoline, lophocerine, papaverine, laudanosine, sendaverine, cularine, yagonine, berberine, canadine, ophiocarpine, mecambridine, corydaline, morphine, codeine, thebaine and sinomenine. Indolizidine alkaloids are swainsonine and castanospermine.

(iii) Alkaloids derived from tyrosine include phenylethylamines (ephedrine, hordenine, mescaline and narceine), isoquinoline (salsoline, lophocerine, papaverine, laudanosine, sendaverine, cularine, yagonine, berberine, canadine, ophiocarpine, mecambridine, corydaline, morphine, codeine, thebaine, sinomenine) and tetrahydroisoquinoline alkaloids (Fig. 3.28). The important alkaloids belonging to phenylethylamine group are ephedrine, hordenine, mescaline and narceine.

Phenylethylamine, phenethylamine or β-phenethylamine is a natural monoamine alkaloid. It has psychoactive and stimulant effects. Phenylethylamine functions as a neuromodulator or neurotransmitter in the mammalian central nervous system. It is sold as a dietary supplement for purported mood and weight loss-related therapeutic benefits. Phenethylamine is widely distributed throughout the plant kingdom and also present in animals, such as humans. Narceine is obtained from the dried latex opium (*Papaver somniferum*) to the extent of 0.1–0.5%. Narcyl is used as a narcotic analgesic and also employed as an antitussive agent.

Isoquinoline alkaloids are salsoline, lophocerine, papaverine, laudanosine, sendaverine, cularine, yagonine, berberine, canadine, ophiocarpine, mecambridine, corydaline, morphine, codeine, thebaine and sinomenine.

Papaverine is an opium poppy alkaloid antispasmodic drug, used primarily in the treatment of visceral spasm, vasospasm, and occasionally in the treatment of erectile dysfunction. Papaverine differs in both structure and pharmacological action from the analgesic opium alkaloids (morphine).Morphine is an opioid analgesic drug and acts directly on the central nervous system (CNS) to relieve pain. A minor constituent of opium, thebaine is chemically similar to both morphine and codeine, but has stimulatory rather than depressant effects.

Tetrahydroisoquinoline alkaloid is a secondary amine. The tetrahydroisoquinoline skeleton is commonly encountered in pharmaceutical drugs, notably quaternary ammonium muscle relaxants such as tubocurarine. Tubocurarine (D-tubocurarine or DTC) is a toxic alkaloid and skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs, used adjunctively in anesthesia to provide skeletal muscle relaxation during surgery or mechanical ventilation.

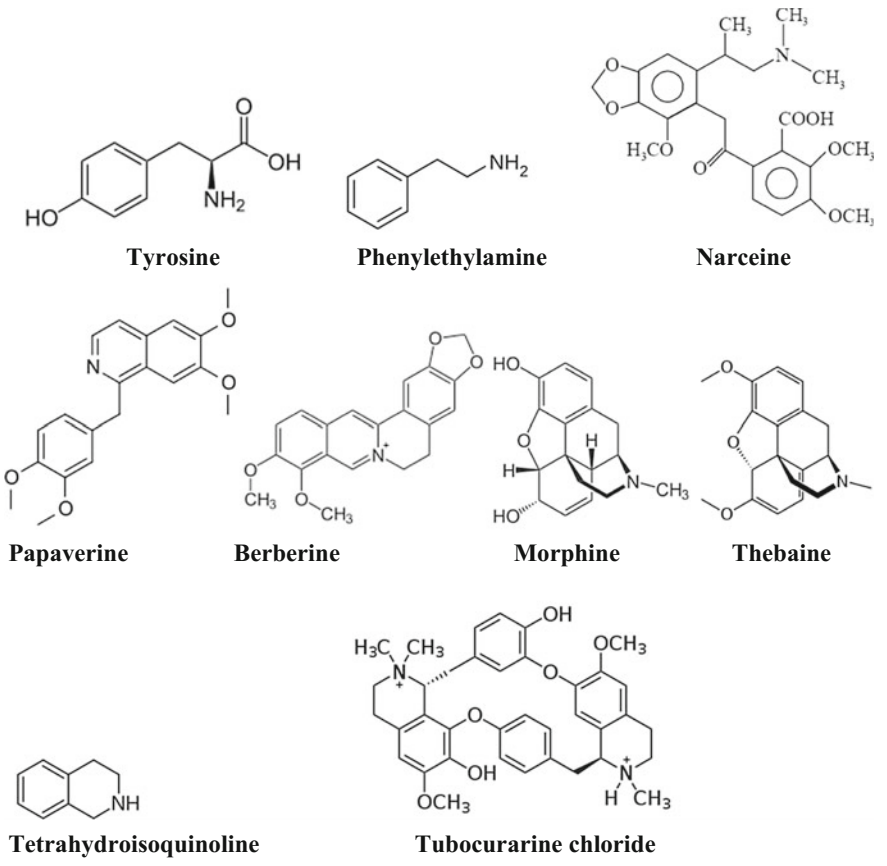


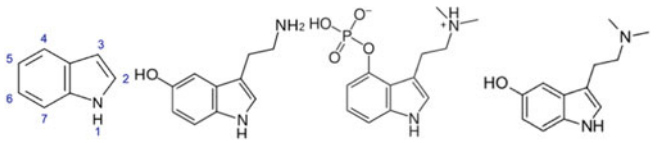
Fig. 3.28 Structure of alkaloids derived from tyrosine

(iv) Alkaloids derived from tryptophan are indole alkaloids. With respect to their structural features, tryptophan derived indole alkaloids can be divided into non-isoprenoid and isoprenoid indole alkaloids (derived from tryptamine and secologanin). The first group includes three types, e.g., (i) simple indole, (ii) β-carboline and (iii) ergot alkaloids and the second group include eight types, e.g., (i) corynanthean or C-type (sarpagine, yohimbine, ajmalicine), (ii) vincosan or d-type (vincoside), (iii) vallesiachotamon or V-type (vallesiachotamine), (iv) strychnan or S-type (vomicine), (v) aspidospermatan or A-type (condylocarpine), (vi) eburnan or E-type (vincamine), (vii) plumeran or P-type (kopsine) and (viii) ibogan or J-type (voaluteine).

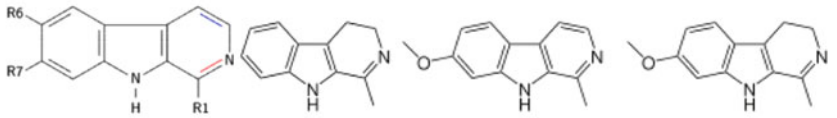
Simple indole alkaloids include serotonin, psilocybin, dimethyltryptamine, bufotenin, etc. (Fig. 3.29).

The indole structure consists of a pyrrole ring and a benzene ring fused together to form two isomeric benzopyrroles. Serotonin is found in mushrooms, fruits—in nuts of the walnut and hickory (25–400 mg/kg) in plantains, pineapples, banana, kiwifruit, plums, and tomatoes (3–30 mg/kg) have been found. and vegetables (0.1–3 mg/kg), Serotonin is one compound of the poison contained in stinging nettles (*Urtica dioica*), where it causes pain on injection in the same manner as its presence in insect venoms. Serotonin, 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter, serotonin is primarily found in the gastrointestinal tract (GI tract), platelets, and the central nervous system (CNS) of animals, including humans. It is popularly thought to be a contributor to feelings of well-being and happiness. The ergot alkaloids are mycotoxins produced by several species of fungi in the genus Claviceps. There are four main groups of ergot alkaloids: the clavines, the lysergic acids, the lysergic acid amides, and the ergo peptides. Psilocybin mushrooms contains derivatives of tryptamine and Claviceps contains derivatives of lysergic acid. Psilocybin is a naturally occurring psychedelic compound produced by more than 200 species of mushrooms, collectively known as psilocybin mushrooms (*Psilocybe azurescens*, *P. semilanceata*, *P. cyanescens*, etc.). In general, the effects include euphoria, visual and mental hallucinations, changes in perception, a distorted sense of time, and spiritual experiences, and can include possible adverse reactions such as nausea and panic attacks. Bufotenin, a dimethyl serotonin, are found in the skin of some species of toads; in mushrooms, higher plants, and mammals. Bufotenine is an indole hallucinogen capable of blocking the action of serotonin (an indole amine neurotransmitter) and is a powerful constrictor of blood vessels, causing a rise in blood pressure.

β-carboline alkaloids consist of pyridine ring that is fused to an indole skeleton producing a three-ringed structure. β-Carboline alkaloids are widespread in plants and animals and include harmane, harmine, harmaline, eleagnine, etc. β-carboline alkaloids are a large group of natural indole alkaloids with different degrees of aromaticity, distributed in nature, including various plants, foodstuffs, marine creatures, insects, mammalians as well as human tissues and body fluids. They show diverse biological activities, e.g., intercalate into DNA, inhibit CDK, topoisomerase, and monoamine oxidase, interact with benzodiazepine receptors and

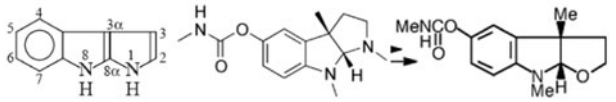


Indolemoiety **Serotonin** **Psilocybin** **Bufotenin**

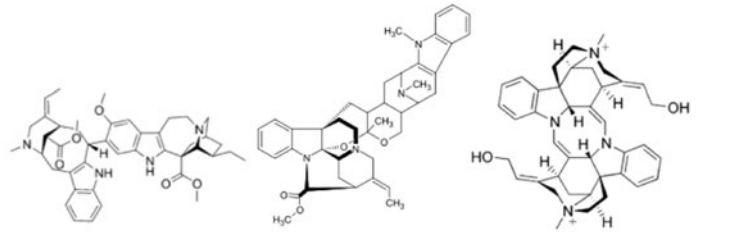


β-carbolines moiety **Harmane** **Harmine** **Harmaline**

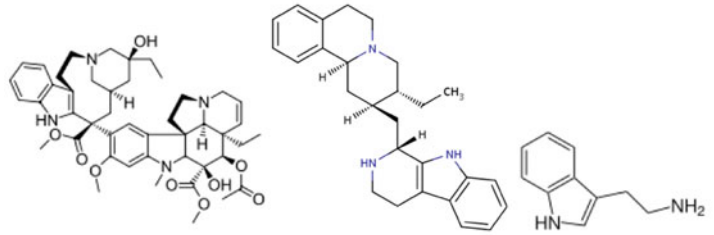
[Harmane (R1=CH3), Harmine (R1=CH3, R6=H, R6=OCH3), Harmaline (R1, R6, R7 same harmine)]



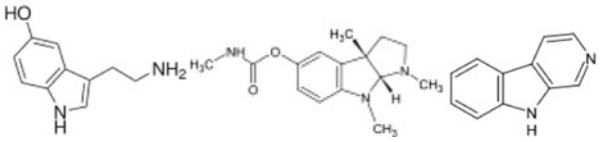
Pyrrolo-indole moiety **Physostigmine** **(−)-Physovenine**



Voacamine **Villalstonine** **Toxiferine**



Vinblastine **Tubulosine** **Tryptamine**



Serotonin **Physostigmine** **β-carboline**

Fig. 3.29 Structure of alkaloids derived from tryptophan

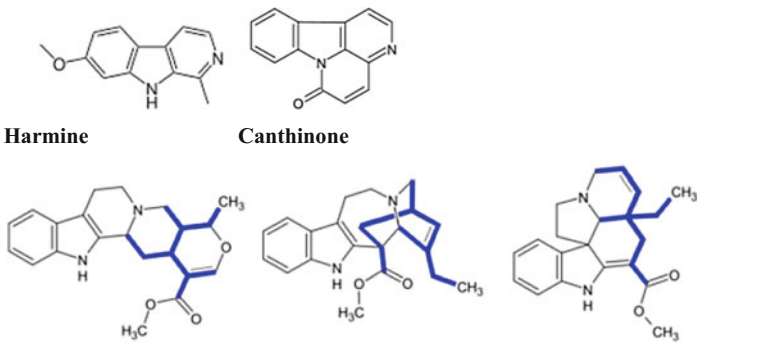


Fig. 3.29 (continued)

5-hydroxy serotonin receptors. They have a broad spectrum of pharmacological properties including sedative, anxiolytic, hypnotic, anticonvulsant, and antitumor, antiviral, antiparasitic as well as antimicrobial activities. The β-carbolines harmine, harmaline, and tetrahydroharmine play a pivotal role in the pharmacology of the indigenous psychedelic drug. β-carboline is a benzodiazepine receptor inverse agonist and can therefore have convulsive, anxiogenic and memory enhancing effects.

The plants rich in non-isoprenoid indole alkaloids include *Peganum harmala* (harmane, harmine, and harmaline), and *Physostigma venenosum* (physostigmine). Some members of the family Convolvulaceae, in particular *Ipomoea violacea* and *Turbina corymbosa*, contain ergolines and lysergamides.

Pyrroloindole includes physostigmine (eserine), etheramine, physovenine, eptastigmine; and ergot alkaloids). Physostigmine is a parasympathomimetic alkaloid, specifically, a reversible cholinesterase inhibitor. It occurs naturally in the Calabar bean.

Isoprenoid indole alkaloids contain residues of tryptophan and isoprenoid building blocks derived from the dimethylallyl pyrophosphate and isopentenyl pyrophosphate and include ergot and monoterpenoid alkaloids. Beside these, bisindole alkaloids are produced in living organisms through dimerization of monomeric indole bases.

Isoquinoline indole alkaloids are ergotamine, ergobasine, ergosine, ajmalicine, sarpagine, vobasine, ajmaline, yohimbine, reserpine, mitragynine, strychnine and strychnine brucine, aquamicine, vomicine, ibogamine, ibogaine, reserpine, strychnine, physostigmine, strychinine, brucine; quinolone alkaloid-cinchonine, quinine, quinidine, campotothecin; vinca alkaloids—voacangine, vincamine, vincristine, vinblastine, vincotine, aspidospermine; quinolone. Depending on their biosynthesis, they are grouped into hemiterpenoids (e.g., ergot alkaloids—ergine, ergotamine, ergosine, ergostine, ergoptine, ergonine, ergocristine, α-ergocryptine,

β-ergocryptine, and ergocornine) and three classes of monoterpenoids (e.g., corynanthe—ajmaline, aquamycin, strychnine, brucine, ajmalicine, yohimbine, reserpine, sarpagine, and mitragynine; iboga—ibogaine, ibogamin, and voacangine; aspidosperma—eburnamin, tabersonine, vindolin, and vincamine).

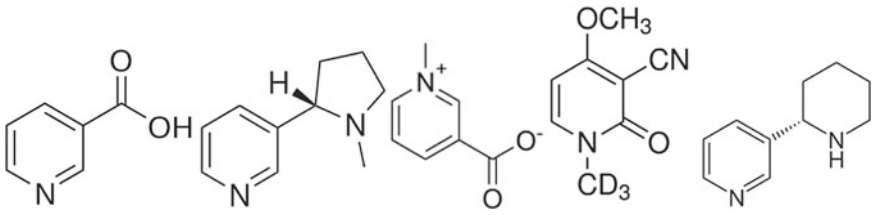
Despite the considerable structural diversity, most of monoterpenoid indole alkaloids is localized in three families of dicotyledon plants: Apocynaceae (Alstonia, Aspidosperma, Rauwolfia and Catharanthus), Rubiaceae (Corynanthe) and Loganiaceae (Strychnos).

(v) Alkaloids derived from nicotinic acid are pyridine alkaloids (trigonelline, ricinine, arecoline, nicotine, nornicotine, anabasine, anatabine, actinidine, gentianine, pediculinine, evonine, hippocrateine, triptonine) (Fig. 3.30).

Nicotine is a potent parasympathomimetic alkaloid found in the members of Solanaceae (Belladonna, Nictiana) and also in various edible plants. It is made in the roots of and accumulates in the leaves. Nicotine appears to have significant performance enhancing effects, particularly in fine motor skills, attention, and memory. These beneficial cognitive effects may play a role in the initiation and maintenance of tobacco dependence. It functions as an antiherbivore chemical; consequently, nicotine was widely used as an insecticide in the past and nicotine analogs such as imidacloprid are currently widely used. In lesser doses (about 1 mg), the substance acts as a stimulant in mammals, while high amounts (50–100 mg) can be harmful. Anabasine is found in the tree tobacco (*Nicotiana glauca*) plant, structurally and chemically similar to nicotine. Its principal industrial use is as an insecticide. Anabasine is present in trace amounts in tobacco smoke, and can be used as an indicator of a person's exposure to tobacco smoke. Anabasine is a nicotinic acetylcholine receptor antagonist. In high doses, it produces a depolarizing block of nerve transmission, which can cause symptoms similar to those of nicotine poisoning and, ultimately, death by asystole.

(vi) Phenylalanine or L-phenylalanine usually contributes only carbon atoms, e.g., C_6C_3, C_6C_2, or C_6C_1 units, without providing a nitrogen atom from its amino group, e.g., ephedrine, norpseudoephedrine (cathine), capsaicin, colchicine, lobeline, etc. (Fig. 3.31).

Capsaicin is an active component of chili peppers (*Capsicum* sp.). Capsaicin is used as an analgesic in topical ointments, nasal sprays, and dermal patches to relieve pain



Nicotinic acid **Nicotine** **Trigonelline** **Ricinine-(methyl-d3)** **Anabasine**

Fig. 3.30 Structure of alkaloids derived from nicotinic acid

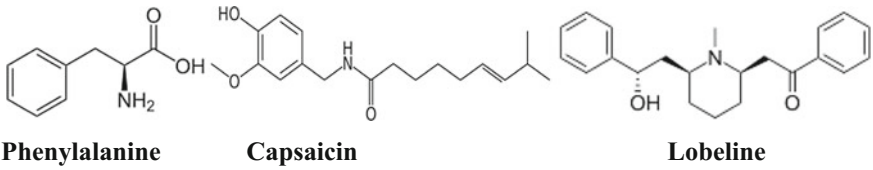


Fig. 3.31 Structure of alkaloids derived from phenylalanine

at loe concentration (0.025–0.25%). It may be applied in cream form for the temporary relief of minor aches and pains of muscles and joints associated with arthritis, backache, strains other *Lobelia* spp. Lobeline has been used as a smoking cessation aid, and may have application in the treatment of other drug addictions such as addiction to amphetamines, cocaine, or alcohol.

(vii) Alkaloids derived from histidine are imidazole alkaloids. Imidazole is an aromatic heterocycle and alkaloids containing one or more imidazole moieties as part of its structure (pilocarpine, pilosine) are imidazole alkaloids (Fig. 3.32).

Pilocarpine is as a drug used to treat dry mouth and glaucoma. It is a parasympathomimetic alkaloid obtained from the leaves of tropical American shrubs from the genus Pilocarpus. It is a nonselective muscarinic receptor agonist in the parasympathetic nervous system, which acts therapeutically at the muscarinic acetylcholine receptor M3 due to its topical application, e.g., in glaucoma and xerostomia. Pilocarpine stimulates the secretion of large amounts of saliva and sweat. It is used to treat dry mouth (xerostomia) particularly in Sjögren's syndrome, but also as a side effect of radiation therapy for head and neck cancer.

(viii) Alkaloids derived from anthranilic acid include quinazoline, quinoline, and acridine alkaloids. Anthranilic acid is a key intermediate in the biosynthesis of L-tryptophan and so contributes to the elaboration of indole alkaloids (quinazoline–vasicine, vasicinone; quinolone and acridine alkaloids—melicopicine, melicopidine, and melicopine, while histidine gives imidazole derivatives, histamine, pilocarpine, isopilocarpine, pilosine, stevensine, etc.) (Fig. 3.33).

Vasicine and also vasicinone are obtained from the leaves of *Adhatoda vasica* (L.) and the seeds of *Peganum harmala.* Vasicine is mostly used as an expectorant and bronchodilator, shows oxytocic properties, abortifacient action, etc. Vasicinone is used mainly as an expectorant which action is solely due to stimulation of the

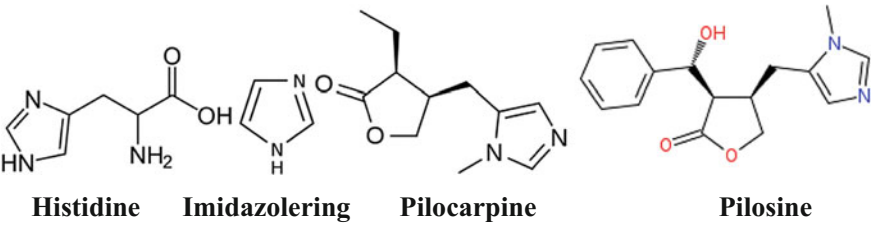


Fig. 3.32 Structure of alkaloids derived from histidine

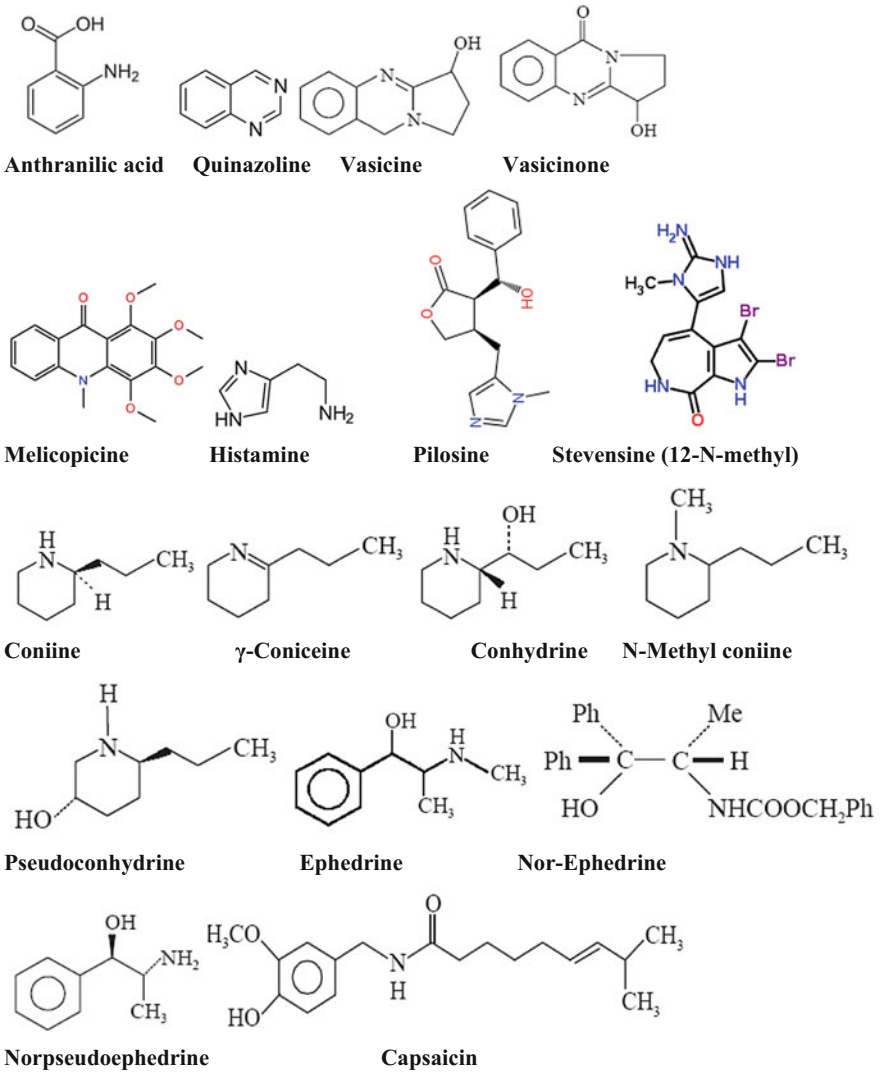


Fig. 3.33 Structure of alkaloids derived from anthranilic acid

bronchial glands. Histamine is involved in local immune responses to foreign pathogens, as well as regulating physiological function in the gut and acting as a neurotransmitter. Histamine is involved in the inflammatory response. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues. Stevensine is a bioactive bromopyrrole alkaloid isolated from marine sponge.

Alkaloids derived from amination reactions include acetate-derived alkaloids, phenylalanine-derived alkaloids, terpenoid alkaloids and steroidal alkaloids.

Amination reaction is the process by which an amine group is introduced into an organic molecule; enzymes which catalyze this reaction are termed aminases. A large number of alkaloids are derived from amino acids (an N-atom as well as an amino acid carbon skeleton or a major part of it). However, a good number of amino acids are synthesized from nonamino acid precursors (predominantly based on terpenoid and steroidal skeleton) and they derive their N-atom later through tranamination reaction (late amination processes) using an appropriate aldehyde or ketone.

Acetate-derived alkaloids include coniine, γ-coniceine, conhydrine, *N*-methyl coniine and pseudoconhydrine derived from hemlock plant (*Conium maculatum*, Apiaceae). It also occurs in the plant *Aethusa cynapium* (Apiaceae) and *Cicuta maculata* (Apiaceae) (Water Hemlock). Socrates was made to drink the decoction of the hemlock plant and died soonafter.

Externally, the coniine salts are used as ointments and infrequently employed for their local analgesic action in the symptomatic relief of pruritis, hemorrhoids and fissures.

Phenylalanine derived alkaloids where L-phenylalanine contributes carbon atoms only (C_6C_1, C_6C_2 or C_6C_3 units) without contributing its N-atom from its amino function. The various typical examples of phenylalanine-derived alkaloids are: ephedrine, norpseudoephedrine (cathine) and capsaicin. Ephedrine exists singly in *Ephedra sinica* (1–3%) and *E. equisetina* (2%), pseudoephedrine) in *E. vulgaris*, norpseudoephedrine from *Catha edulis* Forsk., *Maytenus krukovii* A.C. Smith (Celastraceae) and capsaicin from *Capsicum annum* L. (Solanaceae).

The L-ephedrine is extensively used as a bronchodilator. The D-pseudoephedrine is employed widely as a decongestant. Norpseudoephedrine is widely employed as an anorexic. It is also used in the optical resolution of externally compensated acids. Capsaicin is used as a topical analgesic.

It is often employed as a tool in neurobiological research. It is used in creams to counter neuralgia caused by herpes infections and in other pain-relieving formulations.

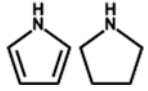
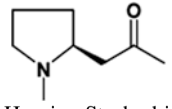
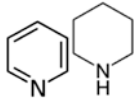
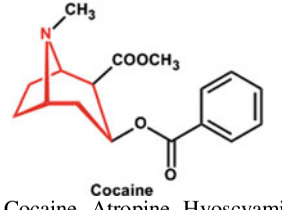
(c) Chemical classification on the basis of heterocyclic ring structure

It is probably the most widely accepted and common mode of classification of alkaloids (into 16 groups) for which the main criterion is the presence of the basic heterocyclic nucleus (i.e., the chemical entity) (Table 3.3).

(d) Pharmacological classification

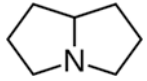
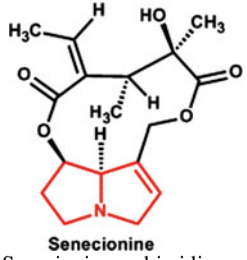
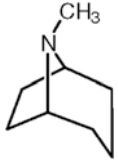
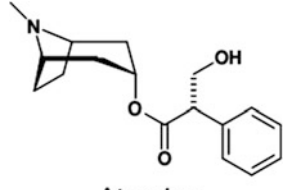
Alkaloids exhibit a broad range of pharmacological characteristics such as analgesics, cardiovascular stimulants, CNS stimulants and depressants, dilation of pupil of eye, mydriatics, anticholinergics, sympathomimetics, antimalarials, antineoplastic, antidysenteric, antihypertensive, antihyperglycemic, purgatives, etc., and they are classified on the basis of such pharmacological characteristics (Table 3.4). Perhaps this might also be used as a strong basis for the general classification of the wide-spectrum of alkaloids derived from the plant kingdom. However, such a classification is not quite common and broadly known.

Table 3.3 Classification of Alkaloids on the basis of heterocyclic ring structure

Alkaloids				
Serial number	Type	Structure	Example	Plant source
1.	Pyrrole, pyrrolidine alkaloids		 Hygrine Stachydrine	*Nicotiana tabacum*, *Erythroxylum coca*
2.	Pyridine and piperidine alkaloids		 Nicotine (Pyridine + Pyrrolidine) Nicotine Lobeline Piperine Conine Trigonelline arecoline, anabasine	*Lobelia tupa*, *Areca catechu*, *Nicotiana glauca*, *Trigonella foenum-graecum*, *and Conium maculatum*
	Tropane (piperidine/*N*-methyl-pyrrolidine)		 Cocaine Cocaine, Atropine, Hyoscyamine, Hyoscine	*Atropa belladonna*, *Datura stramonium*, *Hyoscyamus niger*, *Duboisia myoporoides*, *and Erythroxylum coca*

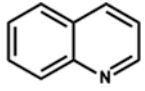
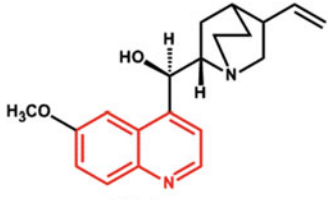
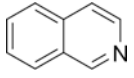
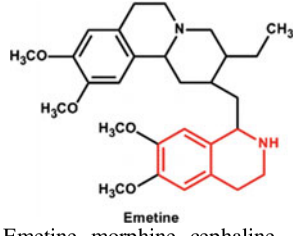
(continued)

Table 3.3 (continued)

Alkaloids				
Serial number	Type	Structure	Example	Plant source
3.	Pyrrolizidinealkaloids		 Senecionine Senecionine, echimidine, seneciphylline, echimidine	*Senecio vulgaris*, *Echium plantagineum*, *Senecio jacobea*, *and Crotalarria juncea*
4.	Tropanealkaloids		 Atropine Atropine, hyoscine, hyoscyamine, coniine, pseudopelletirine	*Atropa belladonna*, *Datura stramonium*

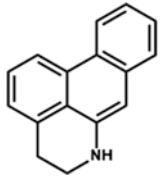
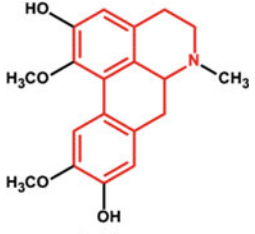
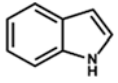
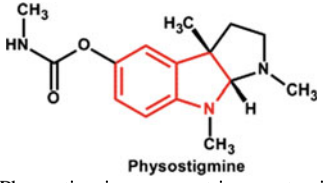
(continued)

Table 3.3 (continued)

Alkaloids				
Serial number	Type	Structure	Example	Plant source
5.	Quinolinealkaloids		 Quinine Quinine,quinidine, cinchonidine, cupreine, camptothecine Cinchonine	*Cinchonapubescens*, *C. officinalis*
6.	Isoquinolinealkaloids		 Emetine Emetine, morphine, cephaline, narcotine, narceine, D-tubocurarine papaverine, narcotine, and codeine	*Papaver somniferum*

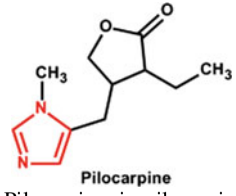
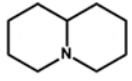
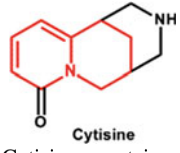
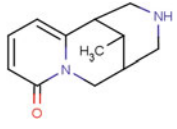
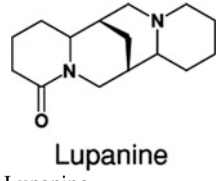
(continued)

Table 3.3 (continued)

Alkaloids				
Serial number	Type	Structure	Example	Plant source
7.	Aporphine (reduced isoquinoline/naphthalene)		 Boldine Boldine, bulbocapnine, glaucine, corytuberine	*Lindera aggregate*, *Corydalis* spp. *Glaucium* spp.
8.	Indole or benzopyrrole		 Physostigmine Physostigmine ergometrine, erotamine, reserpine, vincristine, vinblastine, strychnine, brucine yohimbine, serpentine	*Claviceps paspali* (Ascomyceteae), *Rauvolfia serpentine*, *Catharanthus roseus*, *and Strychnos nux-vomica*

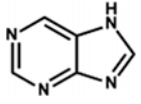
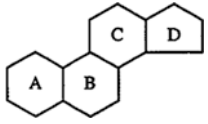
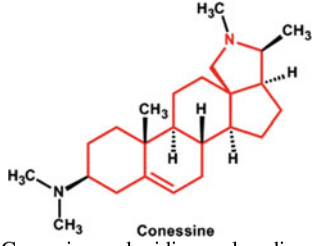
(continued)

Table 3.3 (continued)

Alkaloids				
Serial number	Type	Structure	Example	Plant source
9.	Imidazole alkaloids Imidazole or glyoxaline		 Pilocarpine Pilocarpine, isopilocarpine, pilosine	*Pilocarpus* sp.
10.	Norlupinane=Quinolizidine		 Cytisine Cytisine, sparteine, nupharine, lupanine, laburnine	*Laburnum* sp. *Cytisus* sp. *Lupinus mutabilis*, *Anagyris* sp., *Thermopsis* sp., *Genista* sp., *Retama* sp., *Sophora* sp., and Nymphaea lotus
11.	Diazocin alkaloids		 Lupanine Lupanine	*Lupinus albus*

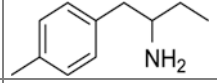
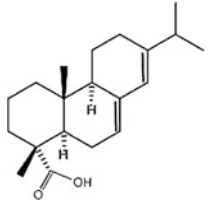
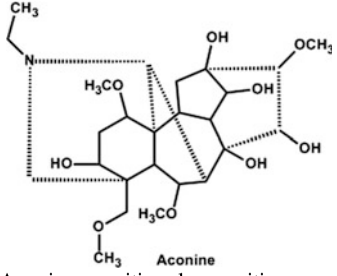
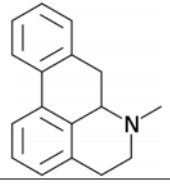
(continued)

Table 3.3 (continued)

Alkaloids				
Serial number	Type	Structure	Example	Plant source
12.	Purine alkaloids (pyrimidine/imidazole)		 Caffeine Caffeine, theobromine, theophylline, cocaine, nicotine	*Coffea* spp., Camellia sinensis, *Ilex paraguariensis*, *Erythroxylum coca*, *and Nicotiana tabacum*
13.	Steroidal alkaloids Steroidal (some combined as glycosides)*		 Conessine Conessine, solanidine, solasodine, tomatidine, solanidine, zygacine, veratramine, cyclopamine, cycloposine, jervine, muldamine	*Solanum* spp. *Capsicum annuum*, *Lycopersicon esculentum*, *Veratrum* spp., and *Zigadenus* spp.

