Bioactive Substances of Plant Origin

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Contents

Abstract

Plant secondary metabolites are rich sources of bioactive compounds eliciting many beneficial health effects in man and animals. Plant-based foods, including vegetables, fruits, grains, seeds, nuts, and legumes, may contain hundreds of different phytochemicals. Recently, research on phytochemicals suggests their possibility as an important source of therapeutic and preventive agents against diseases. The types of foods containing these bioactive components are those

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functional foods that can provide desirable health benefits beyond their natural properties when consumed in a regular and consistent manner through diet. Alternatively, dietary supplements can be supplied to consumers in a concentrated form to deliver a specific bioactive phytochemical or a group of phytochemicals. Usually, these nutraceutical ingredients are administered with higher doses than in normal food or in a medicinal form with the purpose of improving human health. This chapter highlights the four most common groups of plant-derived bioactive components, polyphenols, alkaloids, terpenes, and saponins, mainly focusing on their chemistry, sources, and biological functions.

Introduction

Secondary metabolites are chemical compounds produced within the plants that are not directly involved in the normal growth, development, or reproduction of an organism. Some of them are found to act as defense compounds against diseases, predators, ultraviolet radiation, parasites, and oxidants, to facilitate the reproductive processes (e.g., serve as attractive smells and coloring agents), and for interspecies competition. Bioactive compounds of plant origin are those secondary metabolites possessing desired health/wellness benefit effects in man and animals (Kaur and Das 2011). Consistent evidence from epidemiological, in vitro, in vivo, and clinical studies has demonstrated that a diet rich in plant foods can reduce the risk of some degenerative diseases, such as diabetes, obesity, cardiovascular complications, and cancer. As an example, research studies have shown that about 20–50 % of all cases of cancer can be prevented by the plant-based diets (Glade 1999). Thus, dietary recommendations have always emphasized the consumption of various plant foods to reduce the risk of cancer and other chronic diseases.

With the development of analytical techniques such as gas chromatography (GC), high-performance liquid chromatography (HPLC), mass spectrometry (MS), and nuclear magnetic resonance spectrometry (NMR), the isolation, purification, and structure determination of single compound from plant extracts have become available. These advanced techniques help us to identify a wide range of biologically active compounds, now known as "phytochemicals." These phytochemicals including polyphenols, alkaloids, terpenes, saponins, etc. have been widely used in nutraceuticals as ingredients to provide a health benefit beyond basic nutrition. However, there are some studies suggesting that the potent biological functions could be assumed to be due to the synergistic and/or additive effects of phytochemicals and nutrients present in the plant foods rather than the purified chemicals themselves.

This chapter highlights the chemistry, sources, and biological functions of the four most common groups of phytochemicals including polyphenols, alkaloids, terpenes, and saponins. Also, the commercial nutraceuticals rich in the supplements are briefly introduced.

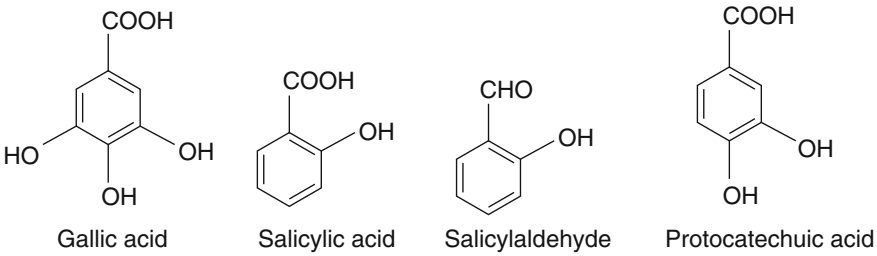


Fig. 1 Chemical structures of hydroxybenzoic acids

Polyphenols

Polyphenols, a class of chemical compounds consisting of one or more hydroxyl groups (−OH) attached directly to an aromatic ring, are the most abundant secondary metabolites distributed in all vascular plants. They are important natural phytochemical compounds that play an important role in the taste, color, and nutritional properties of plant-based foods, such as vegetables, fruits, cereal, whole grains, coffee, tea, legumes, cocoa, and wine. Due to their abundance in the human diet, tremendous investigations have been conducted among nutritionists and food scientists to study the health effects of dietary polyphenols, including simple phenolics, coumarins, lignans, flavonoids, isoflavonoids, anthocyanins, tannins, quinines, and stilbenes in recent years. Increasing evidence indicates that polyphenols have several benefits on humans such as potent antioxidant properties, prevention of various diseases induced by oxidative stress, and prevention of particularly cardiovascular diseases, neurodegenerative diseases, and cancers (Bravo 1998). The health effects of polyphenols depend on the type of polyphenols, the amount consumed, and their bioavailability.

Simple Phenolics

Phenol, with one hydroxyl group (−OH) attached directly to an aromatic ring, is the simplest phenolic. Simple phenolics are substituted phenols (C_6C_n) possessing a singly substituted phenolic ring with carboxylic acid, alcoholic, or aldehydic groups. Phenolic acids, a class of chemical compounds possessing one carboxyl group attached to the benzene ring, have been studied extensively recently because of their potential protective role. Phenolic acids can be divided into two categories, benzoic acid derivatives (i.e., hydroxybenzoic acids) (Fig. 1) and cinnamic acid derivatives (i.e., hydroxycinnamic acids) (Fig. 2), based on the constitutive carbon frameworks.

The hydroxybenzoic acid (C6-C1 derivatives) (e.g., gallic acid, salicylic acid, salicylaldehyde, and protocatechuic acid) (Fig. 1) content is generally very low in edible plants, except for some red fruits. Hydroxybenzoic acids occur in high

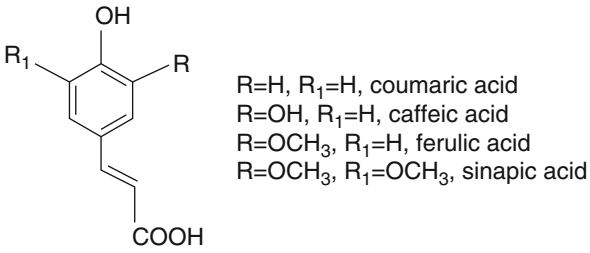


Fig. 2 Chemical structures of hydroxycinnamic acids

concentrations in blackberries (up to 270 mg/kg fresh weight). Protocatechuic acid is an important bioactive constituent of raspberry present up to 100 mg/kg fresh weight, while the concentration of protocatechuic acid is low in olive oil (about 0.22 mg/kg) (D'Archivio et al. 2007). Gallic acid occurs up to 4.5 g/kg fresh weight in tea leaves.

Hydroxybenzoic acids are potent antioxidants that may help protect the body from free radicals. Gallic acid has been used as an astringent and styptic, and it also possesses antineoplastic, bacteriostatic, and antimelanogenic activities. Salicylic acid exerts anti-inflammatory, keratolytic, analgesic, antipyretic, antifungal, and antiseptic properties for several skin conditions (e.g., dandruff and seborrheic dermatitis, acne, ichthyosis, and psoriasis). Protocatechuic acid has also been found to have several bioactivities such as anti-inflammatory, antifungal, free radical scavenging, antioxidant, apoptotic, cytotoxic, antihepatotoxic, chemopreventive, neuroprotective activity, and as platelet aggregation and LDL oxidation inhibitor (Khadem and Marles 2010).

Willow bark (*Salix* spp.), the bark from several varieties of the willow tree, including pussy willow or black willow, European willow or white willow, purple willow, crack willow, and others, is used as herbal medicine to treat low back pain owning to their anti-inflammatory activity. Salicin and related compounds such as salicortin and tremulacin are believed to be the active components inside. Pharmacopoeial-grade willow bark must consist of the dried bark from young branches of willow and must contain at least 1 % of salicin. The final active compound in willow bark is believed to be salicylic acid which is produced by the oxidation of salicyl alcohol, formed upon intestinal hydrolysis of salicin; however, other components such as flavonoids, tannins, and salicin esters from willow bark extracts may also contribute to its overall health effects (Setty and Sigal 2005).

The hydroxycinnamic acids (C_6-C_3 derivatives) are much more common than the hydroxybenzoic acids. The four most common hydroxycinnamic acids are coumaric acid, caffeic acid, ferulic acid, and sinapic acid (Fig. 2). These acids are usually found in plants in the combined forms as glycosylated derivatives or esters of shikimic acid, tartaric acid, and quinic acid rather than in the free form. As an example, chlorogenic acid (Fig. 3), an ester of caffeic acid and quinic acid, is present in high concentrations in many types of fruits. Coffee also contains high concentrations of chlorogenic acid that a single cup may contain between 70 and 350 mg of chlorogenic acid derivatives (Clifford 1999).

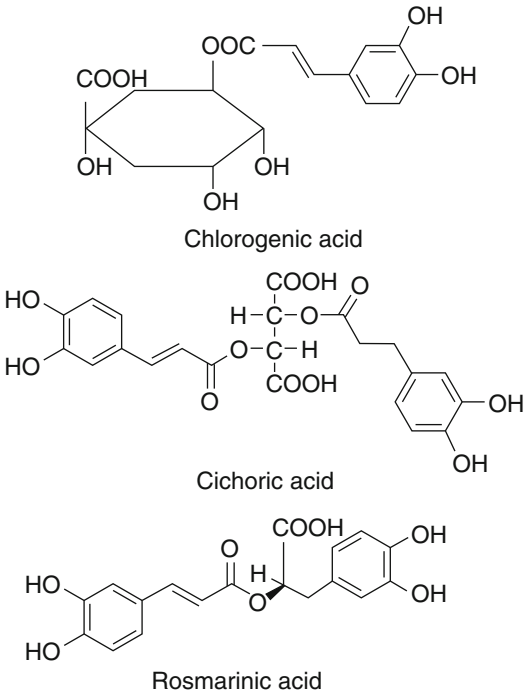


Fig. 3 Chemical structures of chlorogenic acid, cichoric acid, and rosmarinic acid

Although distributed throughout constitutive parts of the fruits, hydroxycinnamic acids occur at the highest levels in the outer parts of ripe fruits. Fruits such as blueberries, kiwis, plums, cherries, and apples have the highest hydroxycinnamic acid concentrations ranging from 0.5 to 2 g/kg fresh weight. Rice, oat, and wheat flours are also rich sources of phenolic acids with a concentration of 0.8–2 g/kg dry weight. Among the hydroxycinnamic acids, caffeic acid accounts for 75–100 % of the total contents in most fruits, and ferulic acid may represent up to 90 % of the total contents in cereal grains (Manach et al. 2004).

Hydroxycinnamic acids are known as potent antioxidants playing an important role in protecting the body from free radicals. Caffeic acid has been proposed to selectively block the biosynthesis of leukotrienes, components involved in allergic reactions, immune-regulation diseases, and asthma. Caffeic acid and some of its esters have also been suggested to possess anticarcinogenic bioactivity against colon carcinogenesis. Recent investigations have shown that a series of phenolic acids have the ability of inhibiting the transcriptional activity of AP-1 which is an activator protein implicated in the processes that control inflammation, cell differentiation, and proliferation. Next to its direct antioxidant effect, ferulic acid was found to induce antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in rats. Animal studies also suggested anticarcinogenic activity of ferulic acid. Ferulic acid was found to have protective effects in the azoxymethane-induced colon carcinogenesis, and the induction of phase II

enzymes such as glutathione-*S*-transferase was suggested as a potential mechanism. Ferulic acid has also been shown to have anti-inflammatory effects (Gallaher and Bunzel 2012). However, further research is needed in order to confirm these benefits of phenolic acids.