(continued)

Table 3.3 (continued)

Alkaloids				
Serial number	Type	Structure	Example	Plant source
14.	Amino alkaloids		Ephedrine	*Ephedra sinica*
15.	Diterpene alkaloids Terpenoid		 Aconine aconitine, lycaconitine	*Aconitum heterophyllum*, *Inula royaleana*, *and Spiraea japonica*
16.	Aporphine (reduced isoquinoline napthalene)		Boldnine	*Lindera aggregata*

* some combines as glycosides

Table 3.4 Pharmacological classification of alkaloids

Pharmacological characteristics	Example	Plant source
i. Narcotic, analgesic	Morphine	Capsule of *Papaver somniferum*
ii. Antimalarial	Quinine, artemisinins (WHO only recommends artemisinins)	Bark of *Cinchona* spp., glandular trichomes of the leaves, stems, and inflorescencesof *Artemisia annua*
iii. Reflexexcitability	Strychnine	Seeds of *Strychnos nux-vomica*
iv. Respiratory stimulant	Lobeline	Leaf and flower of *Lobelia inflata*
v. Choleretics and laxatives	Boldine	Leaf and bark of *Lindera aggregata*
vi. Neuralgia	Aconitine	Whole herb of *Aconitum heterophyllum*
vii. Antiglaucoma and xerostomia agents	Pilocarpine	Leaf of *Pilocarpus microphyllus*
viii. Oxytocic	Ergonovine	Seeds of *Ipomea violaceae*
ix. Bronchodilator	Ephedrine, vasicine	Whole shrub of *Ephedra sinica*, Leaf of *Justicia adhatoda*
x. Analgesic (narcotic), antitussive	Narceine, codeine (3-methylmorphine)	Capsule of *Papaver somniferum*
xi. CNS stimulant	Caffeine	*Seeds of Coffea* spp., leaf of *Camellia sinensis*
xii. Antihypertensive	Reserpine	Root of *Rauvolfia serpentine*
xiii. Anticancer	Vinblistine, vincristine	Leaf of *Catharanthus roseus*
xiv. Antiarrythmic	Quinidine	Bark of *Cinchona* spp.
xv. Antichonergic	Atropine	Foliage and berries of *Atropa belladonna*

(e) Taxonomic classification

The taxonomic classification of alkaloids essentially deals with the taxon—the taxonomic category. The most common taxa are the genus, subgenus, species, subspecies, and variety. Therefore, the taxonomic classification encompasses the plethora of alkaloids exclusively based on their respective distribution in a variety of Plant Families. A few typical examples of plant families and the various species associated with them are stated below.

(i) Amarrilidaceae alkaloids

Amarrilidaceae, a monocot family, include 75 genera and about 1100 species. Plants of this family are among the top 20 in the most widely considered medicinal plant families. Different pharmacologically active compounds such as phenols, alkaloids, lectins, peptides, etc., are present in the members of this family. About 500 structurally diverse Amaryllidaceae alkaloids have been isolated to date. These structurally diverse Amaryllidaceae alkaloids are classified into nine skeleton types, for which the representative alkaloids are: norbelladine, lycorine, homolycorine, crinine, haemanthamine, narciclasine, tazettine, montanine and galanthamine.

Amaryllidaceae alkaloids have important pharmacological properties such as acetylcholinesterase inhibitory activity, cytotoxicity and antitumoral activity (Bastida et al. 2006). Galanthamine, an isoquinoline alkaloid, is obtained from *Galanthus* sp. *Narcissus* spp. and *Leucojum aestivum.* Lycorine, a pyrrolophenanthridine alkaloid, displays a strong antiviral effect against poliovirus, measles and herpes simplex type 1 viruses, as well as high antiret—roviral and strong antimitotic activities. Galanthamine is a long-acting, selective, reversible and competitive inhibitor of acetylcholinesterase, and is used for the treatment of Alzheimer's disease. Amaryllidaceae alkaloids have shown much promise as remarkably potent and selective anticancer agents. Due to interesting biological properties of Amaryllidaceae alkaloids and their abundance in different members, plants of the Amaryllidaceae have provided a diverse and accessible platform for phytochemical-based drug discovery.

(ii) Liliaceous alkaloids

The Liliaceae is one of the largest plant families with about 280 genera and 4000 species distributed throughout the world. They are mostly perennial herbs with starchy rhizomes, corms, tuber or bulbs. Plants belonging to the Liliaceae family have been the topic of research in many phytochemical and pharmacological laboratories because they contain structurally complex and biologically fascinating steroidal alkaloids. Medicinally important genera of the genera are *Asphodelus aestivus*, *Asparagus aphyllus*, *Draceana* spp., *Drimia maritima*, *Smilax aspera*, *Ruscus hypophyllum*, *R. aculeatus*, *Muscari comosum*, *Lilium candidum*, *Hyacinthus orientalis*, *Aloe vera*, *Allium sativum*, *Allium cepa*, *Colchium cupani*, *C. autunnale*, etc. Liliaceae is a rich source of steroidal glycosides and alkaloids.

(iii) Cannabinaceous alkaloids

Cannabis is a psychoactive plant belonging to Cannabaceae family. The two principal varieties are *Cannabis sativa* or textile hemp and the *Cannabis sativa* indica or Indian hemp (Hemp, Marijuana).

(iv) Rubiaceous alkaloids

Rubiaceae family contains 611 genera and about 13,000 species. It is the fourth largest angiosperm family and contains economically important plants like Coffea spp. (caffein), *Cinchona officinalis* (quinine), *Rubia* spp., *Gardenia* spp., *Ixora* spp., *Pentas lanceolata*, *Mitragyna speciosa* (mitragynine, mitraphylline, 7-hydroxymitragynine, mitragynine pseudoindoxyl, raubasine, and some yohimbe alkaloids such as corynantheidine); *Pausinystalia johimbe* (yohimbine, corynanthine).

(v) Solanaceous alkaloids

The family Solanaceae consists of about 98 genera and some 2700 species with a great diversity of habitats, morphology, and ecology. Certain species are universally known for their medicinal uses and their psychotropic effects. Many species contain a variety of alkaloids including solanine, tropane, nicotine, capsaicin, scopolamine, atropine, hyoscyamine, nicotine, etc. Some of the medicinally important members of this family are *Nicotiana tabacum* (nicotine, anatabine, anabasine, etc.), *Petunia* spp., *Browallia* spp., and *Lycianthes* spp., the source of psychoactive alkaloids,

Daturastramonium (tropane alkaloids—atropine, hyoscyamine, scopolamine, etc.), *Mandragora officinarum* (atropine, hyoscyamine, scopolamine, scopine, cuscohygrine, etc.), *Atropa belladonna* (atropine, hyoscine scopolamine, hyoscyamine, etc.) and *Hyoscyamus albus* (piperidone alkaloid, tropane alkaloid, hyalbidone, littorine, etc.), *Brunfelsia uniflorus*, *Capsicum annuum*, *Duboisia myoporoides*, *H. niger*, *Nicotiana glauca*, *Seopolia carniolica*, *Solanum dulcamara*, *Withania somniferum*, etc.

Invariably, alkaloids are grouped together according to the name of the genus wherein they belong to, such as coca, cinchona, and ephedra. Some phytochemists have even gone a step further and classified the alkaloids based on their chemotaxonomic classification. In the recent past, the alkaloids have been divided into two major categories based on the analogy that one containing a nonheterocyclic nucleus, while the other having the heterocyclic nucleus. These two classes of alkaloids, their major groups, synthetic precursors, examples and plant sources are shown in the Table 3.5.

The biological role

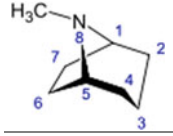
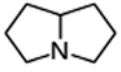
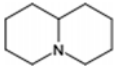
The role of alkaloids for living organisms that produce them is still unclear. It was initially assumed that the alkaloids are the final products of nitrogen metabolism in plants, as urea in mammals. It was later shown that alkaloid concentration varies over time, and this hypothesis was refuted. Most of the known functions of alkaloids are related to protection. For example, aporphine alkaloid liriodenine produced by the tulip tree protects it from parasitic mushrooms. In addition, presence of alkaloids in the plant prevents insects and chordate animals from eating it. However, some animals adapted to alkaloids and even use them in their own metabolism. Such alkaloid-related substances as serotonin, dopamine and histamine are important neurotransmitters in animals. Alkaloids are also known to regulate plant growth. Another example of an organism that uses alkaloids for protection is the Utetheisa ornatrix, more commonly known as the Ornate Moth. Pyrrolizidine alkaloids render these larvae and adult moths unpalatable to many of their natural enemies like coccinelid beetles, green lacewings, insectivorous hemiptera and insectivorous bats.

Applications of alkaloids

In medicine

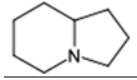
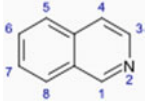
Medical use of alkaloid-containing plants has a long history, and, thus, when the first alkaloids were isolated in the nineteenth century, they immediately found application in clinical practice. Many alkaloids are still used in medicine. Ajmaline—antiarrhythmic; atropine, scopolamine, hyoscyamine—anticholinergic; caffeine—stimulant, adenosine receptor antagonist; codeine—cough medicine, analgesic; colchicine—remedy for gout; emetine—antiprotozoal agent; ergot alkaloids—sympathomimetic, vasodilator, antihypertensive; morphine—analgesic; nicotine—

Table 3.5 Alkaloids with heterocycle and nonheterocycle rings nucleus

Class	Major groups	Synthetic precursors	Examples and plant sources
Alkaloids with nitrogen heterocycles (*true alkaloids*)			
Pyrrolidine derivatives 		Ornithine or arginine	Cuscohygrine, hygrine, hygroline, and stachydrine
Tropane derivatives 	Atropine group	Ornithine or arginine	Atropine, scopolamine, and hyoscyamine
	Cocaine group		Cocaine, ecgonine
Pyrrolizidine derivatives 	Non-esters	In plants: ornithine or arginine	Retronecine, heliotridine, laburnine
	Complex esters of monocarboxylic acids		Indicine, lindelophin, and sarracine
	Macrocyclic diesters		Platyphylline, trichodesmine
	1-amino pyrrolizidines (lolines)	In fungi: L-proline +L-homoserine	Loline, *N*-formylloline, and *N*-acetylloline
Piperidine derivatives 		Lysine	Sedamine, lobeline, anaferine, and piperine
		Octanoic acid	Coniine, coniceine
Quinolizidine derivatives 	Lupinine group	Lysine	Lupinine, nupharidin
	Cytisine group		Cytisine
	Sparteine group		Sparteine, lupanine, and anahygrine
	Matrine group		Matrine, oxymatrine, and allomatridine
	Ormosanine group		Ormosanine, piptantine

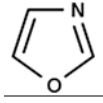
(continued)

Table 3.5 (continued)

Class	Major groups	Synthetic precursors	Examples and plant sources
Indolizidine derivatives 		Lysine	Swainsonine, castanospermine
Pyridine derivatives 	Simple derivatives of pyridine	Nicotinic acid	Trigonelline, ricinine, and arecoline
	Polycyclic noncondensing pyridine derivatives		Nicotine, nornicotine, anabasine, and anatabine
	Polycyclic condensed pyridine derivatives		Actinidine, gentianine, and pediculinine
	Sesquiterpene pyridine derivatives	Nicotinic acid, isoleucine	Evonine, hippocrateine, and triptonine
Isoquinoline derivatives and related alkaloids 	Simple derivatives of isoquinoline	Tyrosine or phenylalanine	Salsoline, lophocerine
	Derivatives of 1- and 3-isoquinolines		N-methylcoridaldine, noroxyhydrastinine
	Derivatives of 1- and 4-phenyltetra hydroisoquinolines		Cryptostilin
	Derivatives of 5-naftil-isoquinoline		Ancistrocladine
	Derivatives of 1- and 2-benzyl-isoquinolines		Papaverine, laudanosine, and sendaverine
	Cularine group		Cularine, yagonine
	Pavines and isopavines		Argemonine, amurensine
	Benzopyrrocolines		Cryptaustoline

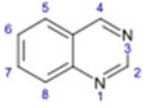
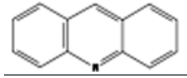
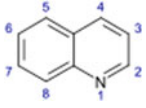
(continued)

Table 3.5 (continued)

Class	Major groups	Synthetic precursors	Examples and plant sources
	Protoberberines		Berberine, canadine, ophiocarpine, mecambridine, and corydaline
	Phthalidisoquinolines		Hydrastine, narcotine (Noscapine)
	Spirobenzylisoquinolines		Fumaricine
	Ipecacuanha alkaloids		Emetine, protoemetine, and ipecoside
	Benzophenanthridines		Sanguinarine, oxynitidine, and corynoloxine
	Aporphines		Glaucine, coridine, and liriodenine
	Proaporphines		Pronuciferine, glaziovine
	Homoaporphines		Kreysiginine, multifloramine
	Homoproaporphines		Bulbocodine
	Morphines		Morphine, codeine, thebaine, and sinomenine
	Homomorphines		Kreysiginine, androcymbine
	Tropoloisoquinolines		Imerubrine
	Azofluoranthenes		Rufescine, imeluteine
	Amaryllis alkaloids		Lycorine, ambelline, tazettine, galantamine, and montanine
	Erythrina alkaloids		Erysodine, erythroidine
	Phenanthrene derivatives		Atherosperminine
	Protopins		Protopine, oxomuramine, and corycavidine
	Aristolactam		Doriflavin
Oxazole derivatives 		Tyrosine	Annuloline, halfordinol, texaline, and texamine

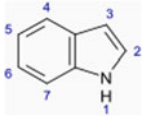
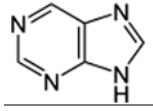
(continued)

Table 3.5 (continued)

Class	Major groups	Synthetic precursors	Examples and plant sources
Isoxazole derivatives 		Ibotenic acid	Ibotenic acid, muscimol
Thiazole derivatives 		1-deoxy-D-xylulose 5-phosphate (DOXP), tyrosine, cysteine	Nostocyclamide, thiostreptone
Quinazoline derivatives 	3,4-dihydro-4-quinazolone derivatives	Anthranilicacid or phenylalanine or ornithine	Febrifugine
	1,4-dihydro-4-quinazolone derivatives		Glycorine, arborine, and glycosminine
	Pyrrolidine and piperidine quinazoline derivatives		Vazicine (peganine)
Acridinederivatives 		Anthranilic acid	Rutacridone, acronicine
Quinoline derivatives 	Simple derivatives of quinoline derivatives of 2-quinolones and 4-quinolone	Anthranilic acid	Cusparine, echinopsine, and evocarpine
	Tricyclic terpenoidss		Flindersine
	Furanoquinoline derivatives		Dictamnine, fagarine, and skimmianine
	Quinines	Tryptophan	Quinine, quinidine, cinchonine, and cinchonidine

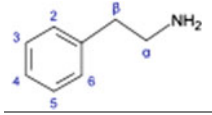
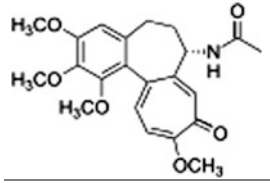
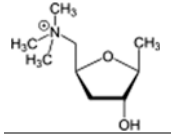
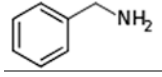
(continued)

Table 3.5 (continued)

Class	Major groups	Synthetic precursors	Examples and plant sources
Indole derivatives 	Non-isoprene indole alkaloids		
	Simple indole derivatives	Tryptophan	Serotonin, psilocybin, dimethyltryptamine (DMT), and bufotenin
	Simple derivatives of β-carboline		Harmane, harmine, harmaline, and eleagnine
	Pyrroloindole alkaloids		Physostigmine (eserine), etheramine, physovenine, and eptastigmine
	Semiterpenoid indole alkaloids		
	Ergot alkaloids	Tryptophan	Ergotamine, ergobasine, and ergosine
	Monoterpenoid indole alkaloids		
	Corynanthe type alkaloids	Tryptophan	Ajmalicine, sarpagine, vobasine, ajmaline, yohimbine, reserpine, mitragynine, groupstrychnine and Strychnine brucine, aquamicine, and vomicine
	Iboga-type alkaloids		Ibogamine, ibogaine, and voacangine
	Aspidosperma-type alkaloids		Vincamine, vinca alkaloids, vincotine, and aspidospermine
Imidazolederivatives 		Directly from histidine	Histamine, pilocarpine, pilosine, stevensine
Purinederivatives 		Xanthosine (formed in purine biosynthesis)	Caffeine, theobromine, theophylline, and saxitoxin

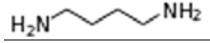
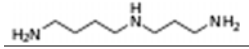
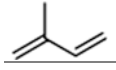
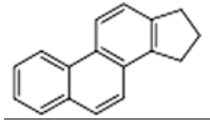
(continued)

Table 3.5 (continued)

Class	Major groups	Synthetic precursors	Examples and plant sources
Alkaloids with nitrogen in the side chain (*protoalkaloids*)			
β-Phenylethylamine derivatives 		Tyrosine or phenylalanine	Tyramine, ephedrine, pseudoephedrine, mescaline, cathinone, and catecholamines (adrenaline, noradrenaline, and dopamine)
Colchicine alkaloids 		Tyrosine or phenylalanine	Colchicine, colchamine
Muscarine 		Glutamic acid	Muscarine, allomuscarine, epimuscarine, and epiallomuscarine
Benzylamine 		Phenylalanine with valine, leucine or isoleucine	Capsaicin, dihydrocapsaicin, nordihydrocapsaicin, and vanillylamine

(continued)

Table 3.5 (continued)

Class	Major groups	Synthetic precursors	Examples and plant sources
Polyamines alkaloids			
Putrescine derivatives 		Ornithine	Paucine
Spermidine derivatives 			Lunarine, codonocarpine
Spermine derivatives 			Verbascenine, aphelandrine
Peptide (*cyclopeptide*) alkaloids			
Peptide alkaloids with a 13-membered cycle	Nummularine C type	From different amino acids	Nummularine C, Nummularine S
	Ziziphine type		Ziziphine A, sativanine H
Peptide alkaloids with a 14-membered cycle	Frangulanine type		Frangulanine, scutianine J
	Scutianine A type		Scutianine A
	Integerrine type		Integerrine, discarine D
	Amphibine F type		Amphibine F, spinanine A
	Amfibine B type		Amphibine B, lotusine C
Peptide alkaloids with a 15-membered cycle	Mucronine A type	From different amino acidsAmino acids	Mucronine A
Pseudoalkaloids (*terpenes and steroids*)			
Diterpenes 	Lycoctonine type	Mevalonic acid	Aconitine, delphinine
Steroids 		Cholesterol, arginine	Solasodine, solanidine, veralkamine, and batrachotoxin

stimulant, nicotinic acetylcholine receptor agonist; physostigmine—inhibitor of acetylcholinesterase; quinidine—antiarrhythmic; quinine—antipyretics, antimalarial; reserpine—antihypertensive; tubocurarine-muscle relaxant; vinblastine, vincristine—antitumor; vincamine—vasodilating, antihypertensive; and yohimbine—stimulant, aphrodisiac.

In agriculture
Prior to the development of a wide range of relatively low-toxic synthetic pesticides, some alkaloids, such as salts of nicotine and anabasine, were used as insecticides. Their use was limited by their high toxicity to humans.

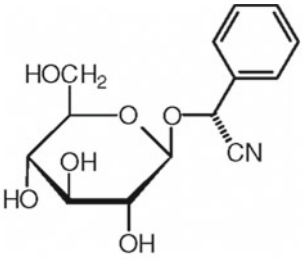
Use as psychoactive drugs
Preparations of plants containing alkaloids and their extracts, and later pure alkaloids, have long been used as psychoactive substances. Cocaine, caffeine, and cathinone are stimulants of the central nervous system. Mescaline and many of indole alkaloids (such as psilocybin, dimethyltryptamine and ibogaine) have hallucinogenic effect. Morphine and codeine are strong narcotic pain killers. There are alkaloids that do not have strong psychoactive effect themselves, but are precursors for semisynthetic psychoactive drugs. For example, ephedrine and pseudoephedrine are used to produce methcathinone and methamphetamine. Thebaine is used in the synthesis of many painkillers such as oxycodone.

Artificial Alkaloids
A number of alkaloids can be prepared artificially, and theophylline, which occurs naturally in minute quantity in tea leaves, was the first to be produced synthetically on a commercial scale. Suprarenine, a synthetic with the actions of epinephrine, is also marketed. In addition, the pharmacopoeia recognizes four bodies which are manufactured from plant alkaloids, viz., apomorphine, prepared from morphine by dehydration; cotarnine, prepared by hydrolyzing narcotine; homatropine, which results from the action of mandelic acid upon tropine, the mother substance of atropine; and hydrastinine, obtained by the oxidation of hydrastine. Two other artificial substances of the Pharmacopoeia, hexamethylenamine, or urotropine, and antipyrine, have close chemic affiliations with the alkaloid group.

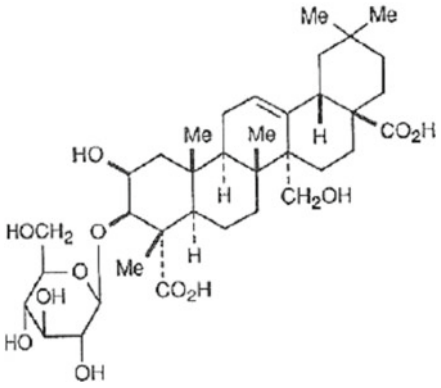
3.6 Glycosides

Gycosides and bitter principles
Besides acid and basic substances, plants furnish a large number of proximate principles which are chemically neutral. The most important are the glycosides (heterosides). A glycoside is a molecule in which a sugar (glycone) group by means of its anomeric carbon (C-1 carbon) bonded to a non-sugar (aglycone or genin) component. Glycosides on hydrolysis yield a sugar part (glycone) and a non-sugar part (aglycone or genin) as shown in the Fig. 3.34 with an example of Ginsenoside.

↓ **Non-sugar part (aglycone or genin)**



Sugar part (glycone) ↑ **↑ Glycosidic bond**



Ginsenoside-glycoside of Ginseng

Fig. 3.34 General structure of a glycoside showing sugar part (glycone) and non-sugar part (aglycone or genin); ginsenoside—glycoside of ginseng

Many plants store chemicals in the form of inactive glycosides. These can be activated by enzymehydrolysis or other decomposing agents such as heat, dilute acids, strong alkalies, bacteria, or fungi, which causes the sugar (glycone) part to be broken off, making the chemical (aglycon, the truly active constituent) available for use. Most of the glucosides yield glucose and a few of them yield other sugars. The glucosidal nature of glycosidic heterosides may be readily demonstrated by warming their mixture with Fehling's solution following hydrolysis by dilute hydrochloric acid. They are classified according to the nature of the non-sugar or aglycone. The names end in—oside, although some prefer to use the traditional names ending—ine (digoxin).

Chemically, glycosides are a loose group, and beyond their readiness of decomposition and their power to yield sugar, have no essential characters in common. They follow no rules as to solubility, taste or importance. Some of them are bitter, soluble in water or alcohol and inert pharmacologically while others are

not. Glycosides are classified based on their therapeutic effects, glycone–aglycon parts, bond between glycone–aglycon parts, name of the source plant, etc.

The glycone can consist of a single sugar group (monosaccharide) or several sugar groups (oligosaccharide). When the glycone group is glucose, fructose or glucuronic acid then the resulting glycoside molecule is a glucoside, fructoside or glucuronide, respectively. The aglycone may be an alcohol, anthraquinone derivative, phenol, aldehyde, acid, ester, or another compound. There are four types of linkages present between glycone and aglycone, e.g., O–, N–, S–, and C–glycosidic bond.

Glycosides play numerous important roles in living organisms. Many such plant glycosides are used as medications. The active principles of digitalis, strophanthus, cascara, willow and poplar barks are being among the most valued remedies. Salicin (named after the genus *Salix*.) is an alcoholic glycoside found in willow and poplar barks. Salicin is converted in the body into salicylic acid, which is closely related to aspirin and has analgesic, antipyretic, and anti-inflammatory effects. Other glycosides are anthraquinones, cardiac glycoside, cyanogenics, coumarine, phenol, flavonoids, ranunculosides, saponins, and sulphurates. The most important groups are the anthraquinonics, cyanogenics, cardiotonics, and cumarinics. In the body, toxic substances are often bonded to glucuronic acid to increase their water solubility; the resulting glucuronides are then excreted.

Classification

Glycosides may be classified based on the characteristics of (a) glycone, (b) glycosidic bond and (c) aglycone, (d) correlation to the parent natural glycoside. A therapeutic classification, although excellent from a pharmaceutical viewpoint, omits many glycosides of pharmacognostic interest, e.g., cardiac glycosides.

(a) Based on the characteristics of glycone

The glycone part of a glycoside may be glucose, galacose, fructose, mannose, arabinose, rhamnose, glucuronic acid, etc., and the corresponding glycoside may be grouped as a glucoside, galacoside, fructoside, mannoside, arabinoside, rhamnoside, glucuronide, etc., respectively. Other monosaccharides include digitoxose, acetyldigitoxose, D-cymarose, L-oleandarose, etc. In the body, toxic substances are often bonded to glucuronic acid to increase their water solubility; the resulting glucuronides are then excreted. Sugar part of the molecule may be consisted of one monosaccharide (monosides, e.g., salicin), two monosaccharides (biosides, e.g., gentobioside), three monosaccharides (triosides, e.g., strophanthotriose), four-, five monosaccharides (triosides, tetrosides, pentosides).

(b) Based on the characteristics of glycosidic bond

Glycosides are classified as α-glycosides or β-glycosides depending on the position of the glycosidic bond below or above the plane of the cyclic sugar molecule. Enzyme α-amylase hydrolyzes α-linkages while emulsin hydrolyzes β-linkages only. Most of the naturally occurring glycosides are of the β-type.

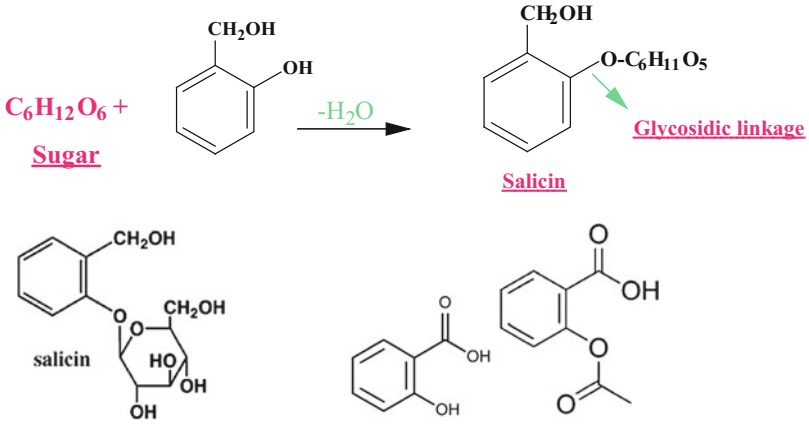
(c) Based on the chemical group of the aglycone involved in glycosidic bond
There are four types of chemical groups of the aglycone involved in glycosidic bond formation:

(i) OH group (O-glycoside),
(ii) SH group (S-glycoside),
(iii) NH group (N-glycoside), and
(iv) CH group (C-glycoside).

(d) Based on the characteristics of aglycone
Glycosides are classified on the basis of the chemical nature of the aglycone moiety. Classification by this method is very helpful for the purposes of biochemistry and pharmacology. When the chemical nature of the aglycone group is used as the basis of systematization, the classification is as follows:

(i) Alcoholic glycosides (O-glycosides),
(ii) Anthracene glycosides (O-glycosides or C-glycosides),
(iii) Phenol glycosides (O-glycosides),
(iv) Steroid glycosides,
(v) Flavonoid glycosides,
(vi) Coumarin and Furanocoumarin glycosides,
(vii) Cyonogenetic glycosides,
(viii) Sulfur-containing or Thioglycosides (S-glycosides),
(ix) Saponin glycosides, and
(x) Aldehyde glycosides.

(i) Alcoholic glycosides (O-glycosides)
Salicin found in the genus *Salix* (willows) is a good instance of an alcoholic β-glycoside (Fig. 3.35). Salicin is converted in the body into salicylic acid, which is



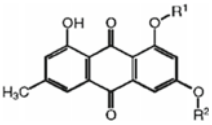
Salicin (salicylic acid + glucose), salicylic acid and aspirin (acetylsalicylic acid)

Fig. 3.35 Showing salicin as example of alcoholic β-glycoside (O-glycoside linkage)

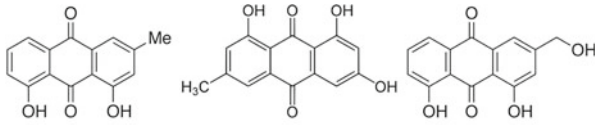
closely related to aspirin and possesses analgesic (pain killing), antipyretic (alleviating fever) as well as anti-inflammatory properties.

(ii) Anthraquinone glycosides

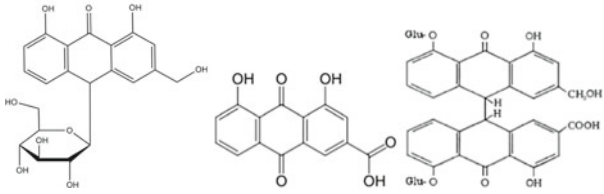
These glycosides enclose an aglycone group that is a derivative of anthraquinones. Anthraquinones are yellow-brown pigments, most commonly occurring as O-glycosides or C-glycosides. The aglycone portions consist of two or more phenols linked by a quinine ring (anthracene derivative). They are found in many families of dicot (e.g., Ericaceae, Euphorbiaceae, Fabaceae, Lythraceae, Polygonaceae, Rhamnaceae, Rubiaceae, Saxifragaceae, Scrophulariaceae, Verbenaceae, etc.), one family of monocot (Liliaceae) plants as well as in certain fungi and lichen. Anthraquinone glycosides (anthraquinones without –COOH moiety) include chrysophanol, physcion, emodin, aloe-emodin, barbaloin, rhein, sennosides, etc., and (anthraquinones with –COOH moiety) include rhein, glucorhein, etc., are found in many herbal drugs, e.g., cascara sagrada (barks of *Rhamnus catharticus*, *R. frangula and Rhamnus pursiana of Rhamnaceae contains cascarosides*, *emodin*, etc.), rhubarb (rhizome of *Rheum palmatum* of Polygonaceae contains chrysophanol, emodin, rhein, etc.), senna (dried leaf lets of *Cassia senna*, *C. angustifolia* of Caesalpinaceae contain sennoside), aloes (leaf *of Aloe barbadensis*, *A. vera* contains aloin, aloe-emodin, barbaloin, etc.). Chrysophanol is a dihydroxy methyl anthraquinone, emodin is a trihydroxy methyl derivative, aloe-emodin is a primary alcohol derived from chrysophanol and rhein is an acid derived from aloe-emodin. These glycosides are important laxative and cathartic drugs. Chrysophanic acid or chrysophanol, a fungal isolate and from the root of *Rheum wittrochii*, is a natural anthraquinone with anticancer activity, induces the necrosis of cancer cells via a reduction in ATP levels, attenuates the effects of lead exposure in mice by reducing hippocampal neuronal cytoplasmic edema, enhancing mitochondrial crista fusion, significantly increasing memory and learning abilities, reducing lead content in blood, heart, brain, spleen, kidney and liver, promoting superoxide dismutase and glutathione peroxidase activities and reducing malondialdehyde level in the brain, kidney and liver. Emodin (1,3,8-trihydroxy-6-methylanthraquinone) is a naturally occurring anthraquinone present in the roots and barks of numerous plants, molds, and lichens, and an active ingredient of various Chinese herbs. It ameliorates diabetes and insulin resistance, emodin from rhubarb exhibits anticancer effects on several human cancers, including human pancreatic cancer and neuroprotective properties against glutamate toxicity.Aloe-emodin, a hydroxyanthraquinone, is present in aloe leaf exudate of *Aloe vera*, in the bark of *Rhamnus frangula* and *Rhamnus purshiana*, in the leaves of *Cassia angustifolia*, and in the rhizome of *Rheum rhaponticum*. It has a strong stimulant-laxative action. It has a marked antiviral effect in vitro against both herpes simplex virus (HSV) types 1 and 2 and has a specific in vitro and in vivo antineuroectodermal tumor activity. Figure 3.36 shows the structures of anthraquinone and different anthraquinone glycosides.



Structure of anthraquinone (R^1R^2 in frangula emodin = HH, in frangulin A = HRha, glucofrangulin A = GlcRha, frangulin B = HApi, in glucofrangulin B = GlcApi; Api = D-apio-β-D-furanosyl,Glc = β-D-glucopyranosyl, Rha = 6-deoxy-α-L-mannopyranosyl



Chrysophanic acid **Emodin** **Aloe-emodin**



Barbaloin **Rhein** **Sennoside A**

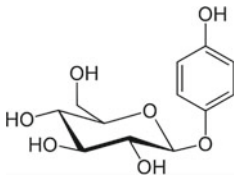
Fig. 3.36 Showing structures of anthraquinone and different anthraquinone glycosides

Barbaloinis or aloin, C-glucoside, is as a bitter, yellow-brown colored compound noted in the exudate of at least 68 Aloe spp. at levels from 0.1 to 6.6% of leaf dry weight (making between 3 and 35% of the total exudate). It is used as a stimulant laxative; remove constipation by inducing bowel movements. Rhein, cassic acid, is a substance in the anthraquinone group obtained from rhubarb (*Rheum undulatum R. palmatum*) as well as in *Cassia reticulata*. Rhein is commonly found as a glycoside such as rhein-8-glucoside or glucorhein. Like all such substances, rhein is a cathartic. They are dimeric glycosides named after their abundant occurrence in plants of the genus Senna. Sennosides or Senna glycosides are many anthraquinone derivatives useful as a laxative.

(iii) Phenol glycosides (O-glycosides)

In phenolic glycosides (simple), the aglycone is a simple phenolic structure, e.g., salicin, arbutin, etc. (Fig. 3.37). Arbutin (a glycosylated hydroquinone) is found in

Fig. 3.37 Showing structures of phenol glycoside arbutin



Arbutin

the common bearberry (*Arctostaphylos uva-ursi*) and thereforebearberry is a traditional treatment for urinary tract infections. Among the medicinal plants whose activity is related to flavonoid content are the passion flower (*Passiflora incarnate*), chamomile (*Chamaemelum glabra*), aquilea (*Achillea millefolium*), liquorice (*Glycyrrhiza glabra*), gingko (*Ginkgo biloba*), thistle (*Silybum marianum*) and white thorn (*Crataegus monogyna*). Phenolic glycosides possess urinary antiseptic effect. It inhibits tyrosinase and thus prevents the formation of melanin. Arbutin is therefore used as a skin-lightening agent. Arbutin is found in wheat, and is concentrated in pear skins. It is also found in *Bergenia crassifolia*.

(iv) Steroidal glycosides or cardiac glycosides

The aglycone component here is a 17-carbon steroidal nucleus consisted of four-ring (e.g., ABCD) structure (three 6-carbon rings-ABC and one 5-carbon ring-D) (Fig. 3.38). Steroidal glycosides or cardiac glycosides (CGs) are of two types, e.g., cardenolide type and bufadienolide type and may be obtained from both plants and animals. Cardiac glycosides (CGs) are present in the leaves of *Digitalis purpurea* and *D. lanata* (Scrophulariaceae). The important glycosides of this group include digoxin, digitoxigenin, digoxigenin, lantoside C, ouabain, strophantin, ouabagenin and scillarenin A. Seeds of *Strophantus gratus*, *S. kombe* (Apocinaceae), *Adonis vernalis* (Ranunculae), bulb of *Scilla siberica* (Asparagaceae), dried scales of bulbs of *Urginea maritima* (Liliaceae) and *Nerium oleander* (Apocynaceae) are sources of cardioglycosides. These are chemically related to the sex hormones, vitamin D and venom of some toads.Cardiac glycosides are highly esteemed for their unique ability to increase the force of cystolic contraction of the heart muscle. In small doses, CG can show a specific effect on the heart muscle. They are therefore highly valuable in the treatment of congestive heart failure and arrhythmia (trouble in the rhythm of the heartbeat), but now instead of CG other agents are preferred. Lanatoside C is a CG composed of four monosaccharides (glucose, 3-acetyldigitoxose and two digitoxoses) and an aglycon named digoxigenin. Figure 3.38 given below shows the structures of a steroid skeleton and three glycosides.

Lanatoside C, a cardiac glycoside available in various species of Digitalis, can be used in the treatment of congestive heart failure and cardiac arrhythmia.Ouabain, also known as g-strophanthin, is a cardiac glycoside and in lower doses, can be used medically to treat hypotension and some arrhythmias. It acts by inhibiting the Na/K-ATPase, also known as the sodium–potassium ion pump. It is a plant-derived toxic substance that was traditionally used as an arrow poison in eastern Africa for both hunting and warfare. k-Strophantin, an analog of ouabain, is a cardenolide in plants of the genus Strophanthus.

Steviol glycosides

Steviol is a diterpene and occurs in the plant as steviol glycosides, sweet compounds that have found widespread use as sugar substitutes (Fig. 3.39). Steviol glicosides from *Stevia rebaudiana* of Asteraceae have been reported to be between

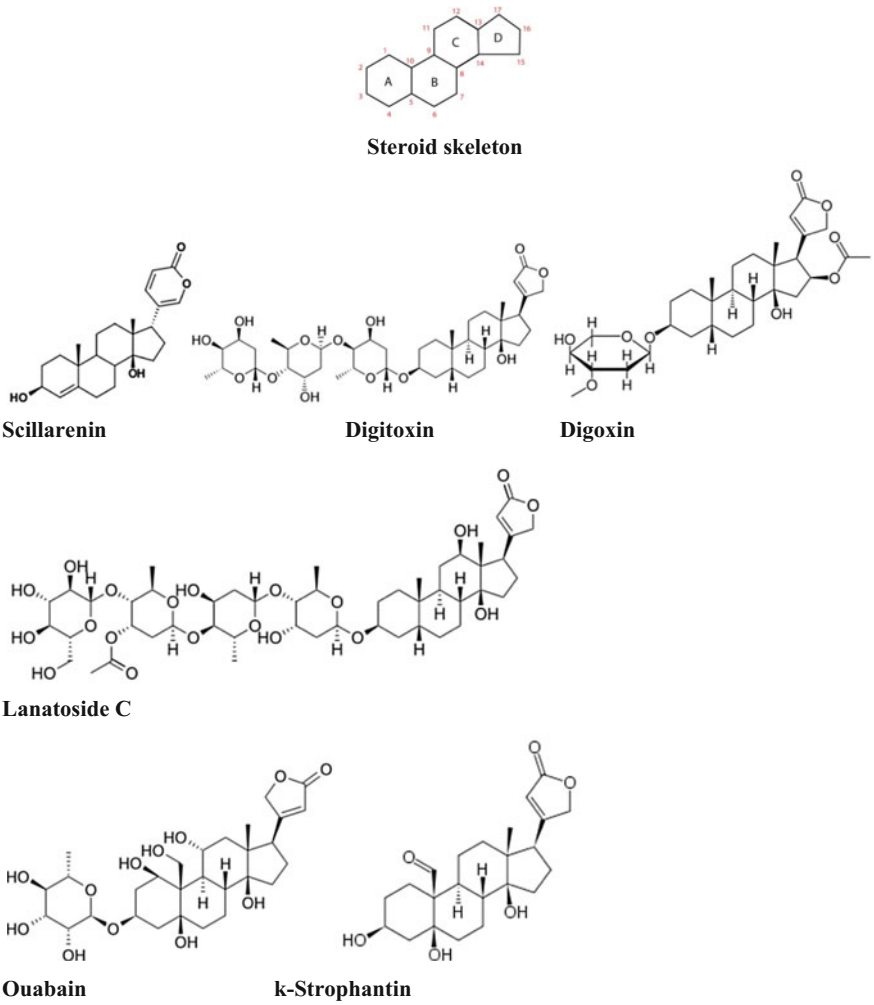


Fig. 3.38 Showing structures of a steroid skeleton and several glycosides—scillarenin, digitoxin, digoxin, lanatoside C, ouabain, and k-strophantin. Each glycoside has three basic structural components: an unsaturated lactone ring, a steroid nucleus, and sugar moieties

30 and 320 times sweeter than sucrose. Steviol glicosides also occur in *Stevia phlebophylla* and in *Rubus chingii* (Rosaceae). These glycosides have steviol as the aglycone part. Glucose or rhamnose–glucose combinations are bound to the ends of the aglycone to form the different compounds. Stevioside and rebaudioside A are two natural sweeteners used in many countries. Rebaudioside A is a steviol glycoside that is 200 times sweeter than sugar. The steviol glycosides are stable to heat, pH changes and are also to fermentation. When these glycosides are consumed,

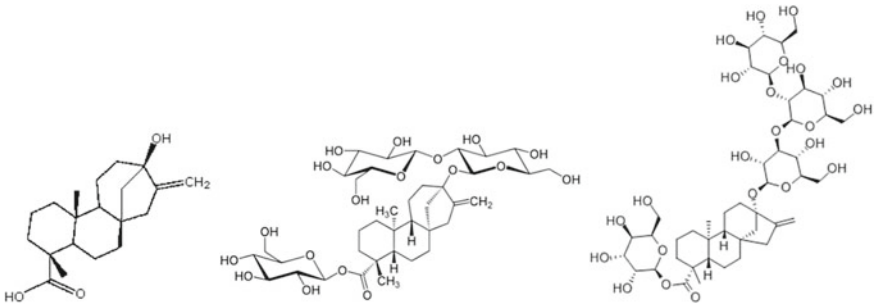


Fig. 3.39 Showing structures of steviol and steviol glycosides—stevioside and rebaudioside A

they also do not stimulate any glycemic response and as a result of this, steviol glycosides are preferred as natural sweeteners for diabetic patients as well as others who take low carbs diets.

(v) Flavonoid glycosides

In flavonoid glycosides, the aglycone components are flavonoids, yellow pigments derived from phenil-benzo γ pirona or phenil cromome. Flavonoids are phenolic compounds composed of three benzene rings with hydroxyl groups and include 6 main classes, e.g., chalcons, flavones, flavonols, anthocyanidins, and condensed tannins, as well as two others, xantones, and aurones; some of the examples of flavonoid glycosides include naringin (aglycone: naringenin, glycone: rutinose), hesperidin (aglycone: hesperetin, glycone: rutinose), quercitrin (aglycone: quercetin, glycone: rhamnose) and rutin(aglycone: quercetin, glycone: rutinose) (Fig. 3.40). Flavonoid glycosides occur in significant amounts usually in the form of heterosides, and they are frequently found in the plant kingdom such as in fruits —apple, berries, cherry, grape, grapefruit, plum; vegetables-cabbage, parsley, seeds, legumes, soy products, onions, black and green tea, red wine, etc. More than 4000 different flavonoids have been identified, some of which are believed to have beneficial effects on human health. Some of the health-related benefits associated with flavonoid glycosides include antioxidant properties (free radical scavenger), strengthening of the immune system, protection against cancer, dilation of blood vessels and reduction in capillary weakness or fragility.

(vi) Coumarin and Furanocoumarin glycosides

Coumarin glycosides

Coumarin is a fragrant organic chemical compound in the benzopyrone (benzo—α pyrones, phenolic active components) chemical class, which is a colorless crystalline substance in its standard state. It is a natural substance found in many

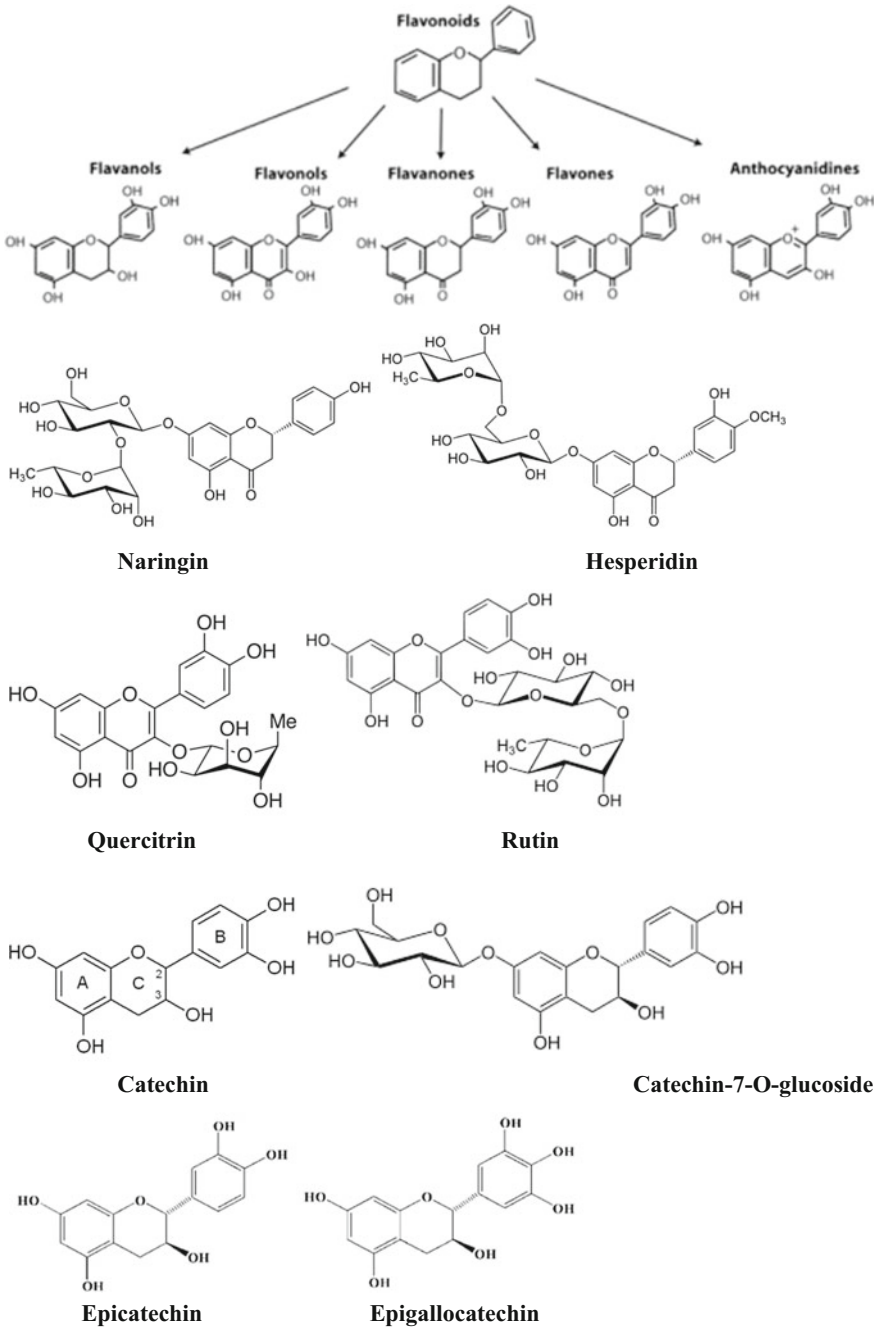
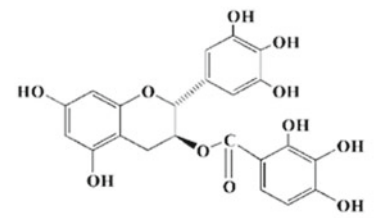
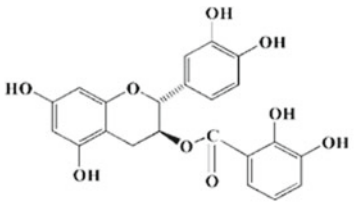


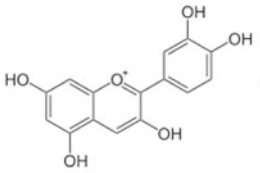
Fig. 3.40 Showing classes of flavonoids and structures of different flavonoid glycosides



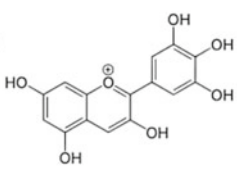
Epigallocatechin gallate



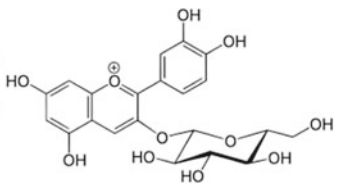
Epicatechin gallate



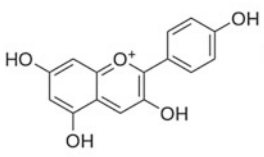
Cyanidin



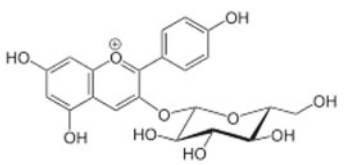
Delphinidin



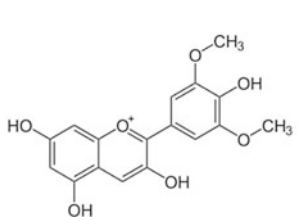
Chrysanthemin (3-glucoside of cyanidin)



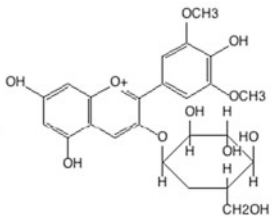
Pelargonidin



Pelargonidin3-glucoside



Malvidin



Malvidin 3-glucoside

Fig. 3.40 (continued)

medicinal plants (*Dipteryx odorata*, *Anthoxanthum odoratum*, *Galium odoratum*, *Verbascum*spp., *Hierochloe odorata*, *Melilotus oficinalis*, and *Dichanthelium clandestinum*, *Cinnamomum cassia* but true cinnamon or Ceylon cinnamon—*Cinnamomum zeylanicum* contains little coumarin). Coumarin is also found in extracts of *Justicia pectoralis*. Coumarins are effective on the vascular system (both on arteries and veins), against venolymphatic insufficiency and in the treatment of psoriasis due to its photosensitizing properties. Esculoside, found in Indian chestnuts (*Aesculus hippocastanum*), acts as both a tonic for the veins and a protector of the cell wall. Visnadine is a dilator of the blood vessels found in the fruit of the visnaga (*Amni visnaga*). Dicumarol is an anticoagulant which forms in Melilotuses

when conditions for conservation are bad. Furanocumarins are photosensitizing and are used to treat psoriasis. Sometimes they are used in sun creams as they enhance melanin production (photodynamic), for example, essence of bergamot (*Citrus bergamia*). Coumarin glycosides contain coumarin or a derivative as aglycone, e.g., apterin is a coumarin glycoside.

It is a furanocoumarin, the glucoside of vaginol. It has been isolated from the root of plants in the Apiaceae (*Angelica* spp. *Zizia aptera*, etc.). Apterin is said to expand the coronary arteries and also functions as a calcium channel blocker. Aesculin is a poisonous coumarin glycoside that naturally occurs in the horse chestnut (*Aesculus hippocastanum*), California buckeye (*Aesculus californica*), prickly box (*Bursaria spinosa*), in daphnin (*Daphne mezereum*) and in dandelion coffee. It is used as a laboratory to aid in the identification of bacterial species. Warfarin is an anticoagulant normally used in the prevention of thrombosis and thromboembolism. Warfarin is an antagonist of vitamin K and it prevents it from synthesizing clotting factors, thereby creating an anticoagulation effect. Figure 3.41 shows the structures of coumarin and different coumarin glycosides.

Coumarins along with its derivatives are abundantly found in plant families like Orchidaceae, Apiaceae, Asteraceae, Clusiaceae, Leguminaceae Rutaceae, Solanaceae and Thymalaceae. Aptering, a furanocoumarin glucoside, isolated from the root of plants in the genus *Angelica*, including Garden Angelica and in *Zizia aptera* of Apiaceae, dilates the coronary arteries as well as blocks calcium channels.

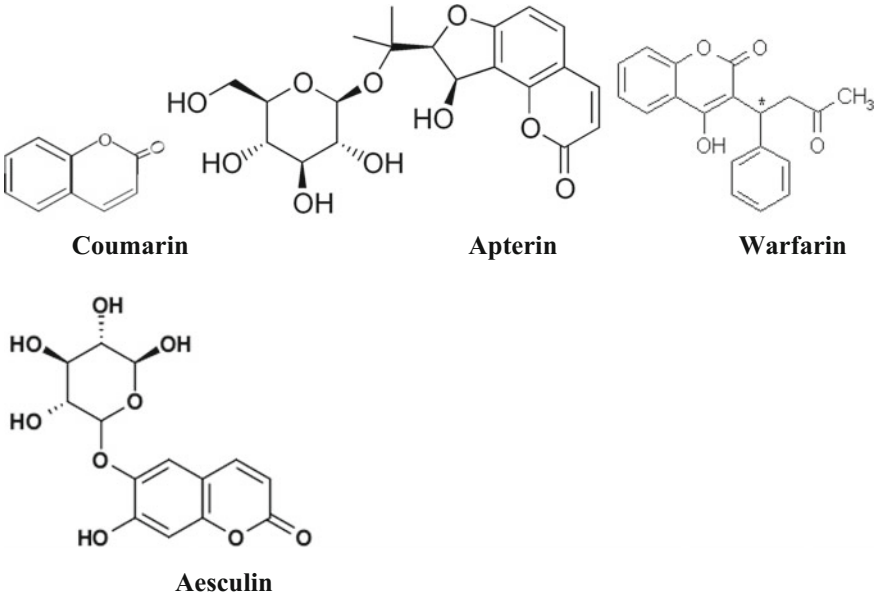


Fig. 3.41 Showing structures of coumarin and different coumarin glycosides

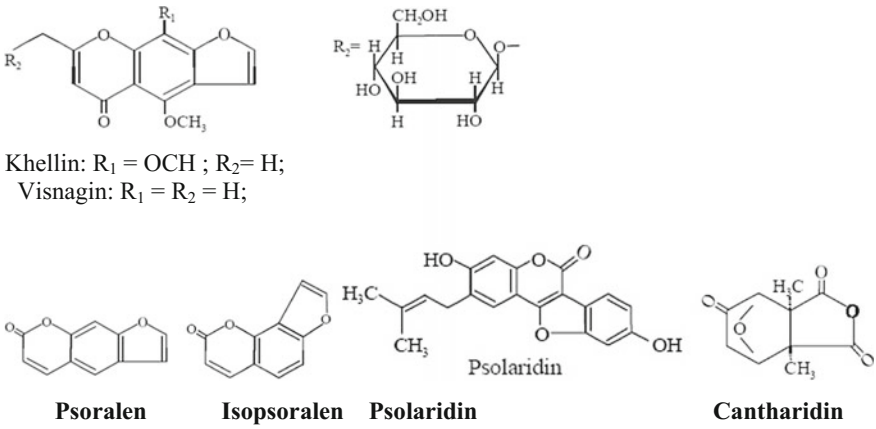


Fig. 3.42 Showing structures of furanocoumarin glycosides

In chromone glycosides (isolated from leaves of *Cassia multijuga* of Leguminosae, *Hypericum japonicum* of Clusiaceae), the aglycone is benzo-gamma-pyrone. Coumarin glycosides from *Daucus carota* have been used in traditional medicine to treat hypertension.

Furanocoumarin glycosides

The furanocoumarins are obtained by the fusion of the furan ring to the coumarin nucleus either at C-6 and C-7 positions or at C-7 and C-8 positions. A few typical examples of furanocoumarin glycosides are khellol glucoside; psoralea and cantharides (Fig. 3.42). Khellol glucoside is obtained from the seeds of *Eranthis hyemalis* of Ranunculaceae, *Ammi visnaga* Lamiaceae. Psoralen is found in dried ripe fruits of *Psoralea corylifolia* of Fbaceae and also found naturally in bergernot, limes, cloves, figs, etc. Cantharides comprises of the dead and dried insects of *Cantharis vesicatoria* Meloidae. Cantharides contains the furanocoumarin derivatives cantharidin ranging from 0.6 to 1%.

(vii) Cyonogenetic glycosides

In cyagenic glycosides, the aglycone contains a benzene ring having a cyanide group. Amygdalin obtained from almonds is a good example of cyanogenic glycosides. Dhurrin, linamarin, lotaustralin, and prunasin are also classified as cyanogenic glycosides. A number of fruits as well as floppy (wilting) leaves of apples, wild cherries, plums, peaches, almonds, apricots, crabapples and raspberries contain cyanogenic glycosides. Root of *Cassava*, a significant food plant found in South America, South East Asia and Africa, also contains cyanogenic glycosides and hence it is essential to carefully wash it under running water and ground before it can be ingested. Even sorghum (*Sorghum bicolor*) possesses cyanogenic glycosides in its roots and hence, it is resistant to rootworms (*Diabrotica* spp.). Plants store cyanogenic glycosides in the vacuole in inactive form and release them in the

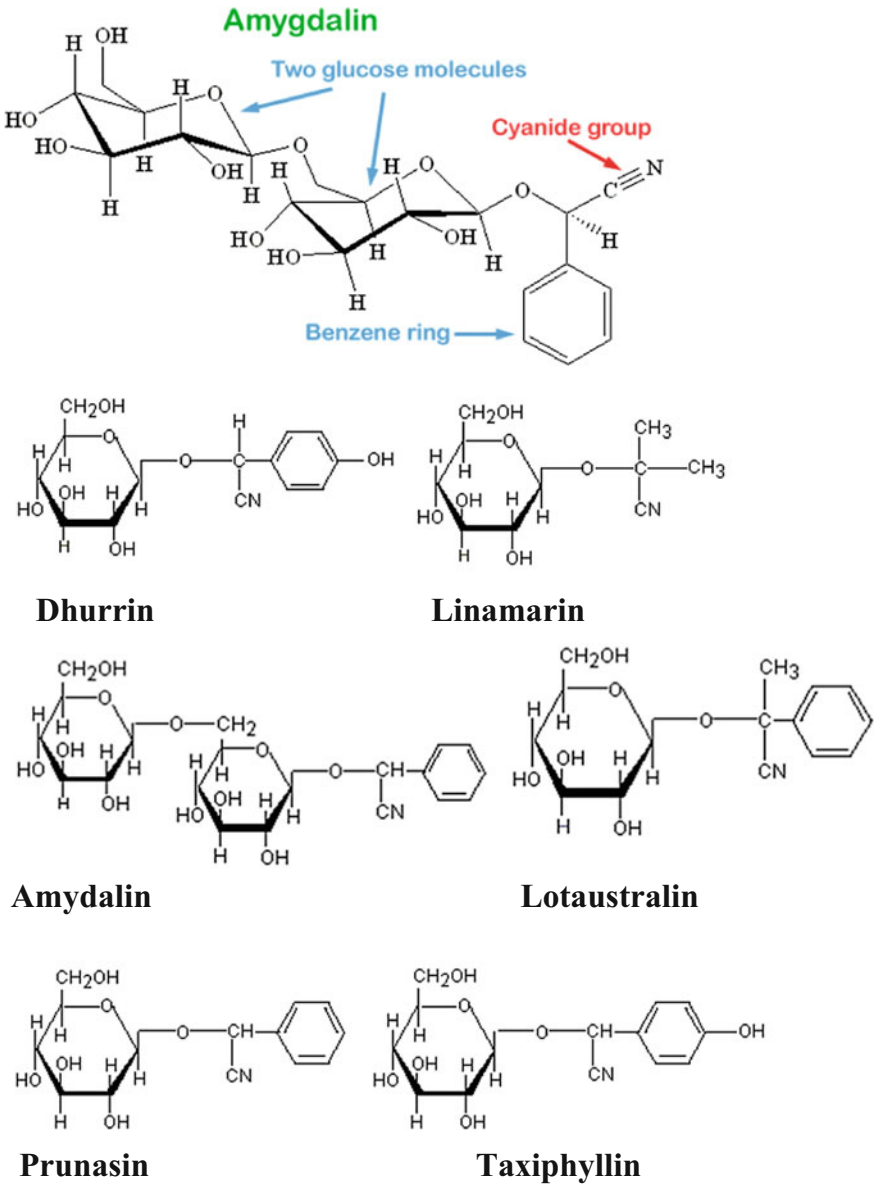


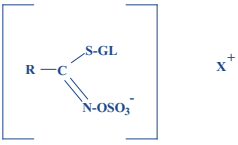
Fig. 3.43 Showing structures of different cyonogenetic glycosides

cytoplasm for defensive purposes when enzymes remove the sugar part set free the toxic hydrogen cyanide. Storing them in inactive forms in the vacuole prevents them from damaging the plant under normal conditions. Increase of CO_2 levels in the atmosphere resulted in much higher levels of cyanogenic glycoside production

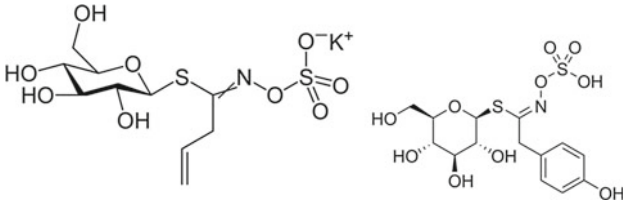
in sorghum and cassava plants, making them highly toxic and inconsumable. Preparations from plants containing cyanogenic glycosides are widely used as flavoring agents. Some of them have been claimed to possess anticancer properties and others have been suggested as possible agents for control of sickle cell anemia. Figure 3.43 shows structures of different cyonogenetic glycosides.

(viii) Sulfur-containing or thioglycosides (S-glycosides)

These glycosides enclose sulfur. Sinigrin and sinalbin, the two glucosinolates (compounds that contain sulfur and nitrogen) present in Indian or brown and black (*Brassica juncea* or *Brassica nigra*) and white (*Sinapis alba*, *S. hirta*) mustard of the Brassicaceae family, respectively, are good examples of two thioglycosides. Sinalbin is found in the seeds of white mustard and in many wild plant species. In contrast to sinigrin of black mustard seeds, sinalbin from white mustard seeds has only a weakly pungent taste. The glucosinolates also occur in other plants such as *Phyllanthus emblica*, *Armoracia lapthifolia*, *Wasabia japonica*, etc. Glucosinolates protect plants from fungal, nematodes and other pathogens and herbivores threats. Sinigrin is a precursor of the anticancer compound allyl isothiocyanate and antimicrobial, anticancer and antilipidimic (lower plasma triglyceride level) activities. Both the seeds and leaves traditionally have been used for medicinal purposes, including historical use as a curative for the common cold and applications in mustard plasters, baths, and treatments for chilblains (Herbst 2001; Downey 2003). Sinigrin is composed of glucose, allylisothiocyanate (volatile oil of mustard) and potassium acid sulfate and sinalbin is consisted of a phenolic isothiocyanate (acrinyl isothiocyanate), glucose and the acid sulfate of a quaternary alkaloid, sinapine^{+}. Figure 3.44 shows general structure of thioglycosides and structures of different sulfur-containing glycosides or thioglycosides.



The general structure of thioglycosides.The anion is called the glucosinolate ion; R may be aliphatic or aromatic. The cation (X) may be a simple metal ion or a complex organic cation, e.g., sinapine ion of sinalbin.