Artichoke (*Cynara scolymus* L.) represents an important component of the Mediterranean diet. Artichoke leaf extracts are widely used alone or in association with other herbs in the production of alcoholic and soft drinks and preparation of herbal teas and herbal medicinal products. In various pharmacological test systems, artichoke leaf extracts have been reported to enhance detoxification reactions so as to protect the liver from damage. Artichoke leaf extracts can also be used as a kind of choleretic, diuretic, and general stimulant. In addition, artichoke leaf extracts have been shown to lower cholesterol levels in the blood by inhibiting cholesterol synthesis in the liver, increasing cholesterol excretion in the bile, and mobilizing fat stores from the liver and other tissues. Findings from clinical studies have confirmed the therapeutic properties of artichoke leaf extracts to be effective in protecting patients from hyperlipoproteinemia and irritable bowel syndrome (IBS) without any adverse events. Moreover, artichoke leaf extracts have been observed to inhibit *N*-formyl-methionyl-leucyl-phenylalanine phorbol-12-myristate-13-acetate and hydrogen peroxide-stimulated reactive oxygen species (ROS) production to inhibit oxidative stress in human leukocytes in a concentration-dependent manner (Mulinacci et al. 2004).

The therapeutic properties of artichoke leaf extracts have often been ascribed to their high levels of bioactive phenolic compounds. Caffeic acid derivatives are the main phenolic constituents of artichoke head and leaf extracts. A wide range of caffeoylquinic acid derivatives are present in artichoke, of which cynarin (1, 3-dicaffeoylquinic acid) and chlorogenic acid (5-*O*-caffeoylquinic acid) (Fig. 3) are the most important ones. Flavonoids apigenin and luteolin, which present as glucosides and rutinosides (e.g., apigenin-7-rutinoside, apigenin-7-*O*-beta-D-glucopyranoside, luteolin-7-*O*-glucoside, and luteolin-7-rutinoside), have also been identified in artichoke tissues. In addition, the bioavailability and metabolism of phenolic compounds from artichoke extract has been investigated in vivo by determining the urinary excretion of absorbed compounds, which demonstrated that the caffeic acid derivatives were metabolized to phenolic acids such as isoferulic, ferulic, vanillic, and dihydro ferulic (Lattanzio et al. 2009).

Echinacea (*Echinacea angustifolia, Echinacea purpurea*, *Echinacea pallida*) tissues such as roots, seeds, flower heads, and aerial parts can be made into extracts and tea as well as capsules and tinctures, and they are also widely used as herbal supplements in North America and Europe. Echinacea was initially used as an herbal remedy to treat headache, common cold, respiratory ailments, snakebites, and other infections by the American Indians and currently is used primarily to treat cold and influenza, build immune system, prevent upper respiratory tract infections, heal skin conditions, etc. (Tyler 1998).

Caffeic acid-derived compounds, unsaturated aliphatic compounds, and polysaccharides are believed to be the bioactive components of Echinacea. Echinacoside occurs at a high concentration of 0.3–1.7 % w/w in the roots of

E. angustifolia. Echinacoside has been shown to exhibit antioxidant and free radical scavenging activity which may account for its anti-inflammatory effects. Cichoric acid (2,3-*O*-dicaffeoyltartaric acid) (Fig. 3) is present in a relative high concentration of 1.2–3.1 % w/w in the flower heads and 0.6–2.1 % w/w in the roots. The concentrations vary generally depending on the species identity as well as the season harvest. Both in vitro and in vivo studies demonstrated the phagocytosis stimulatory activity of cichoric acid. Cichoric acid has also been shown to inhibit hyaluronidase, prevent free radical-induced type III collagen degradation, and inhibit the human immunodeficiency virus type 1 (HIV-I) integrase to prevent HIV from infecting host cells. In addition, other phenolics such as chlorogenic acid, tartaric acid, 2-*O*-caffeoyltartaric acid (caftaric acid), 1,3-*O*-dicaffeoylquinic acid (cynarin), lipophilic alkamides, and ketoalkynes identified in Echinacea may also contribute to different bioactivities for Echinacea (Mistrikova and Vaverkova 2006).

Rosemary (*Rosmarinus officinalis* L.), widespread in Central America, Europe, and other regions, is widely used as flavoring component in foods, beverage drinks, and cosmetics. This plant has been used in folk medicine as an antispasmodic to treat renal colic and dysmenorrhea, for relief of symptoms caused by respiratory disorders, and for promoting growth of hair. Rosemary extracts have also been used as a diuretic, analgesic, choleretic, expectorant, antirheumatic, antimutagenic, hepatoprotective agent, for human fertility, etc. Caffeic acid and its derivatives such as rosmarinic acid (Fig. 3) and chlorogenic acid have been thought to be the most important ones responsible for the therapeutic properties of rosemary extracts. Also, flavonoids, terpenoids (carnosol and carnosic acid), and essential oils are found in rosemary extracts. These compounds may work together to contribute to the bioactive function of rosemary (al-Sereiti et al. 1999).

Coumarins

Coumarins (Fig. 4) are a large class of C_6-C_3 derivatives belonging to the benzo-α-pyrone group, which are presenting in the free form or in combined form as heterosides and glycosides in certain foods or plants. The simple coumarins are the hydroxylated, alkoxylated, and alkylated derivatives of the benzene ring of a coumarin and the corresponding glycosides. Furanocoumarins are furano derivatives of coumarin having a five-membered furan ring fused with the benzene ring of a coumarin, and they can be divided into linear (psoralen) or angular (angelicin) types based on the skeleton structure. Pyrano coumarins are the third type of coumarins consisting of a six-membered pyran ring attached to the benzoid, divided into linear (xanthyletin) or angular (seselin) types (Gopi and Dhanaraju 2011).