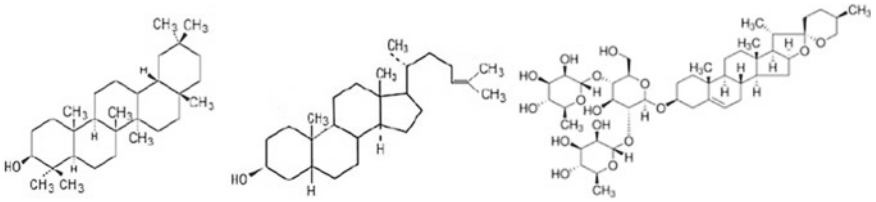


Sinigrin **Sinalbin**

Fig. 3.44 Showing general structure of thioglycosides and structures of different sulfur-containing glycosides or thioglycosides

(ix) Saponin glycosides

Glycosides with foaming features are known as saponins. Saponins comprise polycyclic aglycones (terpenoids, steroids) bound to one or many sugar side chains (Fig. 3.45). Most of the saponins are neutral and soluble in water; contain a dextrose sugar glycone and an aglycone, called sapogenin. The sapogenins are insoluble in water, but soluble in weak alcohol. Saponins are found in soapwort (*Saponaria officinalis* of Caryophyllaceae), soapberry or soapnut (*Sapindus mukorossi* of Sapindaceae), sugar maples (*Acer saccharum* of Aceraceae), jiaogulan (*Gynostemma pentaphyllum* of Cucurbitaceae), soapbark tree (*Quillaja saponaria* of Quillajaceae) and ginseng or red ginseng (*Panax ginseng* of Araliaceae) in various parts of the plant, e.g., leaves, stems, roots, bulbs, blossom, and fruit. Triterpenic saponins (acid) are found in the seed of the Indian chestnut (*Aesculus indica* of Sapidaceae), in liquorice (*Glycyrrhiza glabra* of Fabaceae), the Asian centella (*Centella asiatica* of Apiaceae), and in ginseng (*Panax ginseng* of Araliaceae). Steroidal saponins (neutral) are in Ruscus (*Ruscus aculeatus* of Asparagaceae), agave (*Agave sisalana* of Asparagaceae), and in dioscorea (*Dioscorea* spp. of Dioscoreaceae). Saponins taste bitter and some of them are poisonous. The toxic saponins are called sapotoxins. The compounds also result in the hemolysis of the red blood cells (the breaking down of red blood cells with liberation of hemoglobin). Many saponins are used as fish poisons. Saponin glycosides have a prominent therapeutic benefit. Medicinal value of saponins is due to their expectorant, corticoid and anti-inflammatory effects. Steroid saponins from Dioscorea dioscin is an important starting material for production of semisynthetic glucocorticoids and other steroid hormones such as progesterone. Glycyrrhizin, a sweet compound that is 50 times higher than sugar, increases fluid and sodium retention and promotes potassium depletion in blood (Fig. 3.46). Saponins cause a reduction of blood cholesterol by preventing its reabsorption. Saponins have antitumor and antimutagenic activities and can lower the risk of human cancers by preventing cancer cells from growing.



Tri-terpenoidal skeleton **Steroidal skeleton** **Dioscin (steroid saponin)**

Fig. 3.45 Pentacyclic tri-terpenoidal and tetracyclic steroidal skeletons of saponins. Dioscin—a saponin with steroidal nucleus

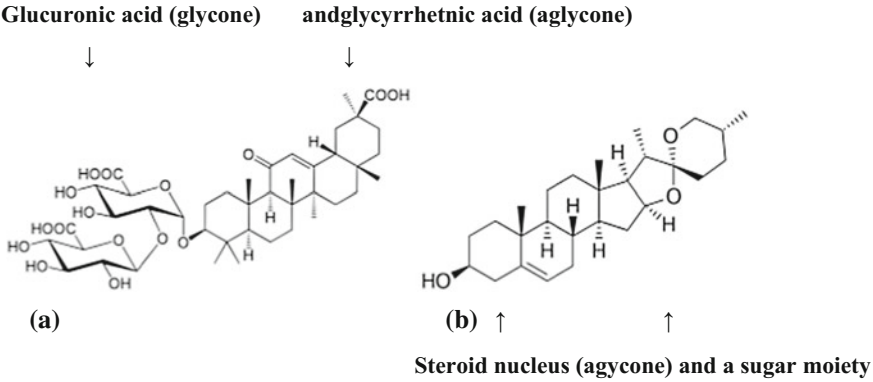


Fig. 3.46 **a** Glycyrrhizin or glycyrrhizinic acid (glycoside), and **b** diosgenin

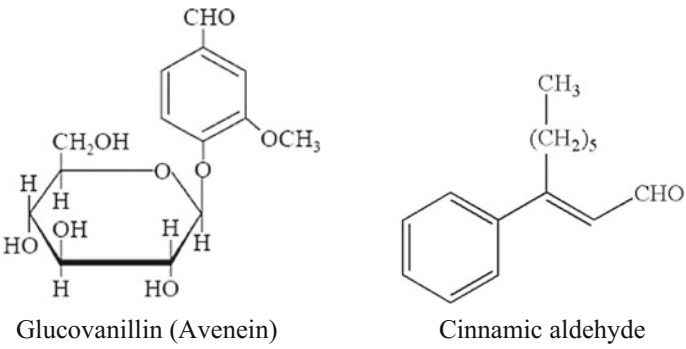


Fig. 3.47 Showing structures of different aldehyde glycosides

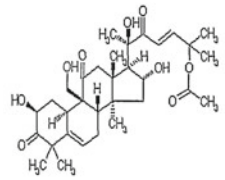
(x) Aldehyde glycosides

Vanilla pod is the most glaring example of a naturally occurring plant that contains an aldehyde glycoside, e.g., glucovanillin, and cinnamon bark is another important example which contains cinnamic aldehyde (Fig. 3.47).

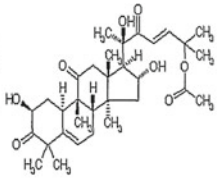
3.7 Bitter Principles

Bitter principles, alkaloidal glycosides, and miscellaneous compounds

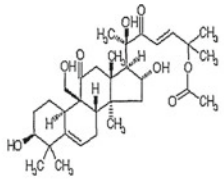
The chemical composition of bitter principles includes a complex pattern of molecular structures. Structurallythey are mostly terpenoid, especially the sesquiterpene lactones, monoterpene iridoids and the secoiridoids (Fig. 3.48). Iridoids are responsible for the chief bitter constituents of *Cichorium intybus*



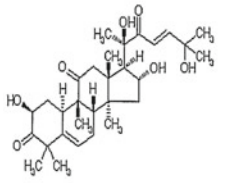
Cucurbitacin A



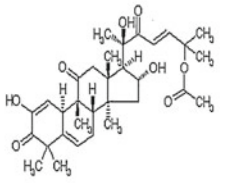
Cucurbitacin B



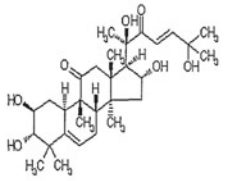
Cucurbitacin C



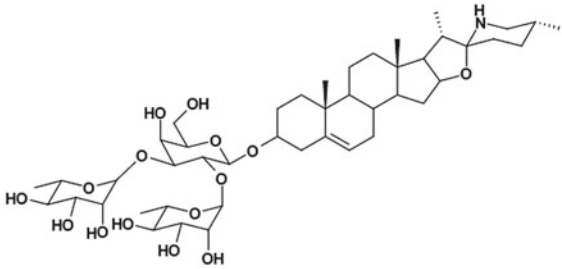
Cucurbitacin D



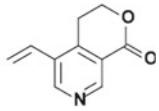
Cucurbitacin E



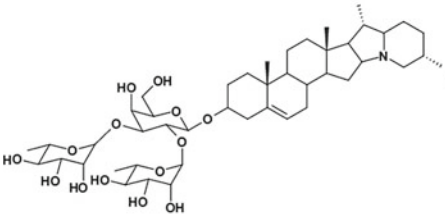
Cucurbitacin F



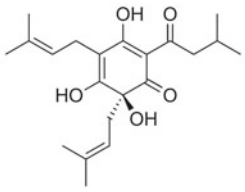
Tomatine



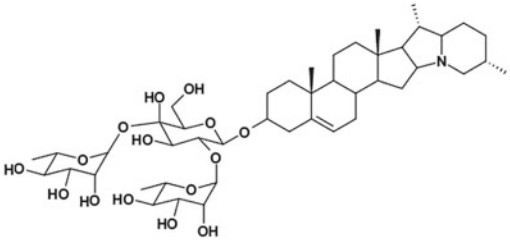
Gentianin



Solanine



Humulone (α-lupulic acid)



Chaconine

Fig. 3.48 Showing structures of different bitter principles

(chicory), dandelion or members of Taxacum genus of Asteraceae, *Valeriana officinalis* (valerian), wild lettuce (*Lactuca virosa*), and quassia bark (*Quassia amara*). Sesquiterpenes account for the bitter taste of the Artemisia wormwood (*Artemisiaabsinthium*), blessed thistle (*Cnicus benedictus*), and ginkgo (*Ginkgo biloba*). Other components which add to the bitterness are diterpene bitters, found in columbo root (*Jateorrhiza palmata*) and white horehound (*Marrubium vulgare*). Triterpenoids are the cause of bitterness in Cucurbitaceous plants including pumpkin, cucumber, colocynth, marrows, and the bryonies. Many genuses of Cucurbits such as *Trichosanthes*, *Cucurbita*, *Cucumis*, *Bryonia*, and *Citrullus* are affluent in cucurbitacins. Outside the Cucurbitaceae, Cucurbitacin-producing plants have also been identified in the members of Scrophulariaceae, Begoniaceae, Primulaceae, Liliaceae, Tropaeolaceae and Rosaceae. Cucurbitacins possess immense pharmacological potential. The structural composition of following cucurbitacins are known and on the basis of side chain derivatives have been designated by the letters: A, B, C, D, E, F, G, H, I, J, K, L, O, P, Q, R, and S (Kaushik et al. 2015). Many alkaloids also contribute to the bitter taste as in the protoberberine isoquinoline alkaloids of golden seal (*Hydrastis canadensis*), and Berberis of Berberidaceae, the morphine alkaloids, the quinoline alkaloids of quinine and angostura and the purine alkaloids (in coffee). In addition to this, many miscellaneous compounds like ketones and amino acids are responsible for the bitterness, as found in hops (*Humulus lupulus*). The bitter principles of hops are (i) lupamaric acid (humulone), (ii) lupamaric acid (lupulinic acid). Cucurbitacins, bitter principles of Cucurbitaceae, occur exclusively as glycosides and the alkaloid glycoside is tomatine. The bitter principle, known as gentianine, is a glucoside, soluble in water and alcohol.

The glycoalkaloid poisons α-solanine and α-chaconine are to be found in the nightshade family of plants, the (*Solanaceae*), in particular in potatoes (*Solanum tuberosum*), tomatoes (*Lycopersicon esculentum*), egg plant (*Solanum melongena*), Sweet and hot peppers (*Capsicum* species) Thorn-apple (*Datura stramonium*), Apple-of-Peru (*Nicandra physalodes*), Black Nightshade (*Solanum nigrum*), and Bittersweet (*Solanum dulcamara*). It is present in small quantities throughout potato tubers, especially in the sprouting shoots, but a lot more is synthesized by the potato if the tuber is exposed to sunlight, where the exposed parts become green (with harmless chlorophyll). It is in and near the green parts where the highest concentration of solanine is to be found. Solanine is not rendered safe by boiling, but deep frying at 170 °C does destroy most of the solanine. Normally, potatoes contain between 20 mg and 150 mg per kg of raw potato, but when turned green by exposure to sunlight may contain as much as 1000 mg/kg, mostly just under the skin (the shoots contain even higher amounts). Solanine adds an un-pleasant bitterness to the flavor of potatoes when its concentration exceeds 200 mg/kg, so potato poisoning is now rare, especially as cooks are now more aware of the dangers of greening or sprouting potatoes.

Bitter principles occupy a central place in herbal therapeutics beating the acrid constituents. A wide range of general actions are attributed to the bitter principle, including increasing saliva secretion, stimulating the appetite, bring about an

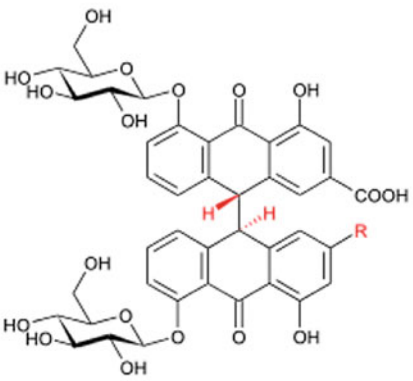
increase in the secretion of digestive juices, improving digestion, protect the tissues found in the digestive tract, boosts up the bile flow and strengthens the pancreas and liver detoxification, as well as some specific actions associated with a specific herb, e.g., valerian (*Valeriana officinalis*) of Caprifoliaceae and hops (*Humulus lupulus*) of Cannabaceae are relaxing nervines; white horehound (*Marrubium vulgare*) of mint family has pulmonary and expectorant actions, while bogbean (*Menyanthes trifoliata*) of Menyanthaceae and devil's claw (*Harpagophytum procumbens*) of Pedaliaceae are anti-inflammatory. Bitters are indispensable when it comes to counter a heavy meal. Sometimes, chicory and dandelion roots are mixed with coffee beans to produce a bitter drink usually taken after meals. The drink vermouth is the good example of an appetizer which gets its name from bitter herb wormwood.

Solanine has a choline esterase inhibitor function and thus affects the central nervous system. The symptoms of solanine poisoning are nausea, vomiting, diarrhea, stomach cramps, burning of the throat, heart arrhythmia, dizziness, and in severe cases hallucinations, loss of feeling, paralysis, jaundice, hypothermia and death. It causes apoptosis in cells; the cells commit suicide. Between 2 and 5 mg/kg of body weight will cause severe poisoning, possibly fatal. Tomatine is also a poisonous glycoalkaloid. It is found in green tomatoes and α-tomatine in tomatoes act as an antifungal, antibacterial and against insects and has been shown to display interesting pharmacological properties against bacteria, virii, fungi and tumors.

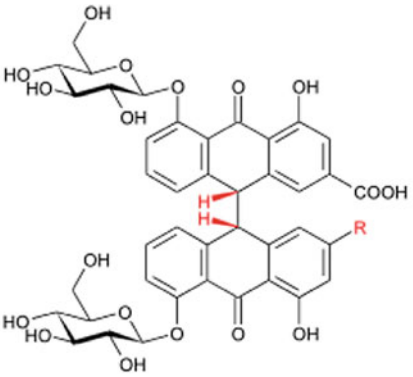
Classification of bitter principles

According to the physiological, therapeutic or pharmacological activities

Laxatives glycosides are cathartic, purgative and aperients compounds or drugs that facilitate or increase bowel movements. Laxative glycosides include (a) sennoside A, B, C, D (from *Senna* leaves and fruits); (b) cascaroside A, B (from *Cascara* bark); (c) frangulin and glucofrangulin (from *Frangula* bark); (d) aloin and barbaloin (from *Aloe vera* and *Aloe barbadensis* juice) (Fig. 3.49). These are the examples of stimulant laxatives that induce bowel movements by increasing the contraction of muscles in the intestines. Cardiac glycosides, on the other hand include (a) digitalis glycosides such as digoxin, digitoxin, gitoxin (from Fox glove leaves); (b) ouabain or G-strophanthin (from *Strophanthus gratus* seeds); c-K-strophanthin (from *Strophanthus kombe*seeds); (d) scillaren A, B (from red and white Squill bulbs); (e) convolloside (from *Convallaria majalis*—lily of the valley). Cardiac glycosides act on the contractile force of the cardiac muscle and they are the cardiac muscles stimulators.



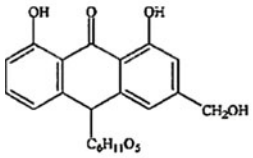
Sennoside A: R=COOH



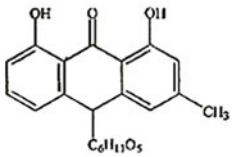
Sennoside B: R=COOH

Sennoside C: R=CH2OH

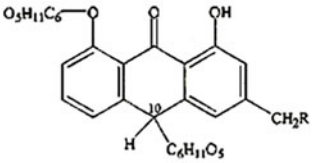
Sennoside D: R=CH2OH



Barbaloin

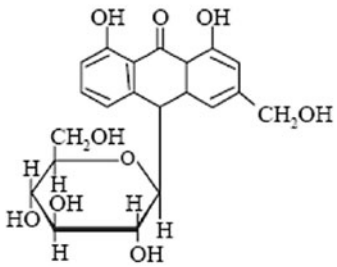


Chrysaloin

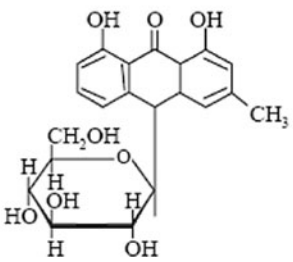


Cascaroside-A- R=OH

Cascaroside-B- R=H



Barbaloin (aloin)



Deoxybarbaloin (chrysaloin)

Fig. 3.49 Showing structures of different bitter principles—laxatives glycosides

According to the plant families

Coniferous glycosides

Coniferae is a large order of cone bearing plants. From this order we obtain the different varieties of pine, hemlock and spruce from which the various preparations of turpentine have been obtained. These are trees or shrubs, mostly evergreen, usually resinous. Leaves needle like or scale like. They are seen through out the world, chiefly in cold regions.

Cathargyroside A and cathargyroside B are labdane diterpene glycosides; vervenone-10-O-β-D-glucopyranoside and vervenone-10-O-β-D-apiofuranosyl-(1″→6′)-β-D-glucopyranoside are monoterpene glycosides; cedrusinin-4-O-α-L-rhamnopyranoside and (+)-cyclo-olivil-9′-O-β-D-xylopyranoside are lignan glycosides were obtained from the twigs and leaves of *Cathaya argyrophylla* of Conifer and some of these glycosides have antimicrobial and cytotoxicities. The antitumor activity of taxol, a diterpene alkaloid from several Taxus species, bark of Taxus brevifolia, the Pacific yew.

Liliaceous glycosides

The Liliaceae family are characterized as monocotyledonous, perennial, herbaceous, bulbous, or rhizomatous flowering plants with simple trichomes (root hairs) and contractile roots. The Liliaceae or lily family is composed of large number of plant with medicinal virtues. Most of these are herbs and rarely shrubs, e.g., Asphodel (*Asphodelus aestivus*), wild asparagus (*Asparagus aphyllus*), seaside squill (*Drimia maritima*), Mediterranean smilax (*Smilax aspera*), Greater butcher's broom (*Ruscus hypophyllum*), Butcher's broom (*Ruscus aculeatus*), Tassel hyacinth (*Muscari comosum*), Madonna lily (*Lilium candidum*), Bluebell (*Hyacinthus orientalis*), Aloe (*Aloe vera*), Garlic (*Allium sativum*), Garden onion (*Allium cepa*), Mediterranean meadow saffron (*Colchium cupani*), Meadow saffron (*Colchium autunnale*)

Asphodel in folk medicine is used to reduce pigmentation of the skin and to stop wound bleeding. Wild asparagus is used as a diuretic, antispasmidic and sedative; it reduces high blood pressure and heart beat. Seaside squill yields a high quantity of glycosides that have various medicinal effects such as expectorant, diuretic and hair toning properties but red squill (*Uriginea indica*) is less effective medicinally, however, used as to kill rodent pests. Mediterranean smilax yields bright red berries. It is used to reduce the blood sugar level, high blood pressure, as a diuretic and a treatment for hemorrhoids. Butcher's broom and greater butcher's broom's emerging shoots are similar to asparagus, and are edible. They are usually used in vascular disorders such as chilblains, varicose veins and haemorrhoids and these effects are attributed to steroid saponins. Additionally, these reduce the blood cholesterol levels. Tassel hyacinth is very similar to onion, in fact, the bulbs are boiled to remove the bitterness and are pickled in vinegar. Medicinally it has stimulant and diuretic effects. Madonna lily's medicinal constituents are found in the bulb and flowers. The bulb contains a high amount of mucilage ideal for skin conditions such as burns, boils and acne. The petals of the flowers, when soaked in oil yield an extract that is beneficial in eczema. Bluebell contains an essential oil that has antimicrobial activity. Aloe gel is widely used in several preparations such as skin and hair products. It has moisturizing and soothing effects especially in cases of sunburn, dermatitis, deep wounds where tissue regeneration is required. Aloe vera gel protects the skin from the ultraviolet irradiation and fights against cancer. It is used also for dry and itchy scalps. Garlic is used medicinally, in the fresh, dried or processed state. It contains an essential oil and alliin that is broken down into allicin as the tissue is disrupted on cutting or pressing. These constituents

make garlic strongly antiseptic, hypotensive and expectorant. Externally it can be applied to boils, insect bites and unbroken chilblains. Onion bulb is used for medicinal purposes. It is antiseptic, hypotensive, hypoglycemic and expectorant similar to garlic. Externally it is used for the treatment of boils and insect bites. Mediterranean meadow contains colchicine and its derivatives that have anticancer properties. Meadow saffron is traditionally used for the treatment of gout and skin cancer due to its colchicine content. It demecolcine is used in the treatment of leukemia.

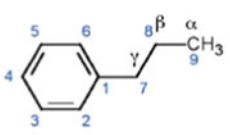
Based on correlation to the parent natural glycoside

Glycosides may be classified as Primary glycosides and Secondary glycosides on the basis of their in the source plant. For example, primary glycosides like amygdalin, purpurea glycoside A, stevioside, rebaudioside A, etc., are originally present in the plant while secondary glycosides like prunasin, digitoxin, etc., are formed from the primary glycosides by certain changes like removal of sugar as in the case of Digitoxin.

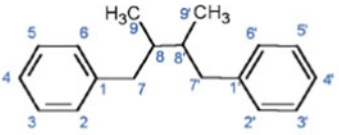
(xi) Miscellaneous glycosides

Lignans and phytoestrogens

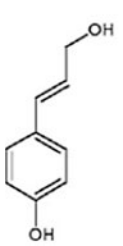
The lignan family is a large group of naturally abundant molecules and they are very common in the plant world. Plant lignans are plant-derived diphenolic compounds (phenylpropanoids dimers) whose structure is the union of two units of phenylpropane (C_6C_3—a propylbenzene skeleton) (1) are linked by their carbon



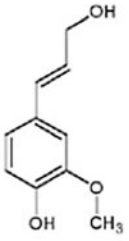
(1) Phenylpropane



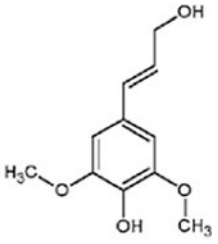
(2) Lignin



(3) p-Coumaryl alcohol



(4) Conyferyl alcohol



(5) Sinapyl alcohol

Fig. 3.50 Showing structures and carbon numbering of (1) phenylpropane and (2) lignin (β-β′ or 8,8′ link); structure of three common monolignols—(3) p-coumaryl alcohol (p-hydroxyphenyl alcohol); (4) conyferyl alcohol; and (5) sinapyl alcohol

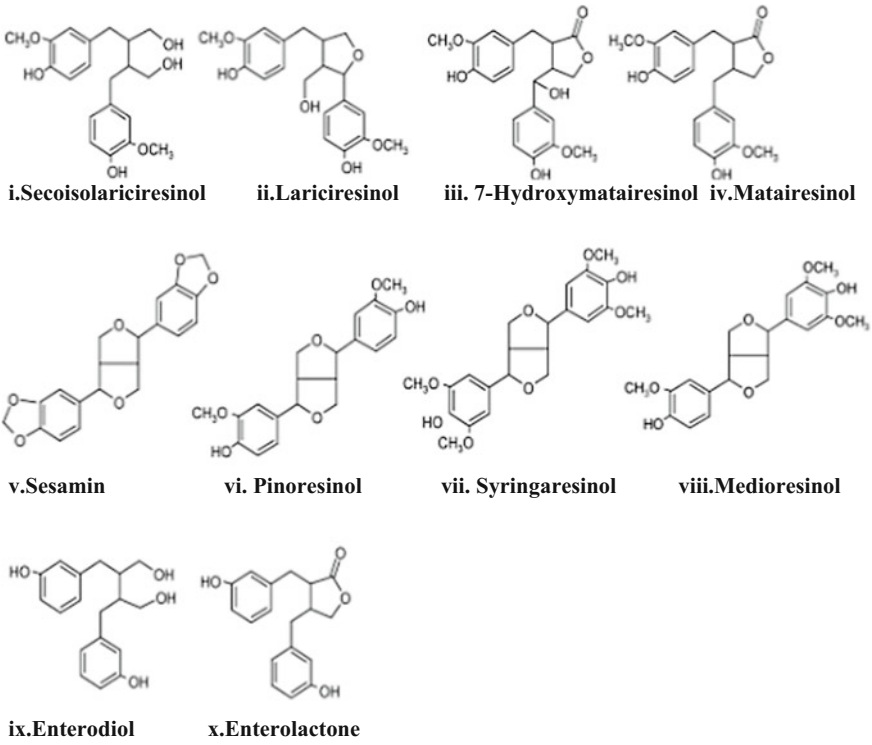


Fig. 3.51 Examples of eight lignans (i–viii) and two enterolignans (ix, x)

8,8′ (β-β′ link) (2) as represented in Fig. 3.50 along with three common monolignols. This definition is largely accepted although some authors prefer to describe lignans as "1,4-diarylbutane" compounds and subsequently the lignan family was extended to a series of compounds where the monomers are linked differently. A term neolignan is given when a structure is formed by joining the two propylbenzene residues at other than the β-carbon atom of the propyl side chain.

The enterolignans, enterodiol and enterolactone are formed by the action of intestinal bacteria on lignan precursors found in plants. Some examples of lignanprecursors are secoisolariciresinol, lariciresinol, 7-hydroxymatairesinol matairesino, sesamin, pinoresinol, medioresinol, podophyllotoxin, steganacin, syringaresinol, enterodiol and enterolactone (Fig. 3.51).

Lignans that can be metabolized to mammalian lignans are pinoresinol, lariciresinol, secoisolariciresinol, matairesinol, hydroxymatairesinol, syringaresinol and sesamin. Some plant lignans are metabolized by intestinal bacteria to mammalian lignans enterodiol and enterolactone. Lignans are one of the major classes of phytoestrogens, which are estrogen-like chemicals and act as antioxidants. The other classes of phytoestrogens are isoflavones and coumestans. Estrogens are signaling molecules (hormones) that exert their effects by binding to estrogen

receptors within cells. Flax seed and sesame seed contain higher levels of lignans than most other sources. The principal lignan precursor found in flaxseed is secoisolariciresinol diglucoside. Other sources of lignans include cereals (rye, wheat, oat and barley—rye being the richest source), soybeans, cruciferous vegetables such as broccoli and cabbage, and some fruits, particularly apricots and strawberries. Lariciresinol and pinoresinol contribute about 75% to the total lignan intake whereas secoisolariciresinol and matairesinol contribute only about 25%. This distribution of lignans in human diet may be changed on the availability of more data. Lignans are high in fiber content and have antiestrogenic effects as well as they have shown anti-inflammatory and antioxidant activity in basic research models of human diseases. There are several potential health benefits from flaxseed and other lignans, e.g., improve breast, prostate, colon, ovarian and uterine health; regulate hormone levels, diabetes, menopause symptoms; scavange free radicals; support immune system, canine cushings treatment, hair growth, etc. Podophilotoxin is found in the podophylle rhizome (*Podofilum peltatum*) and is the forerunner of two substances (etoposide and teniposide) used for antitumor therapy. Silimarin, a protector of the liver obtained from the Marian thistle (*Silybum marianum*). Diets rich in foods containing plant lignans (whole grains, nuts and seeds, legumes, fruits, and vegetables) have been consistently associated with reductions in risk of cardiovascular disease.

Phytoestrogens (dietary estrogens) are plant-derived xenoestrogens (foreign estrogens) not generated within the endocrine system but consumed by eating phytoestrogenic plants. Phytoestrogens include lignans, isoflavones, prenylflavonoids and coumestans, the last three are most active in estrogenic effects. Because of their structural similarity with estradiol (17-β-estradiol), they can cause estrogenic or/and antiestrogenic effects by sitting in and blocking receptor sites against estrogen (Fig. 3.52). Mycoestrogens have similar structures and effects.

In some countries, phytoestrogenic plants have been used for centuries in the treatment of menstrual, menopausal problems, fertility problems, etc. Plants used that have been shown to contain phytoestrogens include *Pueraria mirifica*, *P. Montana*, *Trifolium pratense* (Fabaceae), *Angelica sylvestris*, *Foeniculum vulgare*, *Pimpinella anisum* (Apiaceae), *Panax ginseng*, *P. quinquefolius* (Araliaceae), *Actaea racemosa* (Rananculaceae) and others.

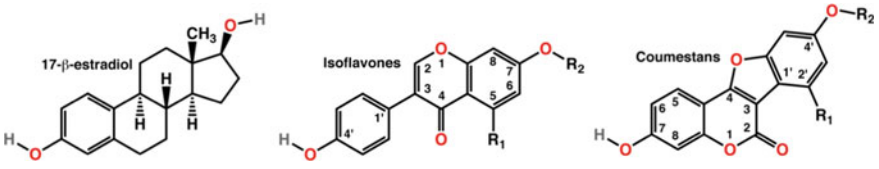
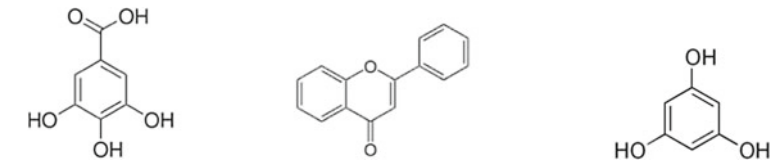


Fig. 3.52 Chemical structures of the most common phytoestrogens are isoflavones (e.g., daidzein —R_1=H, R_2=H, formonetin—R_1=H, R_2=CH_3, genistein—R_1=OH, R_2=H, biochanin A=R_1=OH, R_2=CH_3) and coumestans (e.g., coumestrol—R_1=H, R_2=H, 4 methoxycoumestrol—R_1=H, R_2=CH_3, repensol—R_1=OH, R_2=H, trifoliol—R_1=OH, R_2=CH_3) compared with estrogen (17-β-estradiol) found in animals



Gallic acid (3,4,5-trihydrxybezoic acid) **Flavone** (2-phenyl-1-benzopyran-4-one) **Phloroglucinol** (1,3,5-trihydroxybenzene)

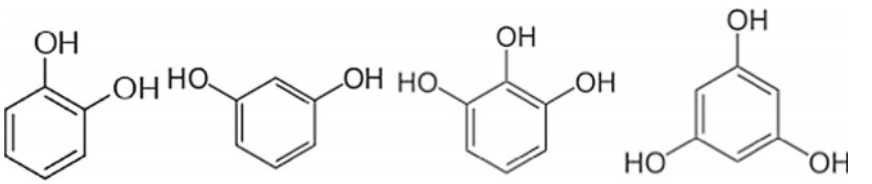
Fig. 3.53 Showing structures of monomer of hydrolyzable, non-hydrolyzable, or condensed tannins and phlorotannins

Tannins

Tannins are non-nitrogenous bitter plant polyphenolic compounds of vegetable origin having a molecular weight between 500 and 3000 (gallic acid esters) and up to 20,000 (proanthocyanidins). They are non-crystallisable colloidal compounds. There may be (a) hydrolyzable tannins, consist of gallic acid or related polyhydric compounds esterified with glucose and they are readily hydrolysed to yield the phenolic acids and the sugar; and (b) non-hydrolyzable or condensed tannins, contain only phenolic nuclei and most of such tannins are formed by the condensation of two or more flavanols, such as catechin. When condensed tannins are treated with hydrolytic agents they yield insoluble, red-colored products, known as phlobaphenes. Most of the time, they occur in glycosidic combinations with sugars. They bind and precipitate various organic compounds including proteins, amino acids, gelatin, alkaloids, heavy metals, etc., and form dark blue or greenish black compounds with ferric chloride. Tannins produce a deep red color with potassium ferricyanide and ammonia and are precipitated by salts of copper, lead and tin.

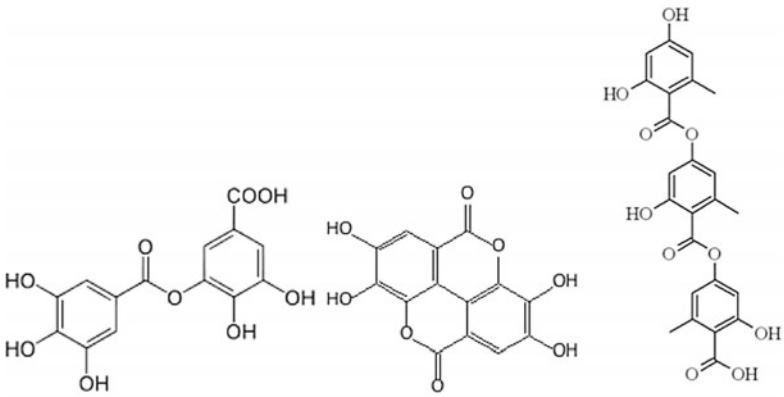
Base unit or monomer of the tannin includes gallic acid, flavone and phloroglucinol for hydrolyzable tannins, non-hydrolyzable or condensed tannins, and phlorotannins, respectively (Fig. 3.53). Hydrolyzable and non-hydrolyzable or condensed tannins may be derived from higher plants while phlorotannins are found in brown algae.

Most polyphenols contain repeating phenolic moieties of pyrocatechol, resorcinol, pyrogallol and phloroglucinol connected by esters (hydrolyzable tannins) or

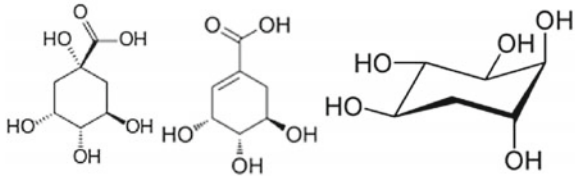


Pyrocatechol **Resorcinol** **Pyrogallol** **Phloroglucinol**

Fig. 3.54 Showing structures of phenolic moieties of pyrocatechol, resorcinol, pyrogallol, and phloroglucinol



Digallic acid **Ellagic acid** **Gyrophoric acid, a depside (meta-depside bond digalloyl ester)**



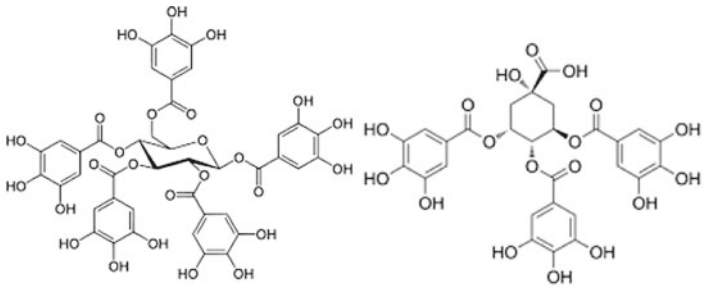
Quinic acid **Shikimic acid** **Quercitol (cyclohexane-1, 2, 3, 4, 5-pentol)**

Fig. 3.55 Showing structures of gallotannin moieties

more stable C–C bonds (non-hydrolyzable condensed tannins) (Fig. 3.54). Proanthocyanidins are mostly polymeric units of catechin and epicatechin. Catechol- and resorcinol- (benzenediol-) types of polyphenols have two, and pyrogallol- and phloroglucinol-(benzenetriol-) types have three phenolic hydroxyl groups, respectively, though mixing of these types within polyphenols is also possible.

Gallotanninand ellagitannins are examples of hydrolyzable tannins and form when gallic or ellagic acids esterify and bind with the hydroxyl group of a polyol carbohydrate. Gallotannins are polymers formed when gallic acid, digallic acid (polyphenol monomer) esterifies and binds with the hydroxyl group of a polyol carbohydrate such as glucoses, quinic acids, shikimic acids, and others—alloside, proto-quercitol, etc. (Figs. 3.55 and 3.56).

Ellagic acid is a natural phenol antiproliferative and antioxidant found oaks species like *Quercus alba* and *Quercus robur* and also macrophyte *Myriophyllum spicatum* and medicinal mushroom *Phellinus linteus*. Quinic acid is a cyclitol (cyclic polyol, cyclohexanecarboxylic acid), a crystalline acid obtained from cinchona bark, coffee beans, and other plant products. It is a constituent of the tara tannins. Quinic acid is used as an astringent and a medication for the treatment of influenza A and B strains.Shikimic acid (cyclitol, cyclohexanecarboxylic acid) is an



1, 2, 3, 4, 6-pentagalloyl glucose 3, 4, 5-tri-O-galloylquinic acid

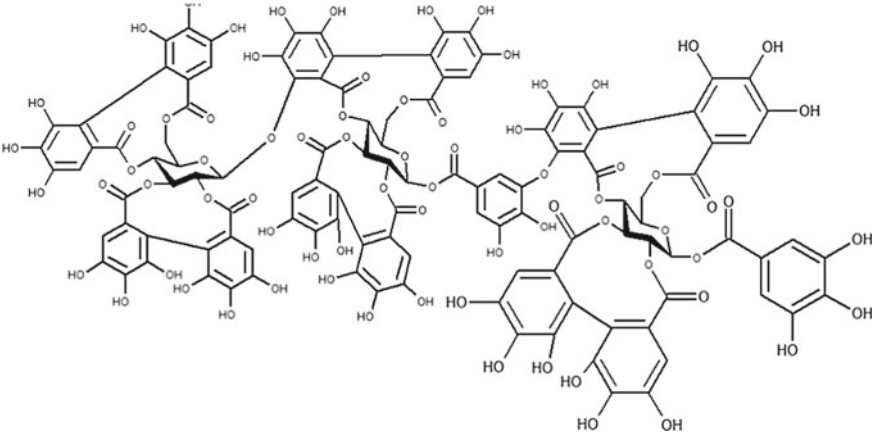


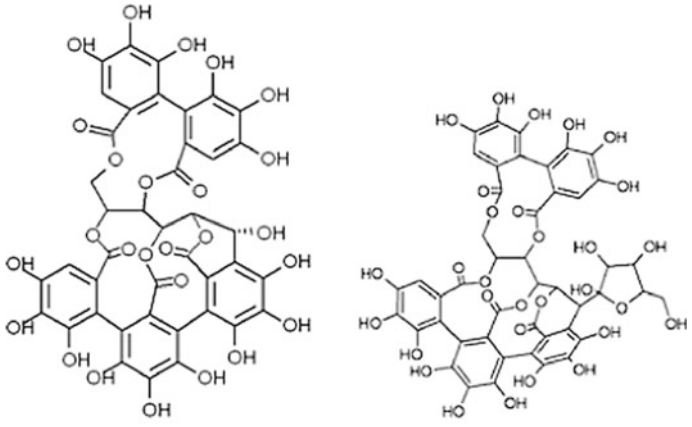
Fig. 3.56 Raspberry ellagitannin composed of 14 gallic acid units around a core of three units of glucose, with two gallic acids as simple esters, and the remaining 12 appearing in 6 ellagic acid-type units. Ester, ether, and biaryl linkages are present

important biochemical metabolite in plants (e.g., Chinese star anise—*Illicium verum*) and microorganisms. It appears in the list of Group 3 carcinogens (i.e., the agent is not classifiable as to its carcinogenicity to humans) of the International Agency for Research on Cancer. Shikimic acid is also the glycoside part of some hydrolyzable tannin. Quercitol (5-Deoxyinositol) is a cyclitol, found in *Quercus* sp., in *Gymnema sylvestre* and also in wines aged in oak wood barrels. A depside is a type of polyphenolic compound composed of two or more monocyclic aromatic units linked by an ester bond. Depsides are frequently found in lichens and in higher plant species of the family Ericaceae, Lamiaceae, Papaveraceae and Myrtaceae. Depsides have antibiotic, anti-HIV, antioxidant, and antiproliferative activity. As inhibitors of prostaglandin synthesis and leukotriene B4 biosynthesis, depsides are potent nonsteroidal anti-inflammatories. Gyrophoric acid of the lichen Cryptothecia rubrocincta is a depside.

Gallotannins are simple polygalloyl esters of glucose. The protypical gallotannin is 1,2,3,4,6-pentagalloyl glucose (PGG), the pentahydroxy gallic acid ester of

glucose (β-1,2,3,4,6-pentagalloyl-O-D-glucopyranose). PGG has 5 identical ester linkages that involve aliphatic hydroxyl groups of the core sugar. It has many isomers with mol. wt. 940 g/mol. The polygalloyl ester chains found in gallotannins are formed by either *meta*—or *para*-depside bonds, involving a phenolic hydroxyl rather than an aliphatic hydroxyl group. The α-anomer of PGG is not common in nature. PGG is a common precursor of gallotannins and the related ellagitannins. Simple gallotannins with up to 12 esterified galloyl groups and a core glucose are found inpomegranate (*Punica granatum*), staghorn sumac (*Elaeocarpus sylvestris* or *Rhus typhina*) and also in tree peony (*Paeonia suffruticosa*). 3,4,5-tri-O-galloylquinic acid is hydrolyzable tannin found in *Lepidobotrys staudtii*, *Guiera senegalensis* and in the resurrection plant *Myrothamnus flabellifolius*. It is classified as a natural product with anti-HIV activity and a DNA polymerase inhibitor. The raspberry ellagitannin is an ellagitannin found in raspberries. It is a polyphenol per se, containing 6 ellagic acid-type components and two additional monomeric phenolics, for a total of 14 gallic acid units. Red raspberry ellagitannins slow the growth of breast, pancreas, esophageal, skin, and prostate cancer cells and kill them (apoptosis). The ellagitannins also produce a breakdown in human leukemia cells. Ellagitannins act as scavengers to bind carcenogenous chemicals, making them inactive. Red Raspberry ellagitannins also protect DNA by blocking carcinogens from binding to the DNA, lower the incidence of birth defects, promote wound healing, reduce heart disease, and may reduce or reverse chemically induced liver fibrosis, show antibacterial and antiviral properties

Gallotannins are hydrolyzable tannin; yield various water-soluble products, such as gallic acid and protocatechuic acid and sugars and other polyols. The ellagitannins are a diverse class of hydrolyzable tannins, a type of polyphenol formed primarily from the oxidative linkage of galloyl groups in 1,2,3,4,6-pentagalloyl glucose (Fig. 3.57). Ellagitannins differ from gallotannins, in that their galloyl



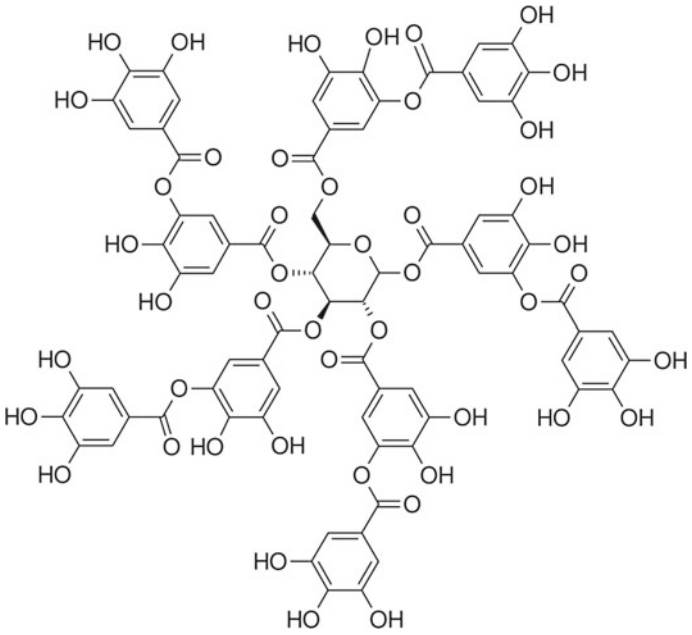
Ellagitannins (Castalagin) **Grandinin**

Fig. 3.57 Showing structures of ellagitannins (castalagin) and grandinin

groups are linked through C–C bonds, whereas the galloyl groups in gallotannins are linked by depside bonds. Condensed tannins, e.g., proanthocyanidins, polyflavonoid tannins, catechol-type tannins, pyrocatecollic-type tannins, or flavolans are polymers formed by the condensation of flavans. They do not contain sugar residues. Examples of some other condensed tannin are procyanidins, propelargonidins, prodelphinidins, profisetinidins, proguibourtinidins or prorobinetidins, formed from flavonoids structures corresponding to the related anthocyanins. Procyanidins, condensed tannins found in grape, are polymers of 2 to >50 flavan-3-ol units joined by carbon–carbon bonds. These are not susceptible to being cleaved by hydrolysis. Castalagin (vescalagin) is an ellagitannin, a type of hydrolyzable tannin, found in oak and chestnut wood and in the stem barks of *Anogeissus leiocarpus* and *Terminalia avicennioides*.

Examples of ellagitannins are castalagin, castalin, casuarictin, grandinin, punicalagin, punicalin, roburin A, tellimagrandin II, terflavin B, vescalagin, etc.

Grandinin is an ellagitannin and a castalagin glycoside by binding of the pentose lyxose. It contains a nonahydroxytriphenic acid moiety, can be found in *Melaleuca quinquenervia* leaves, in white (*Quercus alba*) and red (*Quercus robur*) oaks. It is an astringent compound and shows antioxydant activity. It suppresses the phosphorylation of the epidermal growth factor receptor in human colon carcinoma cells.



Polygalloyl glucoses

Fig. 3.58 Showing structures of polygalloyl glucoses—a tannic acid

Tannic acid is a type of polyphenol, a specific commercial form of tannin (Fig. 3.58). It is weak acidic (pKa around 10) is due to the numerous phenol groups. The chemical formula, $C_{76}H_{52}O_{46}$, corresponds with decagalloyl glucose, but it is a mixture of polygalloyl glucoses or polygalloyl quinic acid esters with the number of galloyl moieties per molecule ranging from 2 to 12 depending on the plant source. Commercial tannic acid is usually extracted from Tara pods (*Caesalpinia spinosa*), gallnuts from (*Rhus semialata* or *Quercus infectoria*—source of Turkish and Chinese gallotannins) or Sicilian sumac leaves (*Rhus coriaria*) or Chinese sumac (*Rhussemialata*-source of Chinese and Korean gallotannins). Gallnutis a plant excretion produced when irritants are released by the larvae of gall insects/gall wasps of the Cynipidae family. A major commercial source of medicinal gallnuts is oak trees and Chinese sumac. The plant secretes the liquid gall that hardens to become the nut. Gallnuts are a native product of China, Turkey, India, Japan, and Korea. The annual yield of gallnuts in China is about 95% of the total world yield. Gallnuts from oak and sumac contain 50–75% tannin (gallotannin) and 2–4% each of gallic acid and ellagic acid. *Quercus infectoria* and *Rhus semialata* are sources of Turkish and Chinese gallotannins, respectively.

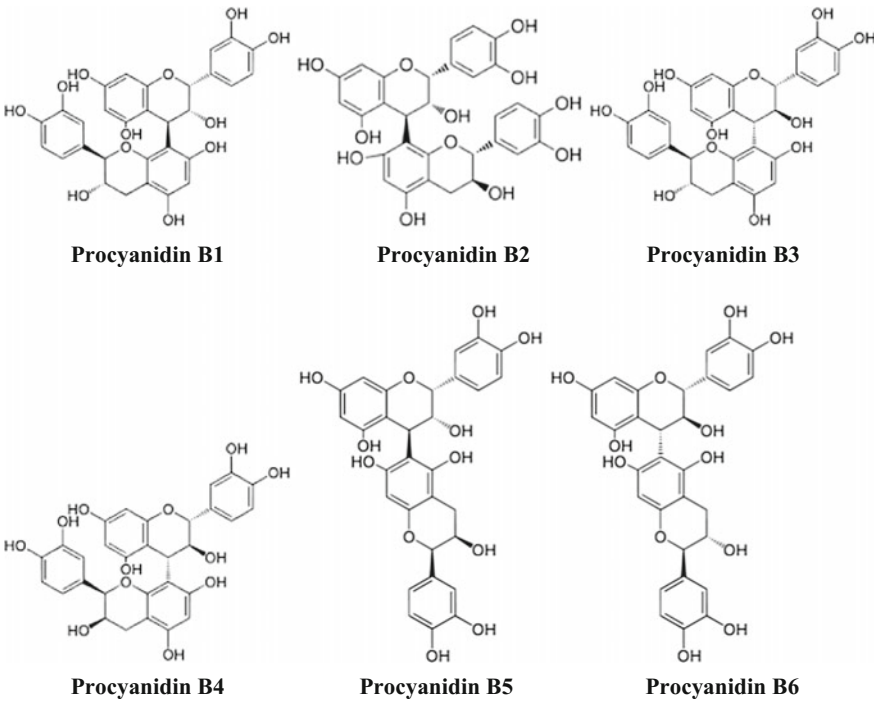


Fig. 3.59 Showing structures of the basic monomer of condensed tannins

Proanthocyanidins (condensed tannins) refer to a larger class of polyphenols, called flavanols, in which occur PCOs (proanthocyanidin oligomers) or OPCs (oligomeric proanthocyanidins), the simplest flavanols. The basic monomer of condensed tannins (proanthocyanidins) is epicatechin and catechin; the successive addition of similar phenol units then extends these to produce polymers (polyphenols) (Fig. 3.59). Traditionally, important commercial sources of condensed tannins are the heartwood of *Schinopsis* spp. (quebracho tannins), the bark and/or heartwood of *Acacia catechu* (catechu tannins) and *Acacia mollissima* (mimosa tannins), and the bark of *Rhizophora* (mangrove) and *Eucalyptus* species. The application of proanthocyanidins has health protective effect as antioxidants.

Procyanidin B1 is a procyanidin dimer. It is a molecule with a 4→8 bond (epicatechin-(4β→8)-catechin). Proanthocyanidin-B1 can be found in *Cinnamomum verum* (Ceylon cinnamon, in the rind, bark or cortex), in *Uncaria guianensis* (cat's claw, in the root), and in *Vitis vinifera* (in the leaf) or in peach. Procyanidin B2 is a B type proanthocyanidin. Its structure is (−)-Epicatechin-(4β→8)-(−)-epicatechin.

Procyanidin B2 can be found in *Cinchona pubescens* (in the rind, bark and cortex), in *Cinnamomum verum* (Ceylon cinnamon, in the rind, bark and cortex), in *Crataegus monogyna* (Common hawthorn, in the flower and blossom), in *Uncaria guianensis* (Cat's claw, in the root), in *Vitis vinifera* (Common grape vine, in the leaf), in *Litchi chinensis* (litchi, in the pericarp), in the apple, and in *Ecdysanthera utilis*. Procyanidin B3 is a B type proanthocyanidin. Procyanidin B3 is a catechin dimer (catechin-(4α→8)-catechin). It can be found in red wine, in barley, in beer, in

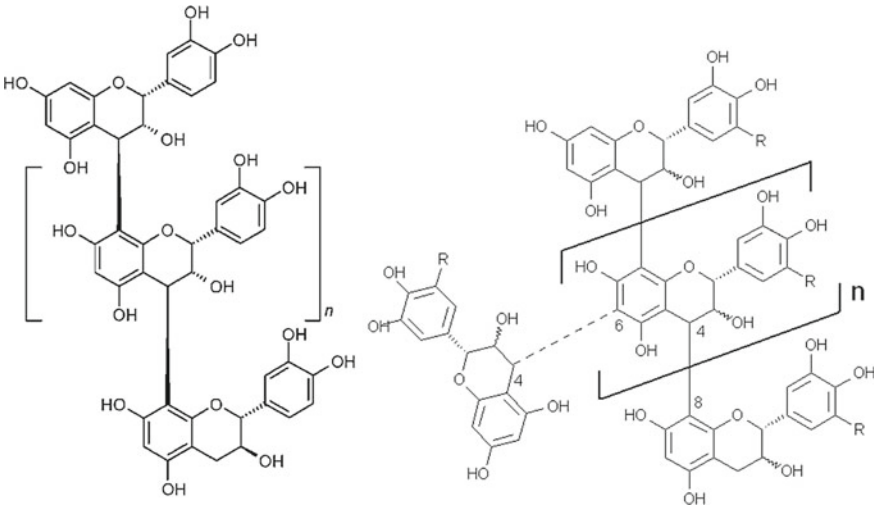


Fig. 3.60 Showing structures of (schematic) of polyflavonoid condensed tannin molecules

peach or in *Jatropha macrantha*. It has been identified as a hair-growth stimulant. Procyanidin-B4 is a catechin-(4α→8)-epicatechin dimer. It is found in the litchi pericarp, in grape seeds, and, along with 4-cis-isomer of procyanidin B4, in beer. Procyanidin B5 is a B type proanthocyanidin. Procyanidin B5 is an epicatechin-(4β→6)-epicatechin dimers. It can be found in grape seeds and in *Hibiscus cannabinus* (kenaf) root and bark. Procyanidin B6 is a B type proanthocyanidin. Procyanidin B6 is a catechin-(4α→6)-catechin dimer. It can be found in grape seeds and in beer. Figure 3.60 shows polyflavonoid condensed tannin molecules—linear with 4→8 carbon–carbon bonds and branched with 4→8 and 4→8 carbon–carbon bonds.

Condensed tannins are ubiquitous plant phenolics, and presented exceptional concentrations in the barks and heartwoods of a variety of tree species. They are oligomers or polymers of flavonoid units (flavan-3-ol) linked by carbon–carbon bonds not susceptible to hydrolysis. Condensed tannins can be linear (with 4→8 bounds) or branched (with 4→6 bounds—dotted line). Condensed tannins (proanthocyanidins, polyflavonoid tannins, catechol-type tannins, pyrocatecollic-type tannins, non-hydrolyzable tannins, or flavolans) are polymers formed by the condensation of flavans. They do not contain sugar residues. They are called proanthocyanidins as they yield anthocyanidins when depolymerized under oxidative conditions. Different types of condensed tannins exist, such as the procyanidins, propelargonidins, prodelphinidins, profisetinidins, proguibourtinidins or prorobinetidins, formed from flavonoids structures corresponding to the related anthocyanins. One condensed tannin, found in grape, are procyanidins, which are polymers of 2–50 (or more) flavan-3-ol units joined by carbon–carbon bonds. These are not susceptible to being cleaved by hydrolysis.

While many hydrolyzable tannins and most condensed tannins are water soluble, several tannins are also highly octanol soluble. Some large condensed tannins are insoluble. Differences in solubilities are likely to affect their biological functions. Tannins of tropical woods tend to be of a catechin nature rather than of the gallic type present in temperate woods. Condensed tannins can be recovered from Lithocarpus glaber or can be found in Prunus sp. The bark of Commiphora angolensis contains condensed tannins. Commercial sources of condensed tannins are plants such as quebracho wood (Schinopsis lorentzii), mimosa bark (*Acacia mollissima*), grapes seeds (*Vitis vinifera*), pine barks and spruce barks. Pycnogenol is a trademark for a French maritime pine bark extract. Condensed tannins are formed in tannosomes, specialized organelles, in Tracheophytes, i.e., vascular plants.

Both types of tannins, the hydrolyzable tannins have long been considered official medicinal agents in Europe and North America and they have been included in many pharmacopoeias as tannic acid. They were recommended for treatment of inflammation and ulceration, including topical application for skin diseases and internal use for intestinal ulceration and diarrhea. Now, the condensed tannins also have important medicinal roles, such as stable and potent antioxidants. In China, tannin-containing substances, such as galls, pomegranate rinds, and terminalia fruits, are used in several medicinal preparations.

Tannins are widely distributed in the plant kingdom and are found in leaf, bud, seed, root, bark and stem tissues, in grapes, persimmon, blueberry, tea, chocolate, legume forages, legume trees (*Acacia* spp., *Sesbania* spp.), grasses (sorghum, corn, etc.). They are found in plant families, especially in Aceraceae, Actinidiaceae, Anacardiaceae, Bixaceae, Burseraceae, Combretaceae, Dipterocarpaceae, Ericaceae, Fabaceae, Grossulariaceae, Myricaceae, Rhizophoraceae, Rosaceae, and Salicaceae for dicot, Najadaceae and Typhaceae in Monocot families and Pinus of Gymnosperm. About 73, 39, 6 and 4% of the species of Fagaceae, Mimosaceae, Solanaceae and Asteraceae, respectively, contain tannin. Some families like the Boraginaceae, Cucurbitaceae, and Papaveraceae contain no tannin-rich species. Tannins are also found in some brown algae.

They are mostly used in the tanning industry for the conversion of animal hides to leather (as they form hydrogen bridges with the fibers of collagen in the skin), in the production of ink and as a laboratory reagent for the detection of proteins, alkaloids, and gelatin. Pharmaceutically, tannins have antibacterial, antiviral, antiparasitic, astringent and antiseptic properties, and may be used in the treatment of hemorrhages (constrict of blood vessels), burns (cicatrizing), diarrhea, and as an antidote for alkaloid poisoning because of their ability to precipitate alkaloids. Tannins of the stem bark of *Myracrodruon urundeuva* are effective against 6-hydroxydopamine-induced toxicity and also have anti-inflammatory and antiulcer activity (Souza et al. 2006; Nobre et al. 2007). Examples of natural drugs containing tannins include Hamamelis leaf and Nutgall.

Quinones

Quinones are a class of cyclic organic compounds containing two carbonyl groups (>C=O by conversion of an even number of –CH=groups) in a six-membered unsaturated ring. These are aromatic diketones which come from phenols through oxidation. In a few quinones, the carbonyl groups are located in different rings. The class representative is quinone (1,4-benzoquinone or cyclohexadienedione) and other important examples include 1,2-benzoquinone, 1,4-naphthoquinone and 9,10-anthraquinone (Fig. 3.61).

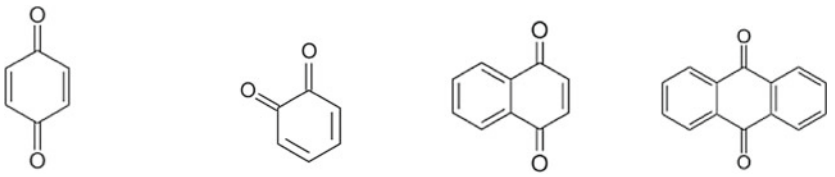


Fig. 3.61 Showing structures of class representative quinone (1,4-benzoquinone or cyclohexadienedione) and other important examples like 1,2-benzoquinone, 1,4-naphthoquinone, and 9,10-anthraquinone

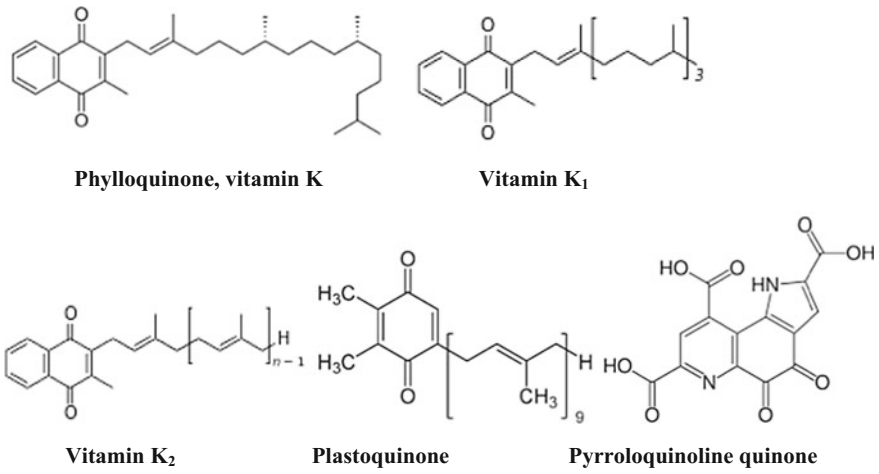


Fig. 3.62 Showing structures of vitamin K, vitamers (vitamin) K_1 and K_2; plastoquinone (PQ) and pyrroloquinoline quinone (PQQ)

Quinones occur as biological pigments, i.e., biochromes and include benzoquinones, naphthoquinones, anthraquinones and polycyclic quinones. The quinones are found in bacteria, in certain fungi, in various higher plant forms and in a few animals (e.g., sea urchins, aphids, lac insects, and certain scale insects). Animals obtain their quinone compounds from the plants they eat.

Parabenzoquinone is a pale yellow solid with a penetrating odor resembling that of chlorine. It is widely used in medicine, herbicides, chemical reagents, dyes, and tanning agents. P-benzoquinone is used in pharmaceutical industry for production of cortisone, in cosmetic industries, leather industries and also used in photographic chemicals. It is used as a chemical intermediate, a polymerization inhibitor and oxidizing agent. It is highly active anti-microbacterial, antifungal agent and highly toxic and fatal if swallowed, inhaled, or absorbed through the skin.

Phylloquinone, vitamin K, contain a functional naphthoquinone ring and an aliphatic phytyl (isoprenoid) side chain. Vitamin K family includes two natural vitamers: vitamin K_1 and K_2 (menaquinone), which consists of a number of related chemical subtypes differing in length of the side chain, made of isoprenoid residues. The most common number of these residues is four, since animal enzymes normally produce menaquinone-4 from plant phylloquinone. Figure 3.62 shows the structures of vitamin K, vitamers (vitamin) K_1 and K_2, plastoquinone (PQ) and pyrroloquinoline quinone (PQQ).

Plastoquinone (PQ), quinone of either plastid or chloroplast alluding to its location, is a 2,3-dimethyl-1,4-benzoquinone molecule with a side chain of nine isoprenyl units. PQ is involved in the electron transport chain in the light-dependent reactions of photosynthesis. Plastoquinone is reduced to plastoquinol on acceptance of two H^+ from the stromal matrix of the chloroplast, coupled to two e^- from

photosystem II. It functions as an electron acceptor during photosynthesis, forming part of the electron transport chain of Photosystem I. It transports the protons to the lumen of thylakoid discs, while the electrons continue through the electron transport chain into the cytochrome b_6f protein complex. Pyrroloquinoline quinone (PQQ) is known as the third redox cofactor after nicotinamide and flavin in bacteria, protects mitochondria from oxidative stress, promotes the spontaneous generation of new mitochondria within aging cells, a neuroprotective—protects brain cells against oxidative damage, reduce heart damage following myocardial infarction.

It is a fat-soluble vitamin that is stable to air and moisture but decomposes in sunlight. It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system. Its best-known function in animals is as a cofactor in the formation of coagulation factors II (prothrombin), VII, IX, and X by the liver. It is also required for the formation of anticoagulant factors protein C and S. It is commonly used to treat warfarin toxicity, and as an antidote for coumatetralyl. Vitamin K is required for bone protein formation.

K vitamins found in alfalfa (*Medicago sativa* of Fabaceae) are antibacterial and antifungal agents; juglonefrom the walnut tree (*Juglans regia* of Juglandaceae) is antioxidant, antiproliferative, bone and cardio protective, lawsona, naphthoquinone, from henna (*Lawsonia inermis* of Lythraceae) has diverse activities: from body art (dye skin, hair, and fingernails), industry (dye fabrics including silk, wool, leather), toiletries (shampoo) to anticancer; plumbago, from the drosera (*Drosera rotundifolia* of Droseraceae), which is anti-expectorant; anthracicflaxnes are nucleus of important antibiotics such as daunomicin and doxorubicin, as well as tetraciclines used in cancer chemotherapy derived from Streptomyces bacterium *Streptomyces peucetius var. caesius*; anthraquinones and fenanthraquinones act as laxatives and purgatives, when in heteroside form. Quinones show a wide range of pharmacological activities, e.g., they may be used as purgative (sennosides—anthraquinone derivatives named after their abundant occurrence in plants of the genus *Senna* of Caesalpinaceae, Aloe-emodin—an anthraquinone from leaf exudates of *Aloe vera*), antibacterial (rhein—anthraquinone group found in rhubarb, *Rheum rhabarbarum* of Polygonaceae and saprorthoquinone—naphthoquinone from *Salbia montbretii* and *S. prionitis* of Lamiaceae), antitumor (emodin—trihydroxyanthroquinone from a Himalayan rhubarb—*Rheum emodi*, Japanese knotweed—*Fallopia japonica* of Polygonaceae and a number of other genus like *Senna*, *Cassia*, *Acalypha*, etc., and juglone—naphthoquinone from *Juglans regia* of Juglandaceae), inhibition of *Prostaglandin* E2, PGE2, biosynthesis (arnebinone and arnebifuranone—two quinonic compounds, monoterpenylbenzoquinones, from the roots of *Arnebia euchroma* of Boraginaceae) and anti-inflammatory, antioxidative, cytotoxic and anti-cardiovascular disease (tanshinone–phenanthrene–quinone derived from roots of *Salvia miltiorrhizae* of Lamiaceae) (Liu 2011).