Higher plants such as Rutaceae and Umbelliferae are the richest sources of coumarins. All the constitutive parts of the plant contain coumarins, while the highest concentrations are found in the fruits, followed by the roots, stems, and leaves. Coumarins are distributed at high levels in some essential oils. Cinnamon bark oil and cassia leaf oil are rich sources of coumarins with the concentration of

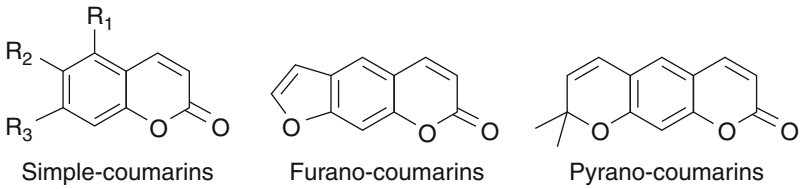


Fig. 4 Chemical structures of coumarins

7,000 and 87,300 ppm, respectively. Coumarins have also been found in lavender oil. In addition, fruits such as cloudberry and bilberry, chicory, and green tea and other foods have been reported to contain coumarins. The coumarin concentrations in diverse parts of the plant vary generally with the environmental conditions, species identity, as well as the seasonal changes (Jain and Joshi 2012).

Due to their diverse pharmacological properties, the coumarins have been studied extensively by food scientists, nutritionists, pharmacologists, and chemists. A growing body of studies demonstrated several bioactivities of coumarins and coumarin derivatives, including free radical scavenging activity, anticancer, anti-inflammatory, antimicrobial, anticoagulant, etc. These beneficial properties make them important starting products for developing novel derivatives as therapeutic agents. As an example, 7-hydroxycoumarin, a metabolite of coumarin, has been found to have antitumor effects against several human tumor cell lines such as breast cancer cell line MCF-7 and lung cancer cell line A549. In addition, coumarins and coumarin-related compounds such as esculetin have been reported to show inhibitory effects on cell growth of several carcinoma cell lines such as leukemia cells HL-60 and myeloid leukemia cells K562 (Lacy and O' Kennedy 2004).

Angelica archangelica L. (*A. archangelica*) is an aromatic, herbaceous plant commercially cultivated in Europe. Essential oils extracted from roots and seeds are widely used as flavoring ingredients in perfumery and cosmetics, in the production of absinthe and other alcoholic drinks, and in the preparation of tea and medicinal products (Bhat et al. 2011). This plant has been used in folk medicine as a remedy to treat disorders of the respiratory tract, nervous system, and gastrointestinal tract, as well as against cerebral diseases, nervous headaches, toothaches, fever, infections, skin rashes, and flu. *A. archangelica* extracts have also been used as a diuretic, antiseptic, and expectorant (Howes et al. 2003).

Essential oils and furanocoumarins are the chief constituents of *Angelica* fruits. Imperatorin and xanthotoxin are the major furanocoumarins in the tincture of the fruits with the concentrations of 0.90 mg/mL and 0.32 mg/mL, respectively. The essential oil and extracts containing furanocoumarins obtained from *Angelica archangelica* seeds showed significant efficacy against *Spodoptera littoralis* larvae in terms of acute toxicity and chronic toxicity, respectively, and both of them caused growth inhibition and showed antifeedant activity against *Spodoptera littoralis* larvae. *Angelica archangelica* seed extracts can serve as efficient substances for the development of botanical insecticides against phytophagous pest larvae (Pavela and Vrchotová 2013). Other secondary metabolites are also found in *Angelica*, including

a bitter principle, angelic acid, astringents, valeric acid, volatile oil, a peculiar resin known as angelicin, etc. These phytochemicals could work in coordination with each other to contribute to the biological function of *Angelica* (Kumar et al. 2013).

Lignans

Lignans are a diverse group of bioactive phenolic compounds formed of two β-β-linked phenylpropane units; they are present in different parts of plant species in the free form or in combined form as glycoside derivatives. Flaxseed contains the most abundant lignans (Fig. 5). Secoisolariciresinol is present up to 3.7 g/kg dry weight, and matairesinol is found in a low quantity of about 10.9 mg/kg dry weight in flaxseed. Other foods such as cereals, fruits, legumes, vegetables, berries, and tea are also sources of lignans but in low amounts ranging from 0.1 to 81.9 mg/kg dry weight (Johnsson 2004).

After consumption, the plant lignans secoisolariciresinol and matairesinol have been described to be effectively metabolized to the mammalian lignans, enterodiol and enterolactone, by the intestinal facultative bacteria (Fig. 5). Thus, plant lignans are known as "phytoestrogens" and may exert the estrogen-like biological activities such as reducing the risk of hormone-dependent cancers (e.g., prostate, breast, and endometrial cancer) (Borriello et al. 1985). Also, plant lignans possess powerful antioxidant activity higher than that of vitamin E and may be effective in the treatment of several other diseases such as cardiovascular disease, coronary heart disease, and diabetes.

Flaxseed oil is also the richest source of the omega-3 fatty acid, a kind of polyunsaturated fatty acid, possessing several health benefits on humans. However, it is lignans in flaxseed that make it to be a hot research topic recently. The concentration of lignans in flaxseed is tens to hundreds of times as high as in most other plant-based foods. Flaxseed exhibits strong antitumor activities against colon, mammary gland, and lung cancer in vivo. Also, a diet rich in flaxseed has been shown to influence the hormone metabolism, thus decreasing the risk of prostate and breast cancer. Flaxseed has also been suggested to be a potential remedy for various diseases such as diabetes, cardiovascular diseases, hyperlipidemia, constipation, memory loss, and hypertension. However, more studies are needed to evaluate the biological activity of flaxseed on humans. The bioactive constituents that account for the function of flaxseed are thought to be the flaxseed lignans, especially secoisolariciresinol and matairesinol, unsaturated fatty acids, sterols, soluble flaxseed fiber mucilage, etc. (Mishra and Verma 2013).

Schisandra chinensis (Turcz.) Baill. (Schisandraceae) is a kind of medicinal plant widely distributed in the eastern parts of Russia, northeastern China, Japan, and Korea. The fruits and seeds of *Schisandra chinensis* (Turcz.) Baill. are widely used in traditional Chinese medicine for sedative, antiaging, and tonic purpose. They are also used in the production of nutraceuticals such as soft drinks and health foods and as an ingredient in some oral, skin, and hair health-care products. Current scientific findings suggest that lignans of *Schisandra chinensis* can stimulate liver regeneration, prevent liver injuries, and inhibit hepatocarcinogenesis as well as

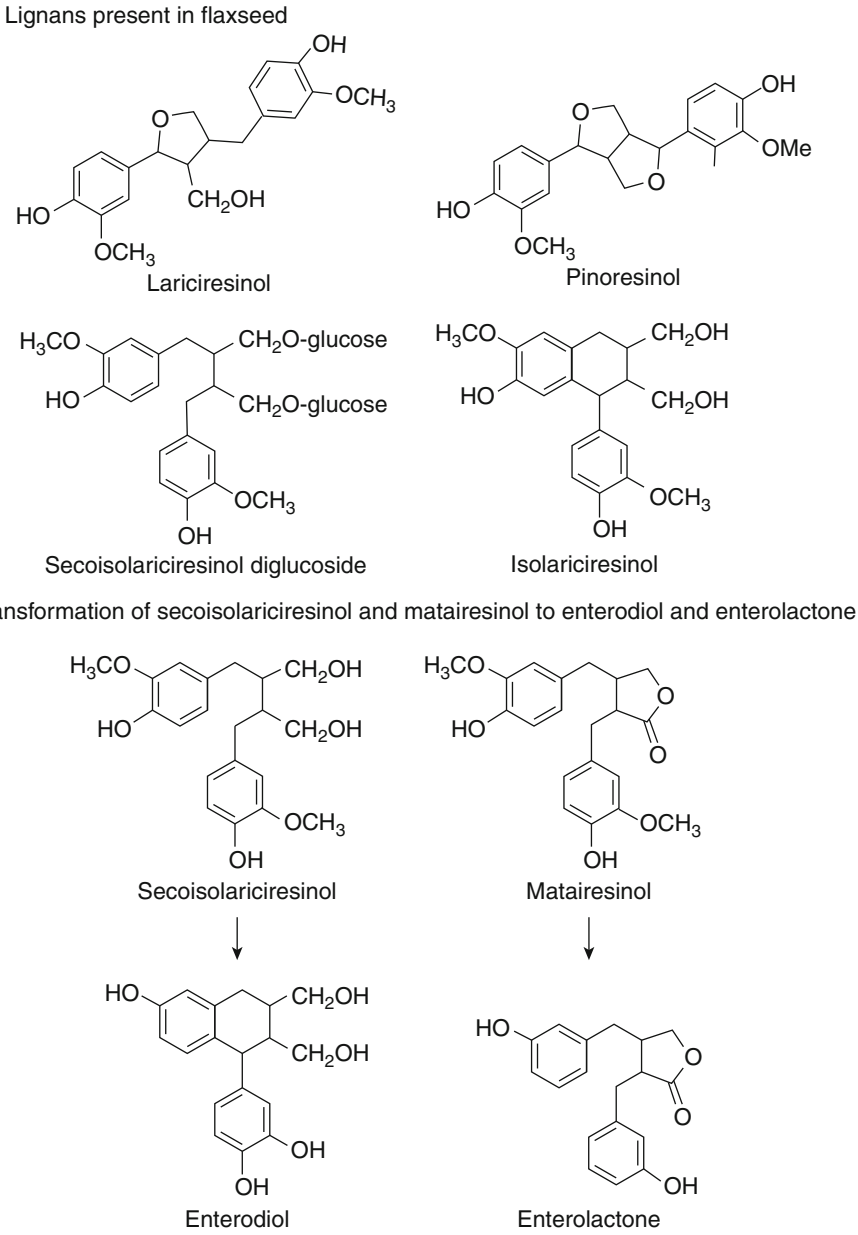


Fig. 5 Chemical structures of flaxseed lignans

lipid peroxidation in rats (Kubo et al. 1992). Also, other pharmacological effects of *Schisandra chinensis* including inhibiting platelet aggregation, lowering the serum glutamate-pyruvate transaminase level, and anti-oxidative, calcium antagonism,

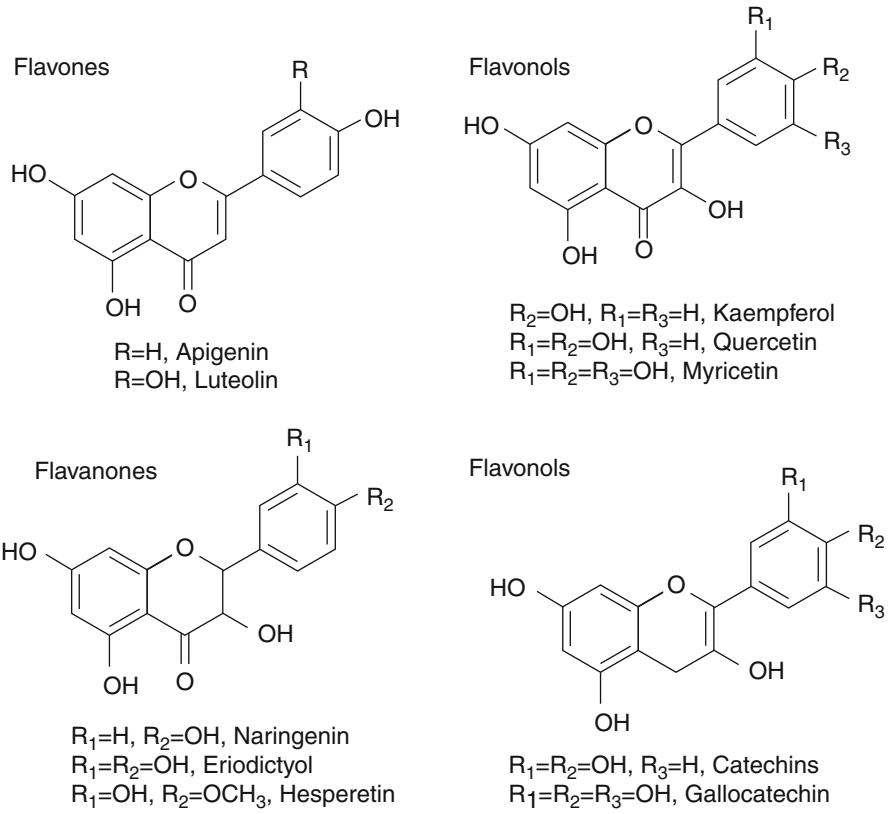


Fig. 6 Chemical structures of flavonoids

anti-HIV, and antitumor effects can also be attributed to its lignan constituents, particularly the dibenzocyclooctadiene-type lignans (Lu and Chen 2009).