3.8 Resins, Saponins, Cardioactive Drugs and Other Steroids

Resins Saponins, cardioactive drugs and other steroids

Saponins are amphiphilic glucoside molecules composed of hydrophilic glycoside glycone and lipophilic triterpene or steroid aglycone. They have a high molecular weight and a high polarity; possess foaming characteristics in aqueous solutions and a high degree of structural diversity. Saponins are generally nonvolatile, surface-active compounds that are widely distributed in nature. A polycyclic aglycone becomes attached to one or more sugar side chains in saponin. The aglycone part (sapogenin) is either steroid (C_{27}) or a triterpene (C_{30}), i.e., saponins are glycosides of triterpenoids or steroids. Saponins on hydrolysis give on hydrolysis yield a triterpenoid or steroid sapogenin and one or more sugars (glucose, galactose, rhamnose or xylose, etc.). The aglycones or sapogenins are characterized by the presence of a spiroketal side chain. Because of amphipathic nature, they are largely used as emulsifying and detergents. Saponins have been used in medicine, foaming agents, in fire extinguishers and fish poisons. Dietary monosaccharides such as D-glucose and D-galactose are among the most common components of the attached chains. The steroidal saponins are called saraponins. Aglycone derivatives can also incorporate nitrogen, e.g., solanine, a monodesmosidic, branched-saccharide steroidal saponin. Their isolation in a state of purity presents some difficulties as they often occur as complex mixtures with the components differing only slightly from one another in the nature of the sugars present, or in the structure of the aglycone. Various chromatographic techniques have been employed for their isolation.

Distribution

Saponins are found in almost all groups of plants, but they have also been isolated from marine organisms such as marine invertebrate sea cucumber and star fish. Saponins derive their name from the soapwort plant genus *Saponaria* because the root of *Saponariaofficinalis* of Caryophyllaceaewas used historically as soap, the root of which was used historically as a soap. Beans and other legumes (e.g., kidney beans, navy beans and haricot beans, soybeans, and chickpeas) as well as garlic, asparagus, etc., are among the richest sources of saponins.Saponins are also found in different members of soapberry, soapnut, washnut (*Sapindus mukorossi*, *Sapindus trifoliatus*), licorice (*Glycyrrhiza glabra*), maples (*Acer*), genus Sapindus, Glycyrrhiza, Acer, etc., of Sapindaceae, soapbark tree (*Quillaja saponaria*) of Quillajaceae, Spanish dagger plant (*Yucca schidigera*) ofAsparagaceae, licorice (*Glycyrrhiza glabra*) of Fabaceaeandhorse chestnuts (*Aesculus hippocastanum*) of Hippocastanaceae. Saponin is also found in *Gynostemma pentaphyllum* of Cucurbitaceae in a form called gypenosides, and ginseng or red ginseng (*Panax*) of Araliaceae in a form called ginsenosides. Saponin is found in various parts of the plant including leaves, stems, roots, bulbs, blossom and fruit. Commercial saponins are mainly extracted from the bark and root of desert plants *Quillaja saponaria* of

Chileand *Yucca schidigera* of Baja California, respectively. They are the two major commercial sources of saponins. *Chenopodium quinoa* of Amaranthaceaehas a long history of use of edible seed (seed coat contains bitter saponin) in South America and is not harmful to humans. Toxic saponins are known as sapotoxins.

Application

Saponins are used in various ways such as liquid soap, jewelry polish, detergent, exzema, dermatitis cure, pesticide, insecticide, pet shampoo, human shampoo, household cleaner, laundry detergent, surfactant, wetting agent, nutrient uptake, spreader, sticker, antimicrobial agents, adjuvant (make other solutions work better), treat malaria, lower blood cholesterol, hypertension aid, kill nematodes, bone health, cancer fighter, support immune system (build it up), parasite remover (tick, flea), automobile cleaner. Because of their surfactant properties, saponins are also used industrially, in mining and ore separation, emulsions for photographic films and cosmetic products like lipstick and shampoo where their antifungal and antibacterial properties are important in addition to their emollient effects. Saponins when mixed with water reduce the surface tension of water, allowing the formation of small stable bubbles. Because of their surface-active properties, saponins are excellent foaming agents (very stable). Today, saponins are used in the manufacture of fire extinguisher foam, toothpaste, shampoos, detergents, liquid soaps, lipsticks, herbal skin balms, and cosmetics and to increase the foaming qualities of beer, beverages, and soft drinks. The soapy characteristics of saponins make them ideal for use as spray adjuvants and make sprays stick or spread better on leaf surfaces. They also allow nutrients to be absorbed better. Another important thing they do is to distribute water more evenly on hard-to-wet substrates. For these reasons saponins are often used in fertilizers, potting soils, and pesticides. Yucca root has high levels of saponin and Native Americans used it for years to make soap and shampoo. They used to wash their hair with Yucca to fight dandruff and hair loss and Yucca has been used to treat headaches, bleeding, gonorrhea, arthritis and rheumatism and many other ailments. Saponins come in powdered or liquid form and can be found in fertilizers (amendments) and soilless potting mixes and certain pesticides (insecticides), and many other things.

Biological activities and health benefits

Their biological and pharmacological activities range from antimicrobial, antifungal, anticancer, to immunomodulatory, etc. The most prominent feature of saponins is linked to their effects on cell membranes; they strongly affect cell membrane structure and integrity by different mechanisms depending on their chemical structure. The ability of saponins to increase membrane permeability can be used to facilitate the passage of drug molecules or other natural products through the cell membrane. The ability of saponins to affect cell membrane structure and integrity makes them interesting natural products in pharmacological and medical research and therapy, in particular, as agents for enhancing drug efficacy.

(i) Saponins have hemolytic, expectorative, anti-inflammatory and immune-stimulating activity; (ii) Saponins control blood cholesterol levels, bone

health, cancer, and building up the immune system; (ii) Saponins demonstrate antimicrobial properties particularly against fungi and additionally against bacteria and protozoa. (iv) Saponinsform complex with cholesterol to develop pores in cell membrane bilayers, e.g., in erythrocyte membranes complexation leads to red cell lysis (hemolysis); (v) The amphipathic nature of saponin gives them activity as surfactants that can be used to enhance penetration of macromolecules such as proteins through cell membranes; (vi) Saponins improve function and pharmaceutical manufacturers often include saponins in vaccines as adjuvants to increase their effectiveness; (vii) Saponins may reduce the risk for high cholesterol, cancer and blood sugar, and saponins from the *Gypsophila paniculata* have been shown to very significantly augment the cytotoxicity of immunotoxins and other targeted toxins directed against human cancer cells (e.g., leukemia, lymphoma and other cancers). (viii) Saponin digitalis of the Foxglove plant is used in heart medicines.

There is tremendous, commercially driven promotion of saponins as dietary supplements and nutriceuticals. Saponins from oat and spinach may enhance nutrient absorption and aid in animal digestion. Saponins appear in beverages and cosmetics as emulsifiers or sweeteners. Yucca and quillaja saponins have both current and potential applications in animal and human nutrition. Yucca extracts are extensively used for ammonia and odor control in pig and poultry-raising facilities and in dog and cat foods. Yucca saponins and perhaps other components of yucca as well, have ammonia-binding activity. When added to the diet, yucca saponins pass through the digestive tract unabsorbed and are excreted in the feces. In the excreta, the yucca components bind to ammonia and certain other odiferous compounds and prevent them from being released into the air. In recent studies in England, feeding of yucca extract to dogs and cats was shown to reduce fecal odor and reduce emission of volatile compounds contributing to fecal odor. Many pet foods and kitty litter products now contain yucca extract to reduce these noxious odors.Saponins are often bitter in taste and so can reduce plant palatability and thus may serve as antifeedants (threatening animal toxicity) and protect the plant against microbes and fungi. Many saponins are used as fish poison. Oral saponins appear to be extremely safe but when injected intravenously saponin glycosides can cause hemolysis of red blood cells. The hemolytic effect seems to be due to increasing cell membrane permeability.

Classification of saponins

Saponins are a structurally diverse class of glycoside compounds occurring in many plant species. Traditionally, they are subdivided into triterpenoid and steroid glycosides, or into triterpenoid, spirostanol, and furostanol saponins (Vincken et al. 2007). Triterpenoid saponins (pentacyclic) are triterpenes to which various sugar molecules become attached. Triterpenes are synthesized from isoprene unit through mevalonate pathway to make a C_{30} compound. Some triterpenes are steroidal in nature, e.g., cholesterol, phytosterols, phytoecdysteroids, etc. Steroidal saponins (commonly tetracyclic triterpenoids) are naturally occurring sugar conjugates of C_{27} steroidal compounds (tetracyclic molecules) that are synthesized from acetyl

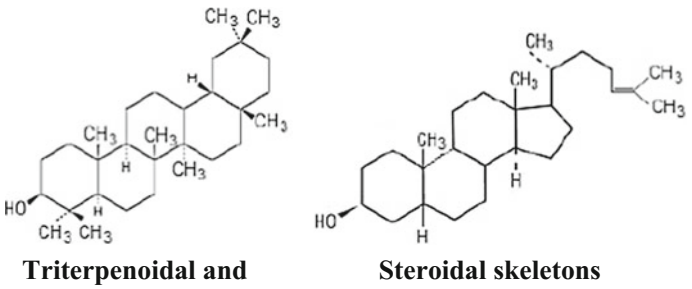


Fig. 3.63 Showing structures of triterpenoidal and steroidal skeletons of saponin glycosides

coenzyme A (CoA). The aglycone of a steroid saponin is usually a spirostanol or a furostanol. The glycone parts of these compounds are mostly oligosaccharides, arranged either in a linear or branched fashion, attached to hydroxyl groups through an acetal linkage. Both have a glycosidal linkage at C_3 and have a common biogenetic origin. A distinct subgroup of the steroidal saponins is that of the steroidal alkaloids which characterize many members of the Solanaceae.

Triterpenoidal (pentacyclic) and Steroidal (tetracyclic) saponins are structurally distinct group of molecules but they have most properties in common (Fig. 3.63). Triterpenoids tend to be acidic in pH and occur more commonly in dicots while steroidal saponins tend to be neutral in pH and occur more commonly in monocots. Triterpenoid saponins are rare in monocotyledons but they are abundant in many dicotyledonous families (e.g., Caryophyllaceae, Sapindaceae, Polygalaceae and Sapotaceae). Other dicotyledonous families in which triterpenoid saponins have been found are the Phytolaccaceae, Chenopodiaceae, Ranunculaceae, Berberidaceae, Papaveraceae, Linaceae, Zygophyllaceae, Rutaceae, Myrtaceae, Cucurbitaceae, Araliaceae, Umbelliferae, Primulaceae, Oleaceae, Lobeliaceae, Campanulaceae, Rubiaceae and Compositae. Altogether some 80 families are involved.

Commercial saponins extracted from *Yucca schidigera* are steroidal saponins while *Quillaja saponaria* extract contains a triterpenoid saponin mixture. Some herbs rich in (i) Triterpenoid saponins are Actaea racemosa (black cohosh), *Azadirachta indica*(neem), *Centella asiatica* (gotu kola), Canoderma lucidum (reishi), *Glycyrrhiza glabra* (licorice), *Glycyrrhiza uralensis* (gan cao), *Panaxginseng* (Asian ginseng), *Panax quinquefolium* (American ginseng), *Zizyphus jujuba* (jujube), and (ii) Steroid saponin (phytosterols) are *Aesculus hippocastanum* (horse chestnut), *Asparagusracemosa* (shatavari), *Commiphora mukul* (guggul), *Dioscorea villosa* (wild yam), *Hedera helix* (ivy), *Ononis spinosa* (spiny restharrow), *Ruscus aculeatus* (butcher's broom), *Smilax officinalis* (sarsparilla), *Withaniasomniferum* (ashwagandha), *Yucca*spp (Yucca). Some of the (i) tetracyclic triterpenoid spaonins (steroidal) are diosgenin, dioscin digitonin, gitonin (Dioscorea bark, seed, etc.), solasodine (Solanum berries), sarsapogenin (Asparagus roots) and

Table 3.6 Showing plant sources of triterpenoidal and steroidal saponins

Name of the compounds	Plant source	
	Common name	Botanical name
α-hederin	Black cumin	*Nigella sativa*
Araloside A	Spikenard	*Aralia mandshurica*
Astragaloside	Huang qi	*Astragalus membranaceus*
Bacoside A	Brahmi	*Bacopa monniera*
Cucurbitacin	Bryonia	*Bryonia alba*
Eleutheroside	Siberian ginseng	*Eleutherococcus senticosus*
Ginsenoside, panaxoside	Ginseng	*Panax ginseng*
Gymnemic acid	Gurmar	*Gymnema sylvestre*
Gypenoside	Jiaogulan	*Gynostemma pentaphyllum*
20-hydroxyecdysone	Maral root	*Rhaponticum carthamoides*
Tangshenoside I	Bellflower	*Codonopsis pilosula*
Tinosporoside	Guruchi	*Tinospora cordifolia*
Withanolide	Ashwagandha	*Withania somnifera*
Aescin	Horse chest nut	*Aesculus hippocastanum*
Glycyrrhizin	Liquorice root	*Glycyrrhiza glabra*
Senegins	Senega	*Polygala senega*
Sarsaponin (Parillin)	Sarsparilla	*Smilax* spp.
Digitonin	Seed	*Digitalis purpurea*, *D. lanata*
Gitonin	Seed and leaves	*D. purpurea*, *D. lanata*
Dioscin	Wild yam	*Dioscorea* spp.

(ii) pentacyclic triterpenoid saponins are gingenoside (Ginseng), glycyrrhizin (Licorice), senegin—II (Senega), quillaia (Quillaja) and sarsapogenin (Sarsaparilla) (Table 3.6).

Pharmaceutically important triterpenoid saponins possess antimicrobial, haemolytic, hypolipidemic, immunomodulating and cytotoxic activities. Steroidal saponins are of great pharmaceutical importance because of their relationship to compounds such as the sex hormones, cortisone, diuretic steroids, vitamin D and the cardiac glycosides. Some are used as starting materials for the synthesis of these compounds. Diosgenin is the principal sapogenin used by industry. Steroidal saponins (phytosterols) decrease cholesterol absorption from the gut, increase cholesterol excretion, and inhibit hepatic synthesis of cholesterol. All saponins tend to be immune modulating and have antineoplastic effects. Saponins of licorice root, (glycyrrhizin and aglycone glycyrrhetinic acid) are anti-inflammatory and antiviral, inhibit cortisol catabolism, and have many other effects. Saponins can cause gastrointestinal distress through an unknown mechanism. Taking them with food tends to eliminate the problem. Saponin-rich herbs (e.g., *Hedera helix*) are consumed orally to cause an increase in the production of mucus in the lungs, as well as

coughing and the effect can be helpful for patients with coughs of all sorts, especially dry cough.

Cardioactive drugs and other steroids

Drugs that influence heart or drugs having an influence on the heart are cardioactive drugs.

(i) Beta-adrenoceptor antagonists, (ii) Calcium channel blocking drugs and (iii) Cardiac glycosides are three major classes of cardioactive drugs.

Cardiac glycosides, a subgroup of cardioactive steroids (CAS) that also contain sugar residues, include a class of organic compounds, mostly secondary metabolites of plant origin, that increase the output force of the heart and decrease its rate of contractions by acting on the cellular sodium–potassium ATPase pump (Patel 2016). Cardioactive glycosides, like digoxin,digitalis, ouabain and related compounds, are drugs that inhibit Na(+)/K(+)-ATPase and have a strong inotropic effect on heart: they cause the Na(+)/Ca(2+) exchanger to extrude Na^+ in exchange with Ca(2+) and therefore increase the [Ca(2+)] concentration and some of these drugs are currently used in the treatment of congestive heart failure and cardiac arrhythmias (Riganti et al. 2011). In addition to inotropic activity, cardiac glycosidesare also important in the pathogenesis and therapy of different human diseases (e.g., stroke, diabetes, neurological diseases, cancer, etc.). Cardioactive steroids are a class of animal and plant-derived compounds with a steroid nucleus and a specific inotropic, chronotropic, and dromotropic effect.

Each molecule of this family consists of three distinct structural motifs such as (i) a steroid nucleus, (ii) a sugar moiety, and (iii) a lactone moiety (Fig. 3.64).

The sugar moiety defines the affinity for specific Na^+/K^+-ATPase isoforms and the lactone moiety defines the functional class of each compound.

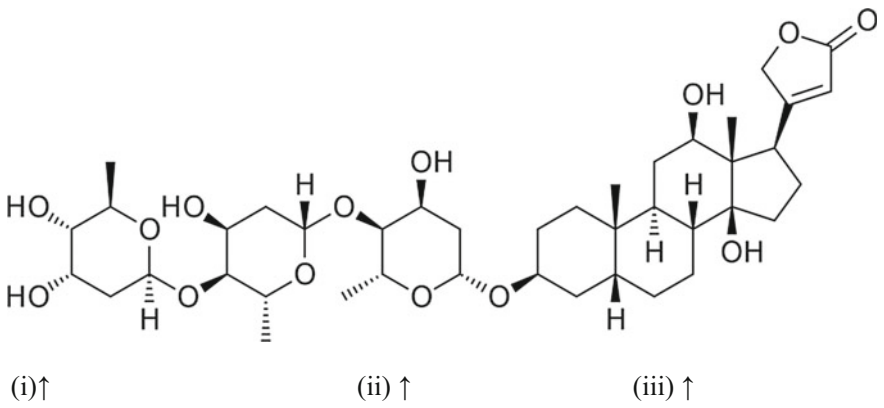


Fig. 3.64 (i) A sugar moiety (glycone), (ii) a steroid nucleus (aglycone genin), and (iii) a lactone moiety

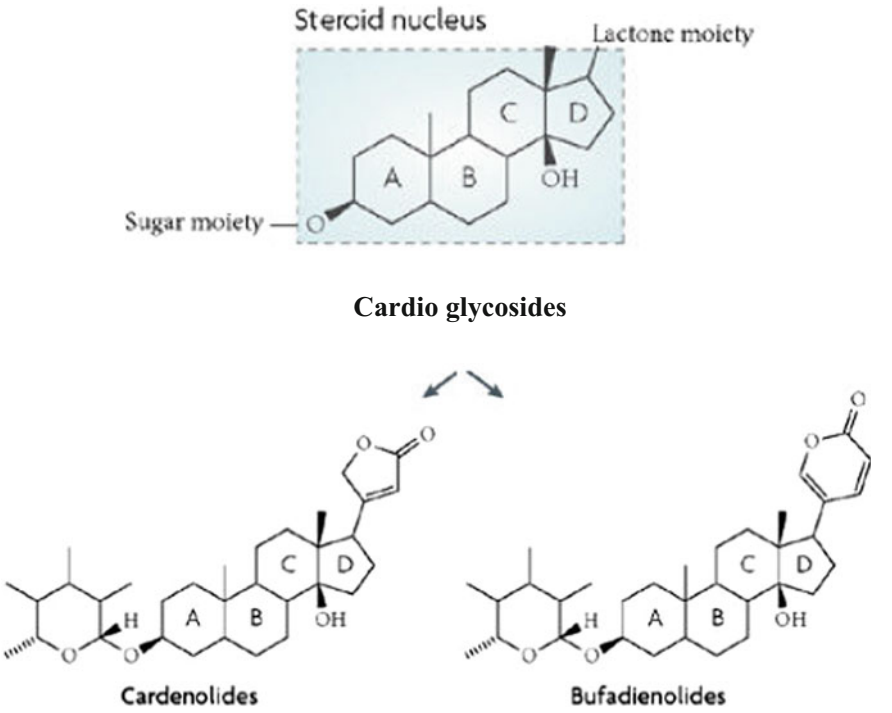


Fig. 3.65 Two groups of cardiac glycosides: a five-membered unsaturated butyrolactone ring—cardenolides and a six-membered unsaturated pyrone ring—bufadienolides

Cardenolides contain a five-membered unsaturated butyrolactone ring and bufadienolides contain a six-membered unsaturated pyrone ring (Fig. 3.65).

Cardioactive steroids (CAS) became the mainstay of treatment for congestive heart failure and to control the ventricular response rate in atrial tachydysrhythmias. The most commonly prescribed CAS in the United States is digoxin while digitoxin, ouabain, lanatoside C, deslanoside, and gitalin are other internationally available but much less commonly used preparations. The most common plant source of cardioactive steroid is *Digitalis lanata* (digoxin), which may be followed by *Digitalis purpura* (digitoxin), *Stropanthus kombe* (ouabian) and *Stropanthus gratus* (stropanthin). Other documented plant sources of CAS include oleander (*Nerium oleander*—oleandrin), yellow oleander (*Thevetia peruviana*—oleandrin), foxglove lily of the valley (*Convallaria majalis*—convallotoxin), dogbane (*Apocynum cannabinum*), milkweed (*Asclepias* sp.—oleandrin), kalanchoe plant (*Kalanchoe daigremontiana* and other *Kalanchoe* spp.—daigremontianin), motherwort (*Leonurus cardiac*—scillarenin) and red squill (*Urginea maritima*—proscillaridin A). Some of the most remarkable poisonings occur with exposures to

plants such as *Digitalis purpurea* and *Nerium oleander* containing CAS, dried toad secretions (bufadienolides) from *Bufo* spp.

3.9 Antibiotics from Higher Plants

Antibiotics are the chemical substances produced by microorganisms and they have the capacity, in low concentration, to inhibit microorganisms through an anti-metabolic mechanism. Antibiotics differ from antiseptics and disinfectants; they vary in their mode of action, chemical and physical properties; they are affected differently by the composition of the substrate in which they act, vary in their toxicity to animals, and, also in their chemotherapeutic potentialities. Antibiotics are produced alone or in mixture by different groups of microorganisms, e.g., bacteria, fungi and actinomycetes; and in many cases by higher plants. The development of resistance among the microorganisms on prolonged contact with the drug is the present-day problems in the field of antibiotics.

About 25–50% of pharmaceuticals are derived directly or indirectly from higher plants but none of them are used as antimicrobials. The traditional healers have been using higher plants or their extracts to prevent or cure infectious conditions. In in vitro analysis, plants extracts containing secondary metabolites like phenolics including phenolic acids (caffeic acid, catachol, chrysin), quinines (hypericin), flavones and flavonoids (catechin, chrysin), coumarins (warfarin, 7-hydroxycoumarin) and tannins (pentagallayl glucose, procyanidin B-2); terpenoids (menthol, artemisinin, capsaicin) and essential oil; alkaloids (berberine, harmane), lectins and polypeptides; polyacetylenes, etc., have been found to show antimicrobial and antiviral properties (Batista et al. 1994; Estevez-Braun et al. 1994; Fujioka and Kashiwada 1994; Pengsuparp et al. 1995; Haslam 1996; Ivanovska et al. 1996; Meyer et al. 1997; Omulokoli et al. 1997; Zhang and Lewis1997; Amaral et al. 1998; Cowan 1999; Alamgir et al. 2013). Structures of common antimicrobial plant chemicals are shown in the Fig. 3.66.

In vivo studies also support the results of many of these in vitro experiments (Cowan 1999). Mainstream medicine is increasingly accepting the use of antimicrobial drugs derived from higher plants because traditional antibiotics (antibiotics derived from microorganisms or synthesized derivatives) are become ineffective with time, and in addition, viral diseases remain intractable to this microbial drug. Cowan (1999), in a review article, mentioned more than 100 higher plants including *Achillea millefolium*, *Acorus calamus*, *Aegle marmelos*, *Agrostemma githago*, *Allium cepa*, *Allium sativum*, *Aloe barbadensis*, *Aloe vera*, *Aloysia triphylla*, *Anacardium pulsatilla*, *Anemone pulsatilla*, *Anethum graveolens*, *Arctium lappa*, *Armoracia rusticana*, *Arnica montana*, *Artemisia dracunculus*, *Barosma setulina*, *Berberis vulgaris*, *Calendula officinalis*, *Camellia sinensis*, *Cannabis sativa*, *Capsicum annuum*, *Carica papaya*, *Carum carvi*, *Cassia angustifolia*, *Centella*

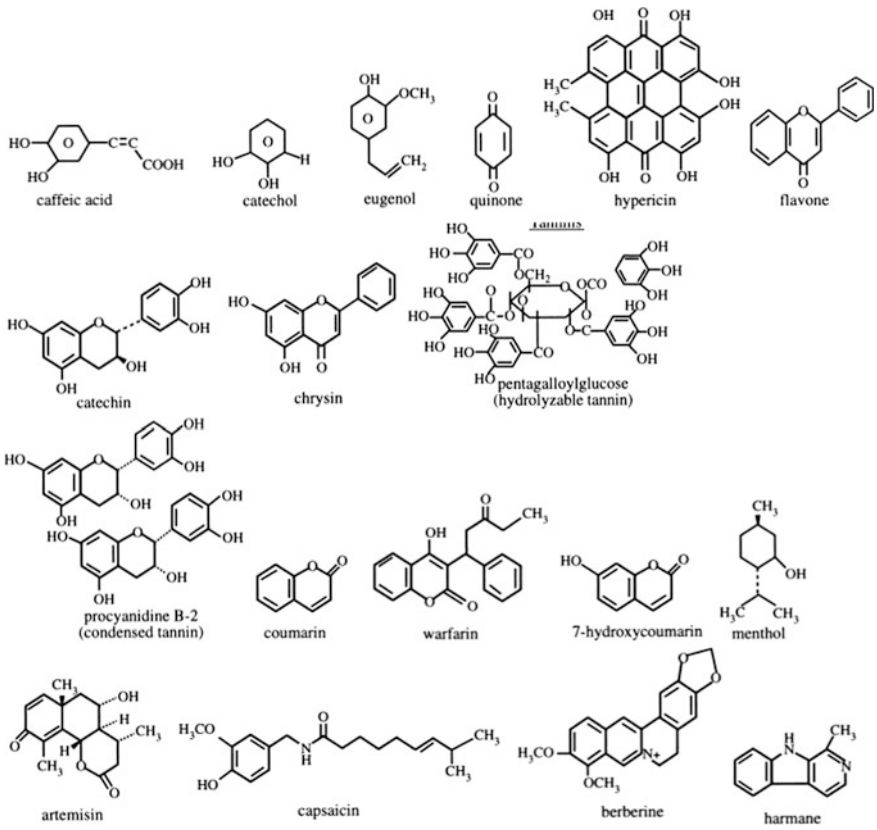


Fig. 3.66 Structure of some secondary metabolites from higher plants with antibiotic properties

asiatica, *Cinchona* sp., *Cinnamomum verum*, *Citrus paradisa*, *Citrus sinensis*, *Coriandrum sativum*, *Curcuma longa*, *Echinaceae angustifolia*, *Erythroxylum coca*, *Eucalyptus globulus*, *Euphorbia pulcherrima*, *Euphorbia tirucalli*, *Galium odoratum*, *Garcinia hanburyi*, *Gaultheria procumbens*, *Gloriosa superba*, *Glycyrrhiza glabra*, *Humulus lupulus*, *Hydrangea arborescens*, *Hydrastis canadensis*, *Hypericum perforatum*, *Hyssopus officinalis*, *Jatropha gossyphiifolia*, *Lantana camara*, *Larrea tridentata*, *Laurus nobilis*, *Lawsonia inermis*, *Lophophora williamsii*, *Mahonia aquifolium*, *Malus sylvestris*, *Matricaria chamomilla*, *Medicago sativa*, *Melissa officinalis*, *Mentha piperita*, *Millettia thonningii*, *Momordica charantia*, *Myristica fragrans*, *Ocimum basilicum*, *Olea europaea*, *Onobrychis viciifolia*, *Panax notoginseng*, *Papaver somniferum*, *Peganum harmala*, *Petalostemum*, *Pimenta dioica*, *Piper betel*, *Piper nigrum*, *Podocarpus nagi*, *Polygonum aviculare*, *Prosopis juliflora*, *Quercus rubra*, *Rabdosia trichocarpa*, *Ranunculus bulbosus*, *Rauvolfia serpentina*, *Rhamnus purshiana*, *Ricinus communis*, *Rivea corymbosa*, *Rosmarinus officinalis*, *Rumex crispus*, *Salix alba*,

Santolina chamaecyparissus, *Sassafras albidum*, *Satureja montana*, *Schinus terebinthifolius*, *Solanum tuberosum*, *Syzygium aromaticum*, *Tanacetum vulgare*, *Taraxacum officinale*, *Thevetia peruviana*, *Thymus vulgaris*, *Tussilago farfara*, *Vaccinium* spp., *Valeriana officinalis*, *Vicia faba Vinca minor*, *Withania somniferum*, etc., for their toxic, antibiotic, and antiviral properties.

3.10 Tumor Inhibitors, Antiprotozoal, Antihepatotoxic, Antihyperglycemic, Antihypertensive, etc., Herbal Products

Tumor inhibitors

For over 40 years, natural products have served us well in combating cancer. The main sources of these successful compounds are microbes and plants. The microbial and plant sources from the terrestrial and marine environments are now providing natural products with antitumor activity. The microbial products were first discovered as antibiotics and higher plant derivatives were the secondary metabolites like alkaloids, taxoids and podophyllotoxins.

Microorganisms produce antitumor compounds or their derivatives, e.g., actinomycetes produces of a large number of natural products with antitumor and antimicrobial activities. One of the earliest applications of a microbial product was actinomycin D for Wilm's tumor in children that had resulted in a 90% survival rate (Chung 2009). Some of the most useful antitumor compounds of microbial origin include aromatic polyketides (daunorubicin, doxorubicin, epirubicin, pirarubicin, idarubicin, valrubicin, amrubicin as we as enediynes calicheamycin, macrolide lactones epotihilones, ixebepilone); glycopeptides (bleomycin, phleomycin), non-ribosomal peptides (actinomycin D); anthracenones (mithramycin, streptozotocin, pentostatin); quinones (mitosanes mitomycin C); indolocarbazoles (glycosides rebeccamycin); nucleosides (2″-deoxycoformycin); halogenated compounds (salinosporamide A), etc. (Rawls 1998; Salas and Mendez 1998; Xue et al. 1999; Neumann et al. 2008) (Fig. 3.67).

Compounds with antitumor activity belong to several structural classes such as anthracyclines, enediynes, indolocarbazoles, isoprenoids, polyketide macrolides, non-ribosomal peptides including glycopeptides, and others. Most of the polyketides are produced by bacteria and fungi (Rawls 1998; Xue et al. 1999). Halogenated antitumor candidates include salinosporamide A and rebeccamycin (Neumann et al. 2008). The antitumor compounds act by several mechanisms such as inducing apoptosis through DNA cleavage mediated by topoisomerase I or II inhibition, mitochondrial permeabilization, inhibition of key enzymes involved in signal transduction (e.g., proteases), or cellular metabolism, and by inhibiting tumor-induced angiogenesis.

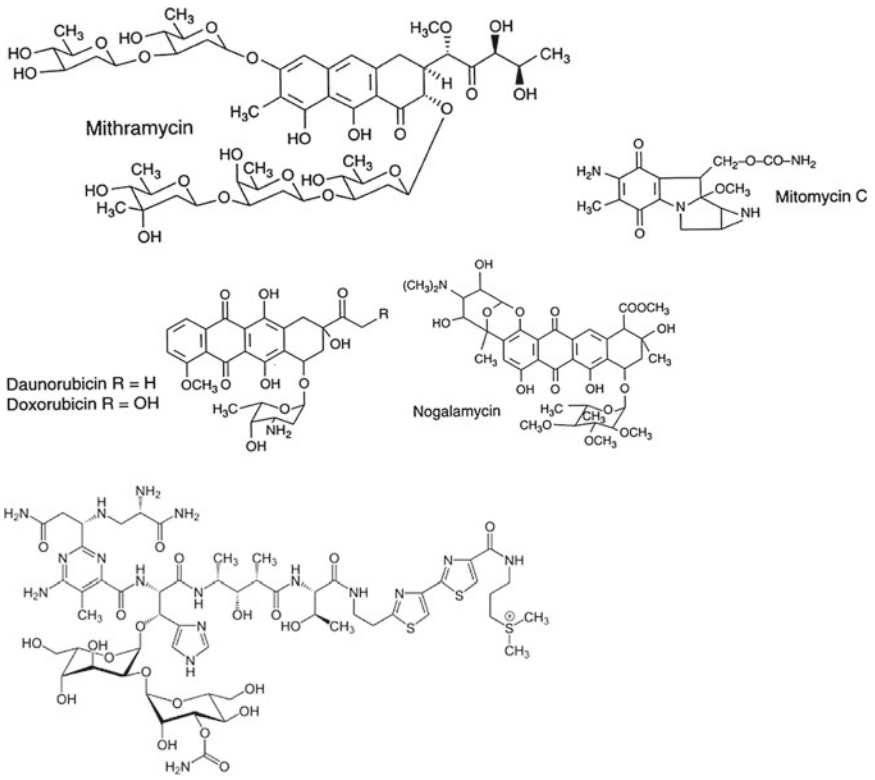


Fig. 3.67 Structures of some antitumor agents with clinical application

Plants have been a useful source of approved anticancer agents and vinblastine (velban), vincristine (oncovin), etoposide, teniposide, taxol (paclitaxel), navelbine (vinorelbine), taxotere (docetaxel), camptothecin (camptosar, campto), topotecan (hycamtin), irinotecan, etc., are some of the known land plant-derived antitumor

compounds (Dholwani et al. 2008). Antitumor compounds monoterpene indole alkaloids vinblastine and vincristine are derived from *Catharanthus roseus*, and now vinblastine is commonly used to treat Hodgkin's lymphoma. Serpentines produced by *C. roseus* have shown promise as anticancer agents and a wide range of halogenated alkaloids with antitumor activity are known (Duflos et al. 2000). Taxol is derived from *Taxus chinensis*, podophyllotoxin, an antimitotic metabolite of the roots of *Podophyllum peltatum*, etc., are antitumor agents. Cell culture products of the plant *Lithospermum erythrorhizon*, naphthoquinone pigment shikonin and two derivatives, were found to inhibit tumor growth in mice bearing Lewis Lung Carcinoma (Lee et al. 2008). Isoflavone genistine, indole-3-carbinol (I3C), 3,3′-diindolemethane, curcumin (−)-epigallocatechin-3-gallate, resveratrol, lycopene, etc., are other plant-derived products that inhibit the growth of cancer cells (Sarker et al. 2009).

Allicin from *Allium sativum*; 14 compounds including flavonoids and labdane diterpenoids from *Andrographis paniculata*; acetogenins from *Annona muricata*; polyacetylenes, flavonoids, terpenoids, phenylpropanoids, etc., from *Bidens pilosa*; a triterpenoid saponin Tubeimoside-V chinese herb *Bolbostemma paniculatum*; components of marijuana from *Cannabis sativa*; mezerein compound from *Daphne mezereum*; seed oil of *Gossypium hirustum*; Petroleum ether and ethyl acetate extracts of *Nervilia fordii*; tanshinone-I and IIA from *Salvia miltiorrhizae*; chebulinic acid, tannic acid, ellagic acid from *Terminalia chebula*; 6-gigerol from *Zingiber officinale*; a protein from honeybee *Apis mellifera*, etc., are considered to have a potential to inhibit the growth of cancer cells or chemotherapeutic potential (Dholwani et al. 2008; Bhutani and Gohil 2010; Poonam and Chandana 2015).

A list of anticancer plants with their active principles is available (Bhutani and Gohil 2010). It includes *Agapanthus africanus* (isoliquiritigenin-chalcone); *Aglaila sylvestre* (silvesterol); *Ailanthus altissima* (ailnthone, ailantenol—quassinoids); *Apium graveolens* (apigenin—flavonoid); *Bleckeria vitensis* (ellipticine—alkaloid); *Brucea antidysenterica* (bruceantin—quassinoid); *Bursera microphylla* (burseran—lignan); *Campotheca acuminate* (campothecin—alkaloid); *Catharanthus roseus* (vincristine, vinblastine—alkaloid); *Centaurea montata* (montamine—alkaloid); *Centaurea schischkinii* (schischkinnin—alkaloid); *Cephalotaxus harringtonia* (homoharringtonine—alkaloid); *Cleistanthus collinus* (cleistanthin, collinusin—lignan); *Combretum caffrum* (combrestatins—stilbenes); *Croton lechleri* (taspine—alkaloid), *Daphne mezereum* (mezerein); *Diphylleia grayi* (diphyllin—lignan); *Dysoxylum binectariferum* (rohitukine—alkaloid); *Erythroxylum pervillei* (pervilleine—alkaloid); *Euphorbia semiperfoliata* (jatrophane—terpenoid); *Fritillaria thunbergii* (zhebeinone—alkaloid); *Gunnera perpensa* [{2-methyl-6(3-methyl 2-butenyl)}-quinone benzo 1–4 quinone]; *Hypericum perforatum* (hypericin—anthraquinone); *Hypoxis colchicifolia* (hypoxoside, rooperol—glycoside); *Indigofera tinctoria* (indirubins—indigoids); *Justicia procumbens* (justicidin A, B-lignan); *Lantana camara* (verbascoside—glucoside); *Larrea tridentate* (terameprocol—lignan); *Linium album* (podophyllotoxin—lignan); *Lonicera japonica* (luteolin—

flavonoid); *Paris polyphilla* (polyphyllin—saponin); *Pestemon deustus* (liriodendrin—lignan); *Phaleria macrocarpa* (pinoresinol, laricinesinol—lignan); *Podophyllum emodi* (epipodophyllotoxin—alkaloid); *Polygonum cuspidatum* (resveratrol—flavonoid); *Pteris multifida* (pterokaurane—terpenoid); *Pygeum africanum* (amygdalin—glycoside); *Vitex rotundifolia* (casticin—flavonoid); *Wikstroemia viridi* (wikstromol—caumarin).

Botanicals could possess effective anticancer compounds that may be used as adjuvants to existing chemotherapy to improve efficacy and/or reduce drug-induced toxicity. Herbal medicines, such as ginseng, potentiated the effects of chemotherapeutic agents via synergistic activities, supported by cell cycle evaluations, apoptotic observations, and computer-based docking analysis (Wang et al. 2012). Some natural compounds including plants induce apoptotic pathways that are blocked in cancer cells through various mechanisms in cancer cells. Multiple surveys reported that people with cancer commonly use herbs or herbal products.Vinca alkaloids, texans, podophyllotoxin, camptothecins, colchicine, ellipticine, lepachol, flavopiridol, colchicine, ellipticine, etoposide, rohitukine, etc., have been clinically used as plant-derived anticancer agents (Mukherjee et al. 2001; Safarzadeh et al. 2014).

Marine microorganisms such as coral reefs, mangroves and sea grass, have been targeted for bioprospecting because they host a high level of biodiversity. Marine sponge produce numerous bioactive compounds with promising anticancer properties, e.g., cytarabine (cytostar) used for non-Hodgkin's lymphoma was originally derived from a sponge (Rayl 1999). Other marine products with antitumor activity are pederin, theopederins, annamides, trabectedin (yondelis), aplidine, ecteinascidin 743 (ET743), etc.

Natural compounds appear to act by interference in multiple cellular signaling pathways, activating cell death signals, and bringing on apoptosis of cancer cells without negatively affecting normal cells. The antitumor agents induce apoptosis (programmed cell death) through DNA cleavage mediated by topoisomerase I or II inhibition; they may also induce mitochondrial permeabilization, inhibition of key enzymes involved in signal transduction (e.g., proteases), or cellular metabolism, inhibition of tumor-induced angiogenesis. Tumor cells secrete growth factors and trigger angiogenesis that allow tumor cells to obtain oxygen and nutrients, vascular endothelial growth factor (VEGF) is involved in angiogenesis and it could be a target for antiangiogenic drugs (Cao and Langer 2008). Fumagillin, product of *Aspergillus fumigatis*, its oxidation product ovalacin and the fumagillin analog TNP470 were antiangiogenesis compound.

Antiprotozoal medicinal plants

Protozoa are microscopic, eukaryotic one-celled animals and antiprotozoal principles are a class of pharmaceuticals used in treatment of protozoan infection. Antiprotozoal traditional medicinal plants, among others, include *Artemisia roxburghiana*, *Roylea cinerea*, *Leucas cephalotes*, *Nepeta hindostana*, *Viola canescens*, etc.; antiprotozoal principles of traditional medicinal plants include

bisbenzylisoquinoline, protoberberine, indole alkaloids, sesquiterpenes, quassinoids, limonoids, etc., and they destroy protozoa or inhibit their growth and ability to reproduce. Antiprotozoal principles effective against one pathogen may not be effective against another because protozoans are very much dissimilar and have little in common with each other. Examples of some of the protozoa of medical importance include Plasmodium (cause malaria); Entamoeba histolytica (cause amebiasis, amebic dysentery), Trichomonas vaginalis (cause vaginal infection); Pneumocystis carinii (cause pneumonia), etc.; and antiprotozoal drugs antimalarials aralen (chloroquine), daraprim (pyrimethamine), lariam (mefloquine), plaquenil (hydroxychloroquine), flagyl (metronidazole), mepron (atovaquone), etc. Antiprotozoal drugs that are used to treat protozoal infections like amebiasis, giardiasis, cryptosporidiosis, microsporidiosis, malaria, babesiosis, trypanosomiasis, chaga's disease, leishmaniasis, toxoplasmosis, pneumocystis carinii pneumonia (PCP), African sleeping sickness, etc. (Khaw and Panosian 1995), but many of the treatments for these infections are limited by their toxicity (Graebin et al. 2009).

Protozoal diseases are a major threat to human and domestic animals and several antiprotozoal synthetic drugs have developed in this century, e.g., quinolines, diaminopyrimidines and triazenes (for malaria and toxoplasmosis); organometallic drugs and diamidines (for trypanosomiasis and leishmaniasis); 5 nitroimidazoles (for amoebiasis, giardiasis and trichomoniasis); and hydroxy-naphthoquinones (for theileriosis and malaria) (Croft 1997). Natural products have also made an important impact, e.g., quinine had been extensively used in malaria therapy since its discovery in 1820 from Cinchona bark, and now artemisinin of *Artemisia annua* is considered to be the most promising lead among the new antimalarial drugs. Similarly, emetine had been used in the treatment of amoebiasis since its discovery from the rhizome of *Cephaelis ipecacuanha* in 1828, but it has now been replaced by its derivative dehydroemetine.

Wild garlic, eucalyptus, thyme, etc., are some of the major plants which can annihilate the giarda cysts (Azadbakht and Azadbakht 2008). Ipecac, mango, papaya, etc., are some of the anti-amebic plants while myrtle, lavender, etc., are effective against *Trichomonas vaginalis*. Extracts of *Artemisia roxburghiana*, *Roylea cinerea*, *Leucas cephalotes*, *Nepeta hindostana* and *Viola canescens* possess good antiprotozoal activity (IC50 < 5 μg/ml) without any cytotoxicity against the protozoal parasites like *Plasmodium falciparum*; *Trypanosoma brucei rhodesiense*; *Leishmania donovani*; *Trypanosoma cruzi* (Dua et al. 2011). Extracts from preparations of Salvia, Valeriana, Hypericum, Silybum, Arnica, and Curcuma exhibited high activity (IC50 < 2.5 μg/mL) against parasites of the genera Leishmania, Trypanosoma, and Plasmodium (Llurba Montesino et al. 2015).

Antihepatotoxic herbal products

Liver plays major role in regulation of metabolism, storage, detoxification, and excretion of xenobiotics and liver injury may happen due to various toxic chemicals, e.g., antibiotic, chemotherapeutic agents, high doses of paracetamol, antitubercular drugs, carbon tetrachloride—CCl_4, thioacetamide—TAA,

dimethylnitrosamine (DMN), D-galactosamine—GalN, lipopolysaccharide—LPS, excessive alcohol consumption, etc., and pathogen microbes. Chronic liver diseases like liver cirrhosis, viral hepatitis B and C, alcoholic liver disease, nonalcoholic fatty liver disease, and hepatocellular carcinoma represent a major health burden worldwide. Currently available therapies for liver ailments are not apposite and systemic toxicity inhibits their long-term use. The synthetic drugs available in the market to treat liver disorders in this condition also cause further damage to the liver and, under the circumstances; antihepatotoxic herbal products have become increasingly popular. Herbal products that prevent or cure the damage of liver and provide strength and stimulant for the functioning of liver are called antihepatotoxic (i.e., hepatoprotective) herbal products and medicinal plants have been traditionally used for treating liver diseases since antiquity as the toxicity factor appears to be on the lower side.

Hepatoprotective effects of different plants, their fruits, and plant products such as natural resin, main polysaccharides present in the cellular wall of yeasts, algae, and cereals are known; they are effective against different toxic compounds that cause hepatic damage; the principal mechanisms of action are their antioxidant potential (Madrigal-Santillán et al. 2014). Herbs containing such principles are antihepatotoxic herbs and they are claimed to restore bile flow and reduced total bilirubin and biliverdin concentration. They inhibit the increase in triglyceride, cholesterol, and total lipids in liver. Thus these plants can be used for the treatment of jaundice and hepatic failure. The hepatoprotective herbal agents generally have strong antioxidative potential and cause induction of antioxidant enzymes like superoxide dismutase, reduced glutathione and catalase; and other mechanisms of hepatoprotection may include stimulation of heme oxygenase-1 activity, inhibition of nitric oxide production, hepatocyte apoptosis and nuclear factor-κB activation.

Plant tissues contain a wide variety of secondary metabolic compounds such as phenolic compounds (flavonoids and phenolic acids), nitrogen compounds (alkaloids, chlorophyll derivatives, amino acids and amines), carotenoids, lignans, terpenes, etc., with antioxidant, hydrogen or electron donation, metal ion chelation, tumor inhibition properties, (Rice-Evans et al. 1996; Levy et al. 2004; Hall and Cuppett 1997). Phytoconstituents with different structure isolated from different plant species including flavonoids, alkaloids, glycosides and saponins obtained from various plant sources have been reported as potent hepatoprotective agents (Flora et al. 1996, 1998).

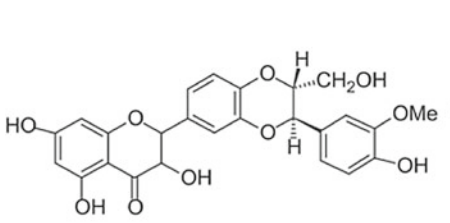
About 300 plants have been reported so far possessing antihepatotoxic activity. Hepatoprotective natural products in this category include *Abelmoschus moschatus*, *Acacia concina*, *Achillea millefolium*, *Aconitum heterophyllum*, *Adiantum capillus*, *Aegle marmelos*, *Alpinia galanga*, *Andrographis paniculata*, *Annona squamosa*, *Azadirachta indica*, *Cassia occidentalis*, *Cassia roxburghii*, *Chamomile capitula*, *Cinnamomum camphora*, *Coccinia grandis*, *Crocus sativus*, *Curcuma longa*, *Eclipta alba*, *Emblica officinalis*, *Ficus carica*, *Flacourtia indica*, *Foeniculum vulgare*, *Garcinia mangostana Gentiana chirata*, *Gymnema sylvestre*, *Indigofera*

Table 3.7 Active compounds with source plant, hepatoprotective functions, and references

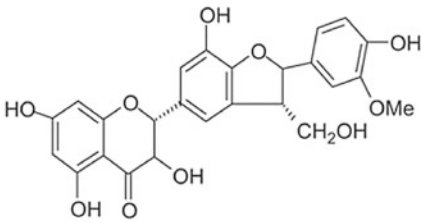
Name of the compounds	Source plant	Portection against	References
Asiaticoside	*Centella asiatica*	Lipopolysaccharide (LPS)/D-galactosamine-induced	Zhang et al. (2010)
Cleomiscosins	*Cleome viscosa*	CCl_4-induced; thioacetamide-induced	Gupta and Dixit (2009)
Puerarin	*Pueraria lobata*	CCl_4-induced	Hwang et al. (2007)
Celosin A (1) and celosin B (2)	*Semen celosiae*	CCl_4-induced	Sun et al. (2010) and Xue et al. (2010)
α- and β-amyrin	*Protium heptaphyllum*	Paracetamol-induced	Oliveira et al. (2005)
Rubiadin	*Rubia cordifolia*	CCl_4-induced	Rao et al. (2006)
Dehydrocavidine	*Corydalis saxicola*	CCl_4-induced	Wang et al. (2008)
Wedelolactone	*Eclipta alba*	CCl_4-induced	Singh et al. (2001)
Cichotyboside	*Cichorium intybus*	CCl_4-induced	Ahmed et al. (2008)

tinctoria, *Jatropha curcas*, *Lepidium sativum*, *Mimusops elengi*, *Morinda citrifolia*, *Mucuna pruriens*, *Myristica fragrans*, *Nigella sativa*, *Orthosiphon stamineus*, *Phyllanthus emblica*, *Picrorhiza kurroa*, *Pinus roxburghii*, *Piper cubeba*, *Plumbago zeylanica*, *Prostechea michuacana*, *Rauwolfia serpentina*, *Saraca asoca*, *Sargassum polycystum*, *Saussurea lappa*, *Solanum nigrum*, *Swertia chirata*, *Semecarpus anacardium*, *Silybum marianum*, *Solanum indicum*, *Strychnos nux-vomica*, *Swertia chirata*, *Symplocos racemosa*, *Tribulus terrestris*, *Trigonella foenum-graecum*, *Vetiveria zizanoides*, *Wedelia calendulacea*, *Woodfordia fruticosa*, *Zingiber officinalis*, *Ziziphus jujuba*, etc. A summary note on active compounds, source plant, hepatoprotective functions and references is shown in Table 3.7.

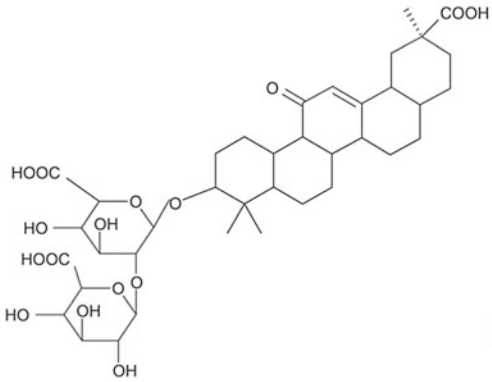
Ghosh et al. (2011) noted plant sources as potential hepatoprotective agents for silymarin, andrographolide, neoandrographolide, curcumin, picroside, kutkoside, phyllanthin, hypophyllanthin, glycyrrhizin, etc. The hepatoprotective potential of several these herbal medicines has been clinically evaluated and among which significant efficacy has been found with silymarin, glycyrrhizin and Liv-52 in treatment of hepatitis, alcoholic liver disease and liver cirrhosis. Structure of some these hepatoprotective compounds are now available (Fig. 3.68). For example, silymarin component, a complex mixture of four flavonolignan: silybin; silychristin from *Silybum marianum*; glycyrrhizin, a triterpenoid saponin from *Glycyrrhiza glabra*; andrographolide, a labdane diterpene lactone and also neoandrographolide from *Andrographis paniculata*; picroside 1, an iridoid glycosides as well as kutkoside 1,10-vanilloylcatalpol from *Picrorhiza kurroa*; curcumin, a phenolic



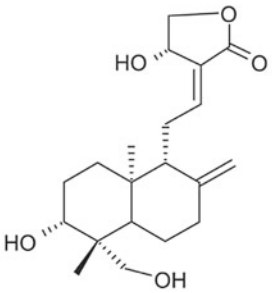
Silybin



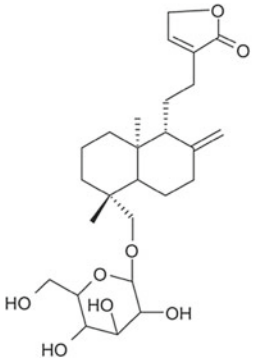
Silychristin



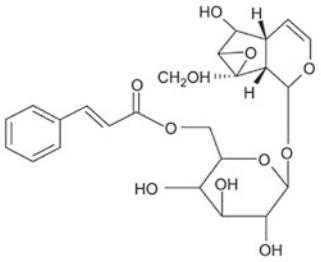
Glycyrrhizin



Andrographolide

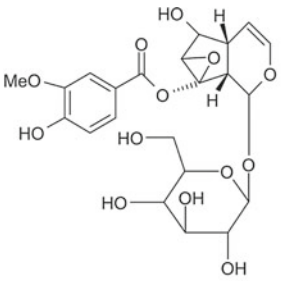


Neoandrographolide

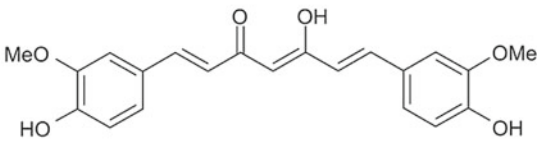


Picroside 1

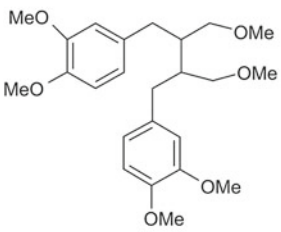
Fig. 3.68 Structure of some the hepatoprotective compounds



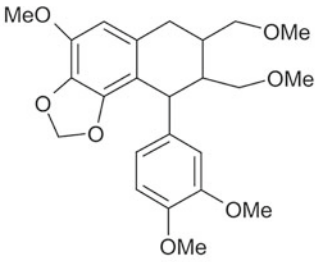
Kutkoside 1, 10-vanilloylcatalpol



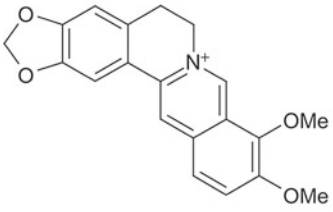
Curcumin



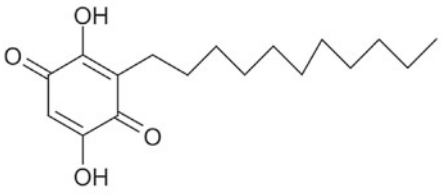
Phyllanthin



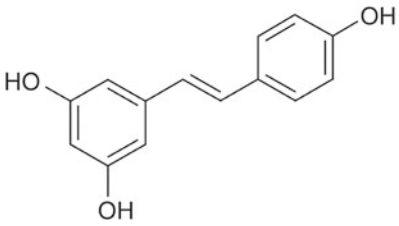
Hypophyllanthin



Berberine

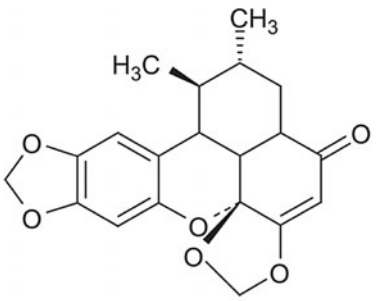


Embelin

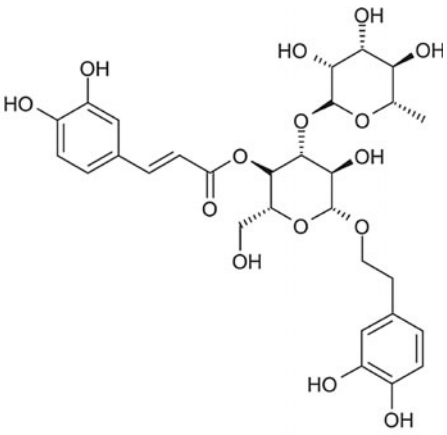


Resveratrol

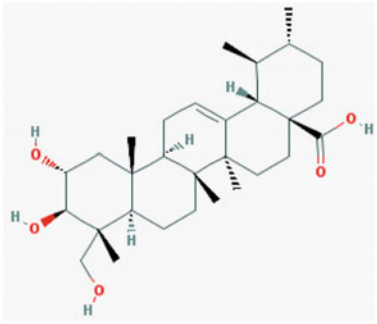
Fig. 3.68 (continued)



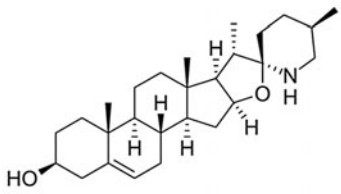
Acteoside



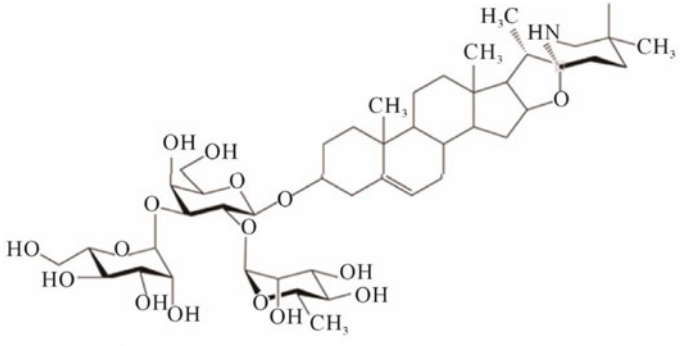
Sauchinone



Asiatic acid (AA)

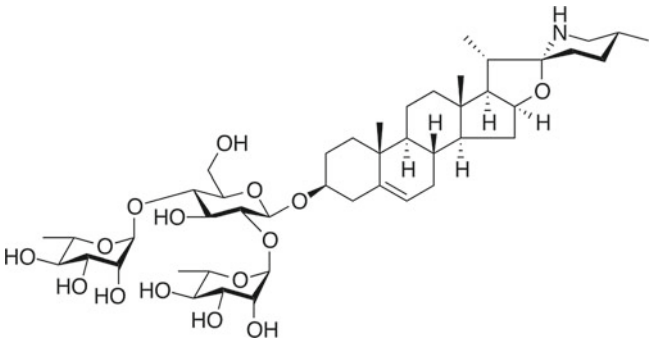


Solasodine



Solasonine

Fig. 3.68 (continued)



Solamargine

Fig. 3.68 (continued)

compound from *Curcuma longa*; phyllanthin and hypophyllanthin, lignans obtained from *Phyllanthus niruri*; berberine alkaloid obtained from *Berberis aristata*; embelin, 2,5-dihydroxy-3-undecyl-1,4-benzoquinone from *Embelia ribes*; resveratrol, a polyphenol (a phytoalexin) present in many plants and fruits, including red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, etc.; acteoside, a phenylethanoid glycoside obtained from *Cistanche tubulosa* and *Syringa vulgaris*; Sauchinone, a diastereomeric lignan from *Saururus chinensis*; asiatic acid (AA), a triterpenoid components of *Terminalia catappa*; Solasodine, a glycoalkaloid derived from the steroidal alkaloid, occurs in plants of the Solanaceae family. Solasonine and solamargine are glycoalkaloid derivatives of solasodine. Solamargine, a glycoalkaloid derived from the steroidal alkaloid solasodine from *Solanum nigrum* and other Solanaceae members such as potatoes, tomatoes, and eggplants.

Antidiabetic (hypoglycemic) herbal products

Diabetes mellitus (DM) has been recognized since antiquity and currently it affects as many as 285 million people worldwide and results in heavy personal and national economic burdens (Cicero et al. 2013). DM is a dreadful lifestyle related metabolic disorder of twenty-first century caused by insufficient or inefficient insulin secretion or insulin physiological unresponsiveness and characterized by increased blood glucose levels (hyperglycemia). Three key defects, e.g., increased hepatic glucose production, diminished insulin secretion, and impaired insulin action cause the onset of hyperglycemia in DM while in DM treatment; efforts are made to diabetes by improving insulin sensitivity, increasing insulin production and/or decreasing the amount of glucose in blood. *Ginseng*, *bitter melon*, *fenugreek*, *banaba*, *Gymnema sylvestre*, *Coptis chinensis*, etc., are most popular hypoglycemic herbs. These herbs act by increasing insulin secretion, enhancing glucose uptake by adipose and skeletal muscle tissues, inhibiting intestinal glucose absorption and inhibiting hepatic glucose production (Prabhakar and Doble 2011).

Conventional drugs treat diabetes by improving insulin sensitivity, increasing insulin production and/or decreasing the amount of glucose in blood. Several herbal preparations (hypoglycemic herbs) such as ginseng, bitter melon and *Coptis chinensis*. Several popular commercially available herbal preparations are also discussed, including ADHF (anti-diabetes herbal formulation), Jiangtangkeli, YGD (Yerbe Mate–Guarana–Damiana) and BN (Byakko-ka-ninjin-to). The efficacy of hypoglycemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from hepatocytes.

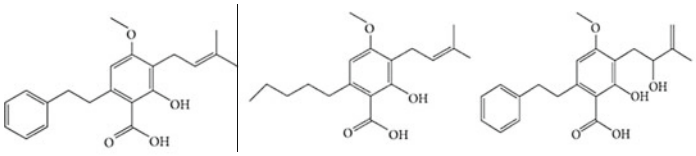
Myrcia Enicostemma littorale, *Biophytum sensitivum*, *Ipomoea batatas*, *Tithonia diversifolia*, *Tithonia diversifolia*, Sangzhi, *Galega officinalis*, *Fenugreek leaves*, *Pterocarpus marsupium*, *Artemisia scoparia*, *Gymnema sylvestre*, Daio (Rhei rhizoma), *Lupinus termis*, *Tea*, *Coccinia indica leaves*, *Clausena anisata*, *Hovenia dulcis*, *Aloes*, *Green Tea*, *Holy Basil*, *Gymnema*, *Fenugreek*, *Licorice*, *Sunflower*, *Ginseng*, *Garlic*, *Turmeric*, *Dandelion*, *Bilberry*, *Parsley*, *Sarsaparilla*, *Gentian Root* and *Olive Leaf. Ashwaghanda*, *Baical*, *Skullcap*, *Camu-Camu*, *Chamomile*, *Damiana*, *Ginseng*, *Gotu Kola*, *Hops*, *Kanna*, *Kava*, *Lavender*, *Linden*, *Liquorice*, *Milk Thistle*, *Motherwort*, *Oats*, *Parsnip*, *Passion Flower*, *Pumpkin*, *Rhodiola*, *Schisandra*, *StJohn'sWort*, *Siberian*, *Ginseng*, *Skullcap*, *Sweet Tea Vine*, *Valerian*, *Vervain*, *Yohimbe.*

Different types of medicinal herbs can be classified based on their modes of action such as insulin resistance (type 1 herbs),—cell function (type 2 herbs), and GLP-1 (type 3 herbs) and glucose (re)absorption (type 4 herbs). (b) The selected plants and compounds exert their antihyperglycemic effect through targeting one single mechanism (insulin resistance (type 1 herbs),—cell function (type 2 herbs), GLP-1 (type 3 herbs), or glucose (re)absorption (type 4 herbs)) or multiple mechanisms.

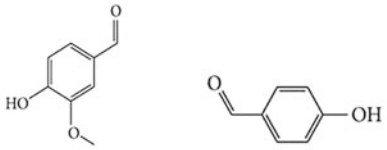
Medicinal herbs contain diverse bioactive compounds and can have multiple actions on insulin action, insulin production, or both. Some plant chemicals with the ability to control blood glucose are shown in Fig. 3.69. These antidiabetic plant chemicals include amorfrutin 1–3 from *Glycyrrhiza uralensis* and vanillin 4-hydroxybenzaldehyde from *G. elata* to regulate insulin resistance; cinnamaldehyde from *Cinnamon* spp.; and diosgenin from *Trigonella foenum-graecum*. Serotonin derivatives, butyl-isobutyl-phthalate, and berberine regulate glucose absorption in the guts while momordicin, capsaicin, and curcumin regulate two or more pathways (lower blood glucose due to their insulin-like chemical structures); regulation of insulin resistance and probably β cells. Ginsenosides and turmerin regulate two or more pathways (regulate β-cell function, improvement of insulin resistance).