Flavonoids

Flavonoids are one of the largest groups of phenolic compounds with more than 3,000 known structures. They are widely distributed throughout the plant kingdom. Flavonoids possess the general structural backbone of 15 carbon atoms (C6–C3–C6) in which the two C_6 units are of phenolic nature and linked by a C_3 group. Flavonoids can be further divided into flavonols, flavones, flavanones, flavanols (catechins), etc. (Fig. 6) according to the oxidation state of the central pyran ring. Isoflavonoids and anthocyanins also belong to flavonoids.

Flavones and their 3-hydroxy derivatives flavonols are the most widespread flavonoids in plant foods. Flavones usually occur as glycosides of apigenin and

luteolin in plants. Apigenin has been shown to suppress 12-*O*-tetradecanoylphorbol-1,3-acetate (TPA)-mediated tumor promotion in mouse skin. Suppression of protein kinase C activity and nuclear oncogene expression is suggested to be the possible action mechanism. Apigenin has also been reported to exhibit anti-inflammatory, hypotensive, and antibacterial effects and diuretic activity and promote smooth muscle relaxation. Luteolin has also been reported to exhibit various biological activities such as antioxidant, antimutagenic, anti-inflammatory, and antibacterial.

Flavones are found in celery. Celery stalks and seeds are used to obtain extracts or essential oils, which are widely used as flavoring or spice and to prepare juice, tea, and medicinal products. Celery extracts alone or combined with other juices provide several health benefits such as lowering blood pressure, lowering total cholesterol and LDL cholesterol levels, and anti-inflammatory and anticancer activities. Apigenin and luteolin which are present in a relative high concentration in celery (22–108 mg/kg fresh weight) as well as coumarins, polyacetylenes, and phthalides identified in extracts of celery have been suggested to be responsible for the bioactive properties (Shahidi and Naczk 2003).

The flavonols, on the other hand, are widely distributed in plants. They are most often presenting in conjugated form as glycosides. To date, 200–300 flavonols have been identified from different kinds of plants with quercetin, myricetin, and kaempferol (Fig. 6) as the three most common ones. Onion is one of the richest sources of flavonoids that onion leaves contain 1,497.5 mg/kg of quercetin, 832.0 mg/kg of kaempferol, and 391.0 mg/kg of luteolin. Red wine is also a prominent source of flavonols (up to 30 mg/L). In addition, black tea contains up to 4.17 mg of quercetin/g in the human diet. Other fruits and vegetables such as berries, apples, broccolis, leeks, and curly kales are also sources of flavonols in our diet. Owning to the fact that the biosynthesis of flavonols is stimulated by light, the concentration of flavonol is generally higher in the outer parts (skins and leaves) of the plant foods than the other parts (Manach et al. 2004).

Flavonols have been reported to interfere with various biochemical signaling pathways, thus exerting several beneficial effects. Considered as the most abundant dietary flavonol, the possible health effects of quercetin have been investigated extensively. Quercetin is a powerful antioxidant playing an important role in protecting the body against reactive oxygen species. It also shows anti-atherosclerosis, anti-inflammatory, anticancer, and cholesterol-lowering properties and protects eye health (Erlund 2004).

Ginkgo (*Ginkgo biloba* L.) is a native Chinese plant now cultivated across the world. Both the leaves and the nuts of the tree have been used in traditional Chinese medicine in the past several centuries. Ginkgo nuts have been used extensively to treat pulmonary diseases (e.g., enuresis, cough, and asthma), bladder inflammation, and alcohol abuse. The leaf extracts are generally used to make extracts for medical purpose to alleviate asthma and cardiovascular disorders and treat skin infections, heart and lung dysfunctions, as well as dementia disorders such as memory impairment and concentration difficulties. In addition, the Ginkgo leaf extracts have the benefits of improving the mental capacities to delay the process of Alzheimer's

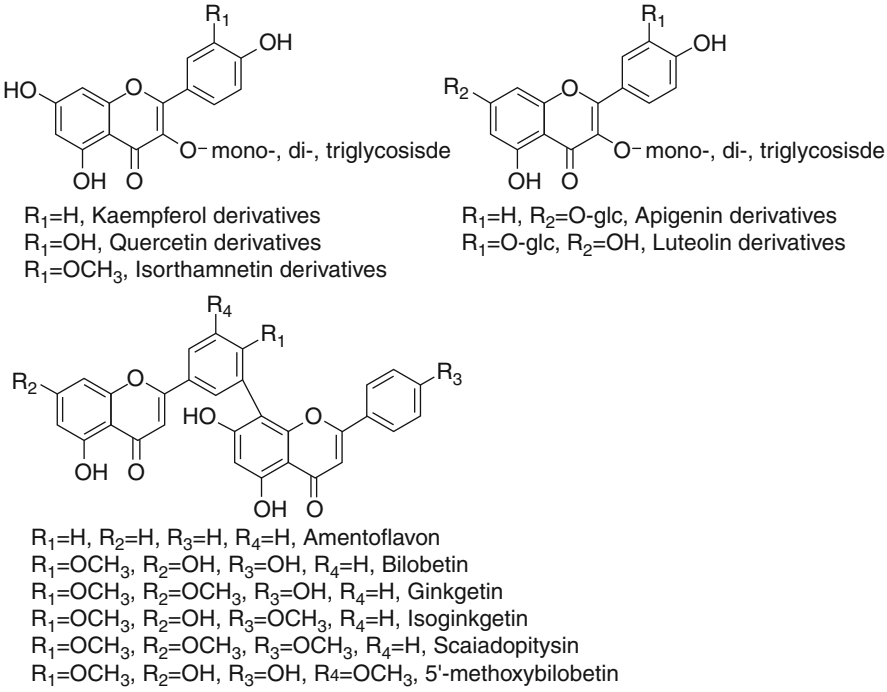


Fig. 7 Chemical structures of flavonoid constituents in Ginkgo

disease (Mahadevan and Park 2008). The physiological benefits of Ginkgo are mainly attributed to the active components, namely, flavonoids and terpenoids (such as ginkgolides and bilobalide), found in them.

The flavonoids (Fig. 7) present in the Ginkgo leaf extract are flavonols, flavonol glycosides, flavones, biflavones, proanthocyanidins, and associated glycosides of quercetin and kaempferol attached to *p*-coumaric esters 3-rutinosides or 3-rhamnosides, of which flavonols (quercetin and kaempferol coumaryl glycosides) are essential for the efficacy of Ginkgo leaf extracts. Rutin and quercetin and a mixture of flavonoids and terpenes from Ginkgo have been found to protect cerebellar granule cells from oxidative damage and apoptosis induced by hydroxyl radicals (Chen et al. 1999). Ginkgo leaves also contain toxic components, ginkgolic acids, the concentration of which must be less than 5 ppm in all commercial Ginkgo leaf products to minimize gastrointestinal and allergic reactions.

Flavanones (Fig. 6) are colorless compounds characterized by the absence of a double bond in the 2, 3-position of the pyrone ring and are isomeric with chalcones. The glycosylated flavanones are generally obtained by a disaccharide at position 7: either a bitter-tasting neohesperidose or a flavorless rutinose in human foods. High flavanone concentrations occur only in citrus fruit. Other plants such as tomatoes and mints contain low concentrations of flavanones. Hesperetin in oranges (*Citrus sinensis*), naringenin in grapefruits (*Citrus paradise*), and eriodictyol in lemons

(*Citrus limon*) are the major flavanone aglycones in the human diet. Hesperidin and narirutin occur in high concentrations at 200–600 and 15–85 mg/L, respectively, in orange juice. Forty to hundred and forty milligram of flavanone glycosides can be obtained from a single glass of orange juice. In addition, the whole orange fruit may contain five times more flavanones than the orange juice as the highest flavanones content is present in the solid tissues, especially the white spongy portion and the membranes separating the segments of the orange fruits (Kaur and Kaur 2014).

Hesperidin and naringenin themselves as well as the citrus fruit juice have been shown to possess anticarcinogenic and antitumor effects in animals studies. Satsuma mandarin juice which is rich in hesperidin has been reported to have possible chemopreventive effect against chemically induced colon carcinogenesis and lung tumorigenesis in rats. Naringenin and its analog liquiritigenin showed potent cancer chemoprevention activity against gastric carcinogenesis in both in vitro and rat studies. Hesperidin and naringin may also prevent cardiovascular diseases by decreasing plasma low-density lipoprotein and hepatic cholesterol levels. Orange juice fed three times daily was found to decrease the ratio of low-density lipoprotein to high-density lipoprotein cholesterol in human studies. However, more human studies are needed to confirm these results. In addition, a mice model of acute colitis study revealed the potent anti-inflammatory function of naringin and the aglycones. The anti-inflammatory activity may be attributed to their relative weak antioxidant activities. Naringenin was also shown to suppress intestine carbohydrate absorption and to promote extra-pancreatic action in a diabetic rat model, which contributes to its antidiabetic effects (Lim and Koffas 2010).

Catechins are the monomer form of proanthocyanidins. They are present in many kinds of fruits, among which apricots have the highest concentration at about 250 mg/kg fresh weight. Red wine also contains high amounts of catechins at the concentration of up to 300 mg/L. But the richest sources of catechins by far are known as green tea and chocolate. Up to 200 mg of catechins can be obtained from a cup of green tea (240 mL), while much less amount can be found in black tea because the monomer flavanols in tea leaves are oxidized to two types of more complex condensed polyphenols, theaflavins and thearubigins, during the "fermentation" procedure involved in producing black tea. Dark chocolate has about 54 mg of catechins per 100 g. Catechin and epicatechin are the most abundant flavanols found in fruits, while the main flavanols found in grapes, in certain seeds of leguminous plants, and more importantly in tea are known as gallocatechin, epigallocatechin, and epigallocatechin gallate (D'Archivio et al. 2007).

The tea plant was first cultivated in China and has been consumed for almost 6,000 years. The first record of the health benefits of green tea appeared in a Chinese medical treatise in 2737 BC. The tea is mainly divided into three types, green, black, and oolong according to the way the leaves are processed. Green tea (unfermented) is produced by lightly steaming the leaves of the plant. Black tea (fully fermented) is produced by allowing the leaves to oxidize. Oolong tea (semi-fermented) is a traditional Chinese type of tea somewhere in between green and black in oxidation. Catechins including catechin (C), epicatechin (EC), gallocatechin (GC), catechin gallate (CG), epicatechin gallate (ECG), epigallocatechin (EGC),