Antihypertensive herbal products

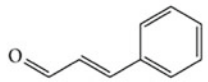
Hypertension is defined as having a systolic blood pressure (SBP) of ≥ 140 mmHg and a diastolic blood pressure (DBP) of ≥ 90 mmHg ($\geq 140/\geq 90$ mmHg). Every 20/10 (SBP/DBP) mmHg increase indicates a higher risk stage of hypertension:



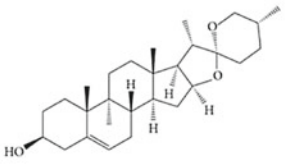
Amorfrutin 1-3



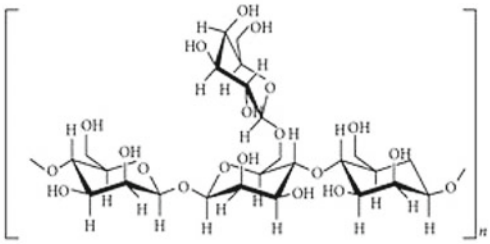
Vanillin 4-hydroxybenzaldehyde



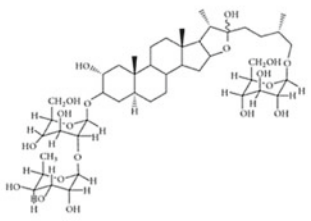
Cinnamaldehyde



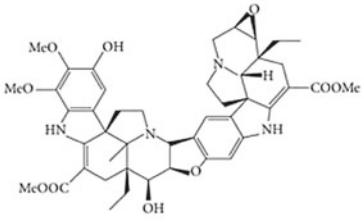
Diosgenin



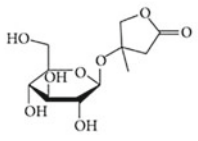
Galactomannan



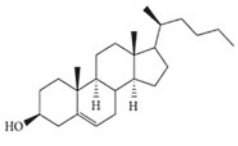
Trigoneoside Xa



Conophylline

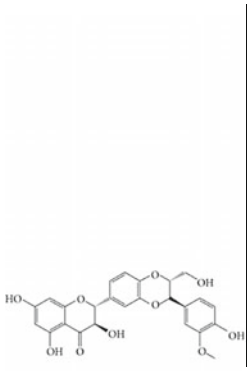


Kinsenoside

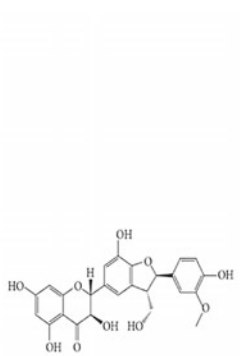


Nymphayol

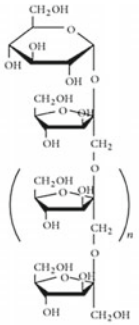
Fig. 3.69 Structure of some antidiabetic (hypoglycemic) herbal principles



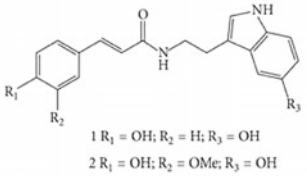
Silybin



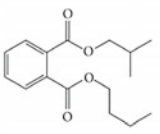
Silychristin



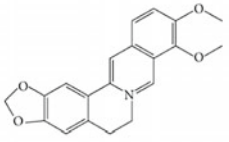
Inulin (dietary fiber)



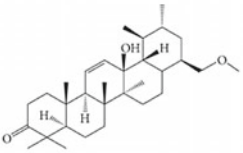
Serotonin derivatives



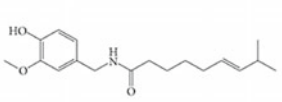
Butyl-isobutyl-phthalate



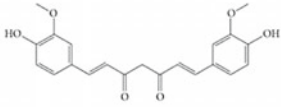
Berberine



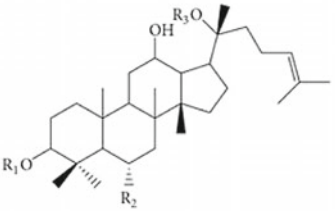
Momordicin



Capsaicin



Curcumin



Ginsenosides	R_1	R_2	R_3
Rb1	Glc-^{2}Glc	H	Glc-^{6}Glc
Rb2	Glc-^{2}Glc	H	Ara(pyr)-^{6}Glc
Rc	Glc-^{2}Glc	H	Ara(fur)-^{6}Glc
Rd	Glc-^{2}Glc	H	Glc-
Re	H	Rha-^{2}Glc-O-	Glc-
Rf	H	Glc-^{2}Glc-O-	H
Rg1	H	Glc-O-	Glc-

Ginsenosides

Fig. 3.69 (continued)

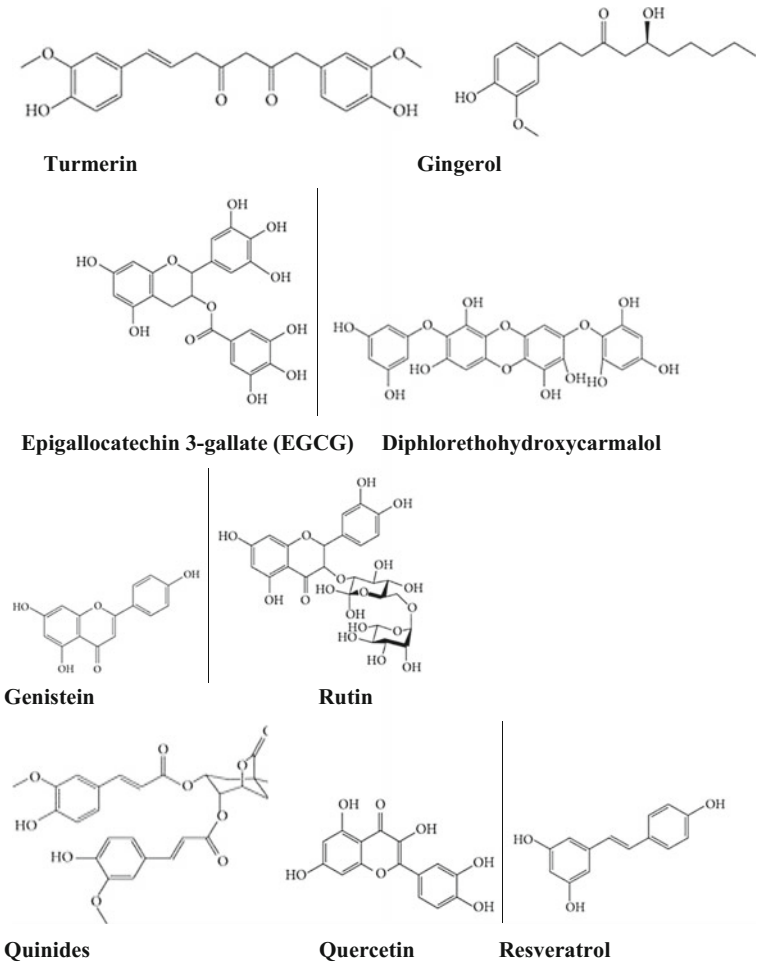


Fig. 3.69 (continued)

stage 1 (140–159/90–99 mmHg), stage 2 ($\geq$160/$\geq$100 mmHg). The American Society of Hypertension and the International Society of Hypertension (ISH) recommend that individuals with blood pressure of 120–139/80–89 mmHg be considered as pre-hypertensives (Weber et al. 2014). Hypertension (HTN) has several subclassifications including, HTN stage I, HTN stage II, and isolated systolic HTN. Isolated systolic HTN refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. Hypertension is by far the most prevalent trigger for cardiovascular diseases (CVDs) than other (diabetes, smoking, dyslipidemia, etc.); hypertension is responsible for around 16.5% of annual deaths worldwide and by 2030, the annual death toll is estimated to reach 23.5 million

people (WHO 2013). HTN besides increasing the risk of heart disease and stroke, HTN can also lead to other conditions such as congestive heart failure, atherosclerosis, peripheral artery disease, coronary artery disease, kidney damage, dementia, and blindness (August 2004; Freedman and Cohen 2016).

Drugs like diuretics (indapamide, furosemide, amiloride), sympathoplegic agents (clonidine, reserpine), renin inhibitor (aliskiren), angiotensin converting enzymes (ACE) inhibitors (enalapril, captopril, quinapril),—losartan, irbesartan, olmesartan), calcium channel blockers (nifedipine, verapamil, diltiazem), α-adrenergic blockers (prazosin, doxazosin), β-adrenergic blockers (nebivolol, atenolol), vasodilators (minoxidil, sodium nitroprusside), etc., are used to manage blood pressure levels in hypertensive patients (Archer 2000; Susalit et al. 2011). Sesquiterpene is the most active dandelion compound which provides the natural remedy with its beneficial diuretic properties. Parsley is rich in beneficial phytochemicals like carotene, lutein, potassium as well as a wide variety of vitamins and minerals. Like most of the other natural diuretics, parsley also works in eliminating water retention by increasing urination through inhibiting the potassium and ion pumps. Celery (*Apium graveolens*) seeds and flavored leaves (contain COX-2 inhibitors, vitamin C, potassium, etc.) are very useful as diuretic in the management of blood pressure.

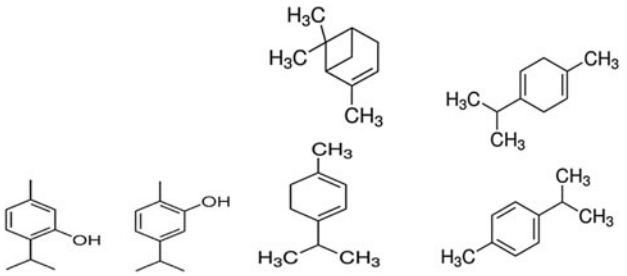
A large number of hypertensive population of the world use herbal medicines because of their low cost, better acceptability and lesser side effects. *Achillea wilhelmsii*, *Allium cepa*, *Allium sativum* (allicin), *Anethum graveolens*, *Apium graveolens*, *Avena sativa*, *Berberis vulgaris*, *Centaurea depressa*, *Cichorium intybus*, *Crataegus* sp., *Hypericum perforatum*, *Laurocerasus officinalis*, *Matricaria recutita*, *Nigella sativa*, *Panax quinquefolius*, *Passiflora edulis*, *Rumex acetosella*, *Viscum album*, *Ziziphus zizyphus*, etc., are some of the commonly used anti-hypersive medicinal plants. Other plants used as hypotensive agents are *Agathosma betulina* (diureic and anti-inflammatory), *Annona muricata*, *Apium graveolens*, *Aristolochia manshuriensis* (aristolochic acid, aristoloside, magnoflorine, oleanolic acid, hederagenin, and tannins. magnoflorine has been found to possess hypotensive properties), *Artocarpus altilis*, *Avena sativa* (soluble fiber), *Blond psyllium*, *Camellia sinensis*, *Capparis cartilaginea*, *Carum copticum*, *Cassia absus*, *Cassia occidentalis*, *Castanospermum australe* (saponin fraction and medicogenic acid glucoside), *Coleus forskohlii*, *Commelina virginica*, *Crataegus pinnatifida*, *Crinum glaucum*, *Cuscuta reflexa*, *Daucus carota*, *Desmodium styracifolium*, *Fuchsia magellanica*, *Glycine max*, *Gossypium barbadense*, *Hibiscus sabdariffa*, *Lavandula stoechas*, *Lepidium latifolium*, *Linum usitatissimum*, *Lumnitzera racemosa*, *Lycopersicon esculentum*, *Moringa oleifera*, *Musanga cecropiodes*, *Ocimum basilicum*, *Peganum harmala*, *Phyllanthus amarus*, *Pinus pinaster*, *Pueraria lobata*, *Punica granatum*, *Raphanus sativus*, *Rauvolfia serpentina*, *Rhaptopetalum coriaceum*, *Sesamum indicum*, *Solanum sisymbriifolium*, *Theobroma cacao*, *Triticum aestivum*, *Uncaria rhynchophylla*, *Urtica dioica*, *Viscum album*, *Vitex doniana*, *Zingiber officinale*, etc.

Secondary metabolites of herbs and spices exhibit antihypertensive effects. Commonly used antihypertensive plants with antioxidant activity are *Allium sativum* (garlic's hypotensive effects are based on garlic's organosulfur constituents

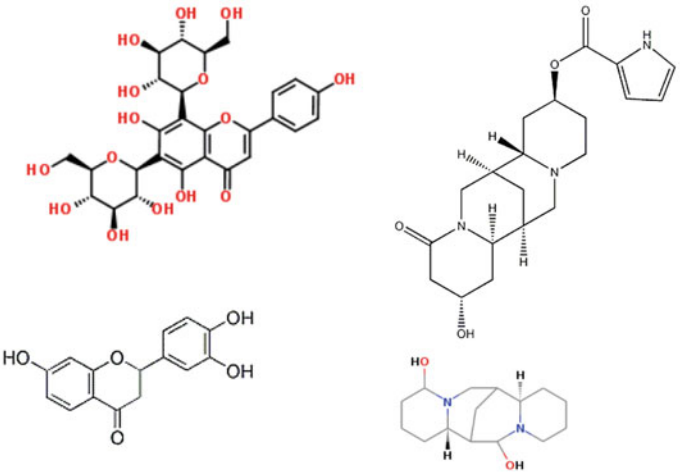
such as Allicin, and methyl thiosulfonate); *Andrographis paniculata* (several hypotensive labdane-type diterpenoid compounds include andrographolide, 14-deoxy-11,12-didehydroandrographolide and 14-deoxyandrographolide); *Apium graveolens* (Apigenin, a flavone isolate of *A. graveolens*); *Camellia sinensis* (catechins, the major flavonoids in tea, include (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epigallocatechin-3-gallate); *Coptis chinensis* (main component Berberine (BBR); *Coriandrum sativum*, *Crataegus* spp. (antihypertensive actions are credited to the plant's multiple components: flavonoids—hyperoside, quercetin, rutin, and vitexin, and oligomeric proanthocyanidins—OPCs, epicatechin, procyanidin, and procyanidin B-2); *Crocus sativus* (main components include crocin, picrocrocin, safranal, and crocetin); *Hibiscus sabdariffa*; *Panax* (heterogeneous triterpenoid saponins and steroid glycosides or ginsenosides or panaxosides are the active principle components); *Salviae miltiorrhizae* (most effective components include salvianolic acid A—SalA, salvianolic acid B—SalB, danshensu, and tanshinones); *Zingiber officinale* (6-gingerol and 6-shogaol); *Apium graveolens*, *Bidens pilosa*, *Cymbopogon citratus* (antihypertensive principle citral), *Nigella sativa* (thymoquinone—TQ as abundant bioactive component of seed); *Rauvolfia serpentina* (reserpine alkaloids). Figure 3.70 shows the structure of some antihipertensive (hypotensive) herbal principles.

Reserpine, an alkaloid found in the roots of *Rauwolfia serpentina* and *R. vomitoria*. Reserpine inhibits the uptake of norepinephrine into storage vesicles resulting in depletion of catecholamines and serotonin from central and peripheral axon terminals. It has been used as an antihypertensive and an antipsychotic as well as a research tool, but its adverse effects limit its clinical use.

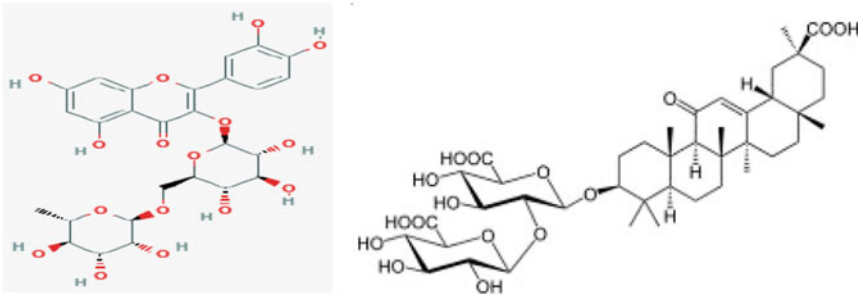
Commonly used antihypertensive plants possess vasorelaxant, anti-inflammatory, antiproliferative, diuretic, etc., activities. The mechanisms of action of antihypertensive herbal preparations are based on their function as antioxidant, diuretic agent, ROS scavenger, increases the bioavailability of endogenous signaling gases like NO and H_2S, inhibition of Angiotensin Converting Enzyme (ACE), decrease ACE and ROS activities, attenuation of NAPDH oxidase production, flow-mediated dilation (FMD), increase the antioxidant enzyme—SOD, decrease formation of endothelial microparticles (EMPs), prevent MI by inhibiting myofibrillar damage, up-regulate antioxidant enzymes (SOD, CAT) and augment the concentration of the reducing glutathione -GSH; regulation of voltage operated calcium channels (VOCCs), vasorelaxant pathways, inhibit cardiac hypertrophy and decrease heart rates, increase secretion of urea, calcium, sodium, and potassium in urine, etc.



Thymol Carvacrol α-Pinene α-Terpiene p-Cymene γ-Terpinene



Digittine 4β 13α-dihydroxylupanine, quinolizidine alkaloids (the flavonoids vicenin-2, butin, 3'-hydroxydaidzein, etc.)



Rutin **Glycyrrhizin**

Fig. 3.70 Structure of some antihipertensive (hypotensive) herbal principles

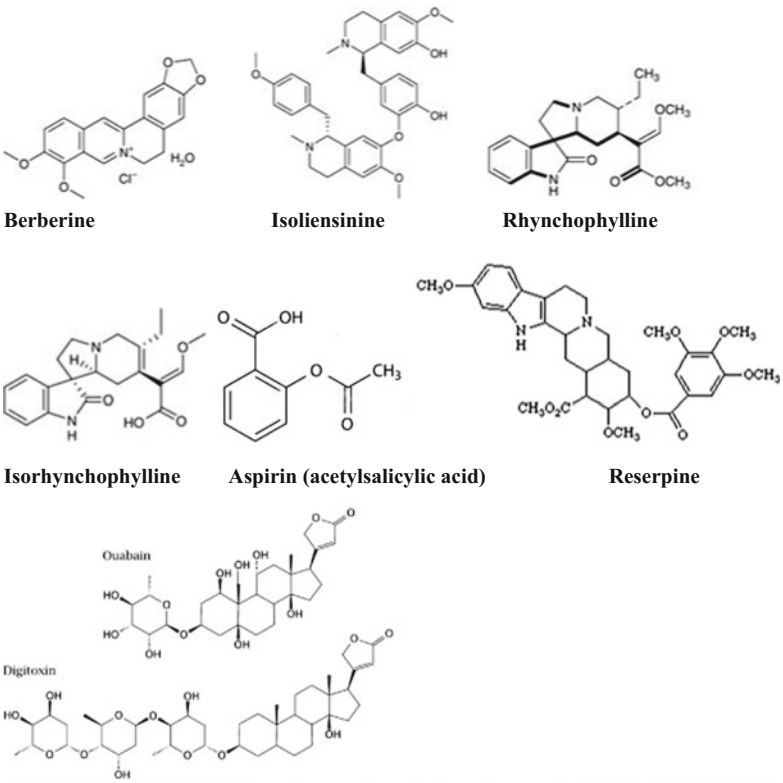


Fig. 3.70 (continued)

3.11 Sources, Chemistry, and Health Effects of the Bioactive Compounds of Secondary Metabolic Origin; Biotechnology of Bioactive Compounds

Bioactive compounds of secondary metabolic origin belonging to several groups of phenolics, terpenes and terpenoids, alkaloids, glycosides, etc., exhibit important health effects and play a central role in high-value pharmaceutical product development in the pharmaceutical industry. Bioactive compounds have been identified from diverse sources and their therapeutic benefits, nutritional value and protective effects in human and animal healthcare have underpinned their application as pharmaceuticals and functional food ingredients. The orderly study of biologically active products and the exploration of potential biological activities of these secondary metabolites, including their clinical applications, standardization, quality control, mode of action and potential biomolecular interactions, have emerged as one of the most exciting developments in modern natural medicine.

Biotechnology of bioactive compounds describes the current stage of knowledge on the production of bioactive compounds from microbial, algal and vegetable

sources. In addition, the molecular approach for screening bioactive compounds is also important, as well as examples of applications of these compounds on human health. The bioactive compounds profiled include compounds such as C-phycocyanins, glycosides, phytosterols and natural steroids. Importance of the usage of bioactive compounds as antioxidants and anti-inflammatory agents, anti-allergic compounds and in stem cell research, and also the medicinal applications of plant-derived compounds deserve special attention.

References

Ahmed B, Khan S, Masood MH, Siddique AH (2008) Anti-hepatotoxic activity of cichotyboside, a sesquiterpene glycoside from the seeds of *Cichorium intybus*. J Asian Nat Prod Res 10:223–231

Alamgir ANM, Rahman M, Rahman A (2013) Phytochemical characteristics, antimitotic, cytotoxic and antitumor activities of bark extract of Streblus asper Lour. Bangladesh J Bot 42(1):17–22

Amaral JA, Ekins A, Richards SR, Knowles R (1998) Effect of selected monoterpenes on methane oxidation, denitrification, and aerobic metabolism by bacteria in pure culture. Appl Environ Microbiol 64:520–525

Archer JS (2000) Evaluation and treatment of hypertension. Prim Care Update Ob Gyns 7:1–6

August P (2004) Overview: mechanisms of hypertension: cells, hormones, and the kidney. J Am Soc Nephrol 15:1971–1973

Azadbakht M, Azadbakht M (2008) Five prevalent antiprotozoal herbal drugs. J Mazandaran Univ Med Sci 18(67):118–132

Bastida J, Lavilla R, Viladomat F (2006) Chemical and biological aspects of Narcissus alkaloids. In: Cordell GA (ed) The Alkaloids, 63:87–179. Elsevier Inc.

Batista O, Duarte A, Nascimento J, Simones MF (1994) Structure and antimicrobial activity of diterpenes from the roots of *Plectranthus hereroensis*. J Nat Prod 57:858–861

Bhutani KK, Gohil VM (2010) Natural product drug discovery research in India: status & appraisal. Indian J Exp Biol 48:199–207

Bishayee A, Bhatia D, Thoppil RJ, Darvesh SA, Nevo E, Lansky EP (2011) Pomegranate-mediated chemoprevention of experimental hepatocarcinogenesis involves Nrf2-regulated antioxidant mechanisms. Carcinogenesis 32:888–896

Buckingham J (2004) Dictionary of natural products, web version 2004. Chapman and Hall, London. Available at: http://www.chemnetbase.com

Cao Y, Langer R (2008) A review of Judah Folkman's remarkable achievements in biomedicine. PNAS 105:13203–13205

Chang CLT, Lin Y, Bartolome AP, Chen Y-C et al (2013) Herbal therapies for type 2 diabetes mellitus: chemistry, biology, and potential application of selected plants and compounds. Evid Based Complement Alternat Med 2013:33. Article ID 378657

Chung KT (2009) H. Boyd Woodruff (b. 1917): antibiotics hunter and distinguished soil microbiologist. SIM News 59:178–185

Cowan MM (1999) Plant products as antimicrobial agents. Clin Microbiol Rev 12(4):564–582

Croft SL (1997) The current status of antiparasite chemotherapy. Parasitology 114:3–15

Crowell PL (1999) Prevention and therapy of cancer by dietary monoterpenes. J Nutr 129 (3):775S–778S

Davey MP, Bryant DN, Cummins I, Gates P, Ashenden TW, Baxter R et al (2004) Effects of elevated CO_2 on the vasculature and phenolic secondary metabolism of Plantago maritima. Phytochemistry 65:2197–2204

Dholwani KK, Saluja AK, Gupta AR, Shah DR (2008) A review on plant-derived natural products and their analogs with antitumor activity. Indian J Pharmacol 40(2):49–58

Downey RK (2003) Mustard. In: Katz SH and Weaver WW, Encyclopedia of Food and Culture. Gale virtual reference library. New York: Scribner. ISBN 0684314169

Dua VK, Verma G, Agarwal DD, Kaiser M, Brun R (2011) Antiprotozoal activities of traditional medicinal plants from the Garhwal region of North West Himalaya. Indian J Ethnopharmacol 136(1):123–128

Duflos A, Fahy J, Thillaye du Boullay V, Barret JM, Hill B (2000) Vinca alkaloid antimitotic halogenated derivatives. US Patent 6127377

Ebada SS, Lin WH, Proksch P (2010) Bioactive sesterterpenes and triterpenes from marine sponges: occurrence and pharmacological significance. Mar Drugs 8(2):313–346

Estevez-Braun A, Estevez-Reyes R, Moujir LM, Ravelo AG, Gonzalez AG (1994) Antibiotic activity and absolute configuration of 8*S*-heptadeca-2(*Z*),9(*Z*)-diene-4,6-diyne-1,8-diol from *Bupleurum salicifolium*. J Nat Prod 57:1178–1182

Flora KD, Rosen HR, Benner KG (1996) The use of naturopathic remedies for chronic liver disease. Am J Gastroenterol 91:2654–2655

Flora K, Hahn M, Rosen H, Benner K (1998) Milk thistle (*Silybum marianum*) for the therapy of liver disease. Am J Gastroenterol 93:139–143

Freedman BI, Cohen AH (2016) Hypertension-attributed nephropathy: what's in a name? Nat Rev Nephrol 12(1):27–36

Fujioka T, Kashiwada Y (1994) Anti-AIDS agents. 11. Betulinic acid and platanic acid as anti-HIV principles from *Syzigium claviflorum*, and the anti-HIV activity of structurally related triterpenoids. J Nat Prod 57:243–247

Ghosh N, Ghosh R, Mandal V, Mandal SC (2011) Recent advances in herbal medicine for treatment of liver diseases. Pharm Biol 49:970–988

Gould MN (1997) Cancer chemoprevention and therapy by monoterpenes. Environ Health Perspect 105:977–979

Graebin C, Uchoa F, Bernardes L, Campo V, Carvalho I, Eifler-Lima V (2009) Antiprotozoal agents: an overview. AntiInfect Agents Med Chem 8(4):345–366

Gupta NK, Dixit VK (2009) Evaluation of hepatoprotective activity of *Cleome viscosa* Linn. extract. Indian J Pharmacol 41:36–40

Hall CA, Cuppett SL (1997) Structure-activities of natural antioxidants. In: Auroma OI, Cuppett SL (eds) Antioxidant methodology in vivo and in vitro concepts. AOCS Press, Champaign, IL, pp 141–172

Haslam E (1996) Natural polyphenols (vegetable tannins) as drugs: possible modes of action. J Nat Prod 59:205–215

Herbst ST (2001) The new food lover's companion: comprehensive definitions of nearly 6000 food, drink, and culinary terms. Barron's cooking guide. Barron's educational series, Hauppauge, NY. ISBN 0764112589

Hwang YP, Choi CY, Chung YC, Jeon SS, Jeong HG (2007) Protective effects of puerarin on carbon tetrachloride-induced hepatotoxicity. Arch Pharm Res 30:1309–1317

Ivanovska N, Philipov S, Istatkova R, Georgieva P (1996) Antimicrobial and immunological activity of ethanol extracts and fractions from *Isopyrum thalictroides*. J Ethnopharmacol 54:143–151

Kaushik U, Aeri V, Mir SR (2015) Cucurbitacins—an insight into medicinal leads from nature. Pharmacogn Rev 9:12–18

Khaw M, Panosian CB (1995) Human antiprotozoal therapy: past, present, and future. Clin Microbiol Rev 8(3):427–439

Kim W, Seong KM, Youn B (2011) Phenylpropanoids in radioregulation: double edged sword. Exp Mol Med 43(6):323–333

Lee HJ, Lee HJ, Magesh V, Nam D, Lee EO, Ahn KS et al (2008) Shikonin, acetylshikonin, and isobutyroylshikonin inhibit VEGF-induced angiogenesis and suppress tumor growth in Lewis lung carcinoma-bearing mice. Yakugaku Zasshi 128:1681–1688

Levy C, Seeff LD, Lindor KD (2004) Use of herbal supplements for chronic liver disease. Clin Gastroenterol Hepatol 2:947–956

Liby K, Royce DB, Williams CR, Risingsong R, Yore MM, Honda T et al (2007) The synthetic triterpenoids CDDOmethyl ester and CDDO-ethyl amide prevent lung cancer induced by vinyl carbamate in A/J mice. Cancer Res 67:2414–2419

Liu ZJ (2011) Next generation sequencing and whole genome selection in aquaculture. Wiley-Blackwell

Llurba Montesino N, Kaiser M, Brun R, Schmidt TJ (2015) Search for antiprotozoal activity in herbal medicinal preparations; new natural leads against neglected tropical diseases. Molecules 20(8):14118–141138

Madrigal-Santillán E, Madrigal-Bujaidar E, Álvarez-González I, Sumaya-Martínez MT, Gutiérrez-Salinas J, Bautista M et al (2014) Review of natural products with hepatoprotective effects. World J Gastroenterol 20(40):14787–14804

Meyer JJM, Afolayan AJ, Taylor MB, Erasmus D (1997) Antiviral activity of galangin from the aerial parts of *Helichrysum aureonitens*. J Ethnopharmacol 56:165–169

Mukherjee AK, Basu S, Sarkar N, Ghosh AC (2001) Advances in cancer therapy with plant based natural products. Curr Med Chem 8:1467–1486

Neumann CS, Fujimori DG, Walsh CT (2008) Halogenation strategies in natural product biosynthesis. Chem Biol 15:99–109

Nobre HV Jr, Maia FD, de Oliveiraa RA, Bandeira MAM, do Ó Pessoa C, Moraesa MO et al (2007) Neuroprotective actions of tannins from myracrodruon urundeuva on 6-hydroxydopamine-induced neuronal cell death. J Herbs Spices Med Plants 13(2):41–57

Oliveira FA, Chaves MH, Almeida FR, Lima RC Jr, Silva RM, Maia JL et al (2005) Protective effect of alpha- and beta-amyrin, a triterpene mixture from *Protium heptaphyllum* (Aubl.) March. trunk wood resin, against acetaminophen-induced liver injury in mice. J Ethnopharmacol 98:103–108

Omulokoli E, Khan B, Chhabra SC (1997) Antiplasmodial activity of four Kenyan medicinal plants. J Ethnopharmacol 56:133–137

Patel S (2016) Plant-derived cardiac glycosides: role in heart ailments and cancer management. Biomed Pharmacother 84:1036–1041

Pengsuparp T, Cai L, Constant H, Fong HH, Lin Z, Kinghorn AD et al (1995) Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. J Nat Prod 58:1024–1031

Petronelli A, Pannitteri G, Testa U (2009) Triterpenoids as new promising anticancer drugs. Anticancer Drugs 20:880–892

Poonam S, Chandana M (2015) A review on anticancer natural drugs. Int J Pharm Tech Res 8(7):131–141

Prabhakar PK, Doble M (2011) Mechanism of action of natural products used in the treatment of diabetes mellitus. Chin J Integr Med 17(8):563–574

Rabi T, Gupta S (2008) Dietary terpenoids and prostate cancer chemoprevention. Front Biosci 13:3457–3469

Raffauf RF (1996) Plant alkaloids. A Guide to their discovery and distribution. The Haworth Press, New York

Rao GM, Rao CV, Pushpangadan P, Shirwaikar A (2006) Hepatoprotective effects of rubiadin, a major constituent of *Rubia cordifolia* Linn. J Ethnopharmacol 103:484–490

Rawls RL (1998) Modular enzymes. Chem Eng News 76:29–32

Rayl AJS (1999) Oceans: medicine chests of the future? Scientist 13:1

Rice-Evans CA, Miller NJ, Paganga G (1996) Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 20:933–956

Riganti C, Campia I, Kopecka J, Gazzano E, Doublier S, Aldieri E et al (2011) Pleotropic effects of cardiovascular glycosides. Curr Med Chem 18(6):872–885

Safarzadeh E, Sandoghchian S, Baradaran B (2014) Herbal medicine as inducers of apoptosis in cancer treatment. Adv Pharm Bull 4:421–427

Salas JA, Mendez C (1998) Genetic manipulation of antitumor-agent biosynthesis to produce novel drugs. Trends Biotechnol 16:475–482

Sarker D, Reid AH, Yap TA, de Bono JS (2009) Targeting the PI3K/AKT pathway for the treatment of prostate cancer. Clin Cancer Res 15:4799–4805

Setzer WN, Setzer MC (2003) Plant-derived triterpenoids as potential antineoplastic agents. Mini Rev Med Chem 3:540–556

Singh B, Saxena AK, Chandan BK, Agarwal SG, Anand KK (2001) In vivo hepatoprotective activity of active fraction from ethanolic extract of *Eclipta alba* leaves. Indian J Physiol Pharmacol 45:435–441

Souza SMC, Aquino LC, Milach AC Jr, Bandeira MA, Nobre ME, Viana GS et al (2006) Antiinflammatory and antiulcer properties of tannins from Myracrodruon urundeuva Allemão (Anacardiaceae) in Rodents. Phytother Res 21(3):220–225

Sun ZL, Wang Y, Guo ML, Li YX (2010) Two new hepaprotective saponins from *Semen celosiae*. Fitoterapia 81:375–380

Susalit E, Agus N, Effendi I, Tjandrawinata RR, Nofiarny D, Perrinjaquet-Moccetti T et al (2011) Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril. Phytomedicine 18:251–258

Vincken JP, Heng L, Groot A, Gruppen H (2007) Saponins, classification and occurrence in the plant kingdom. Phytochem 68(3):275–297

Wagner KH, Elmadfa I (2003) Biological relevance of terpenoids. Overview focusing on mono-, di- and tetraterpenes. Ann Nutr Metab 47(3–4):95–106

Wang T, Sun NL, Zhang WD, Li HL, Lu GC, Yuan BJ et al (2008) Protective effects of dehydrocavidine on carbon tetrachloride-induced acute hepatotoxicity in rats. J Ethnopharmacol 117:300–308

Wang CZ, Calway T, Yuan CS (2012) Herbal medicines as adjuvants for cancer therapeutics. Am J Chin Med 40:657–669

Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG et al (2014) Clinical practice guidelines for the management of hypertension in the community a statement by the American society of hypertension and the international society of hypertension. J Hypertens 32:3–15

WHO (2013) Cardiovascular diseases (CVDs). World Health Organization, Geneva. Fact sheet no 317

Xue J, Duda L-C, Smith KE, Fedorov AV, Johnson PD, Hulbert SL et al (1999) Electronic structure near the Fermi surface in the quasi-one-dimensional conductor $Li_{0.9}Mo_6O_{17}$. Phys Rev Lett 83:1235–1238

Xue Q, Sun ZL, Guo ML, Wang Y, Zhang G and Wang XK (2010) Two new compounds from Semen celosiae and their protective effects against CCl(4)-induced hepatotoxicity. Nat Prod Res 1–8

Zhang Y, Lewis K (1997) Fabatins: new antimicrobial plant peptides. FEMS Microbiol Lett 149:59–64

Zhang L, Li HZ, Gong X, Luo FL, Wang B, Hu N et al (2010) Protective effects of Asiaticoside on acute liver injury induced by lipopolysaccharide/D-galactosamine in mice. Phytomedicine 17:811–819