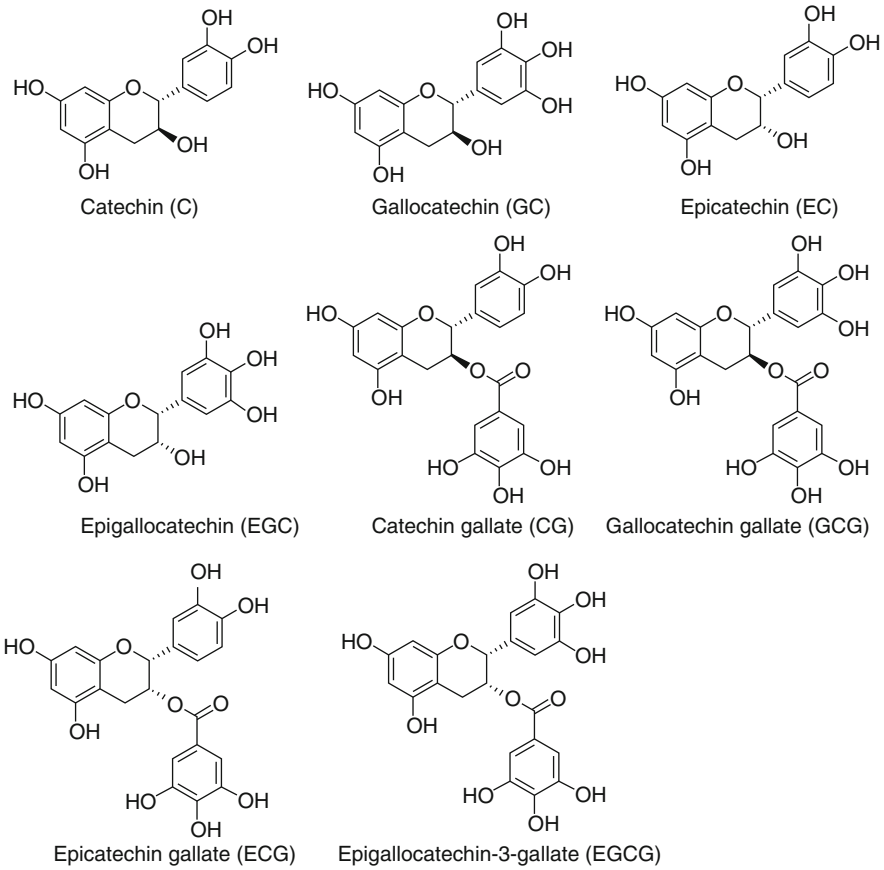
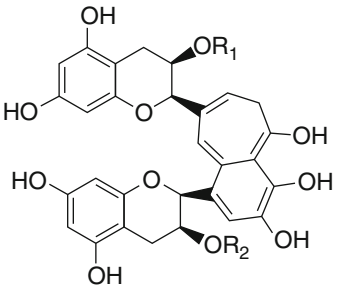


Fig. 8 Chemical structures of green tea catechins

epigallocatechin-3-gallate (EGCG), and gallocatechin gallate (GCG) (Fig. 8) are the main polyphenols present in green tea (Vidal et al. 2014). The total percentage of catechins in dried green tea leaves can reach approximately 30 %. They are thought to be responsible for the majority of green tea's beneficial effects. Theaflavins and thearubigins (Fig. 9) are the major bioactive compounds in black tea. More than 20 % thearubigins, 3–10 % catechins, and 2–6 % theaflavins are present in brewed black tea (Yang et al. 2008).

Mouthwashes of both green tea and black tea have shown to decrease dental plaque formation by inhibiting the growth of bacteria such as *Escherichia coli, Streptococcus salivarius*, and *Streptococcus mutans* that cause cavities in some studies. Green tea polyphenols also inhibited the growth of *Porphyromonas gingivalis* and its adherence to oral epithelial cells. Both green tea and black tea have been showing cardioprotective activity by lowering serum cholesterol, lipid peroxides, and triglycerides in animal and human studies. EGCG itself and the green tea have been shown to reduce the risk of Parkinson's disease in some



Theaflavin-1; R_1=R_2=H
Theaflavin-3-gallate-A; R_1=galloyl, R_2=H
Theaflavin-3'-gallate-B; R_1=H, R_2=galloyl
Theaflavin-3, 3'-digallate; R_1=R_2=galloyl

Fig. 9 Chemical structures of black tea theaflavins

experiments. Twenty-eight percent of Parkinson's disease was shown to be reduced by consuming three or more cups of tea every day in a case–control study in China. Green tea also has anticarcinogenic and antimutagenic properties. Green tea and/or green tea polyphenols have been shown to protect against carcinogenesis induced by ultraviolet light or chemicals in mice. The organ sites include the colon, breast, liver, pancreas, duodenum, esophagus, liver, and lung. EGCG is now believed to be the polyphenolic constituent that mainly contributes to the cancer chemopreventive effects of green tea. However, more laboratory, epidemiologic, and clinical studies should be conducted to further confirm the protective effect of tea against cancers and cardiovascular diseases (Rodriguez et al. 2006).

Isoflavonoids

Isoflavonoids, members of flavonoids that have their ring B fused with the C_3 position of ring C, are naturally occurring phenolics with phytoestrogenic activity (Fig. 10). Soybeans and soybean-derived products are the major sources of dietary isoflavones in the human diet. The concentrations of isoflavones in soybean products vary generally depending on the geographic zone, growing conditions, and processing. 580–3,800 mg of isoflavones is present in per kilogram of fresh soybeans, and 30–175 mg of isoflavones is found in per liter of soymilk (Kaur and Kaur 2014). Genistein, daidzein, glycitein, biochanin A, and formononetin are the main isoflavones found in soy. Each one of these compounds is present in four chemical forms, unconjugated (aglycone, IFA), sugar-conjugated (isoflavone glucoside, IFG), acetylglucosides, and malonylglucosides. Red clovers are also rich in isoflavones.

Since soybeans and soybean-derived products are a major part of human diet in many cultures, the role of isoflavones, thus, is of greatest interest. The soy isoflavones have structures similar to mammalian estrogens which confer them the capacity of working as phytoestrogens. These phytoestrogens can bind to the mammalian estrogen receptors and induce estrogenic and/or antiestrogenic effects both in vitro and in vivo. This might be the reason why the populations exposed to high dietary levels of soybeans generally have a reduced risk of estrogen-dependent cancers (e.g., prostate, breast, and perhaps colon cancer) (Kushwaha et al. 2014).

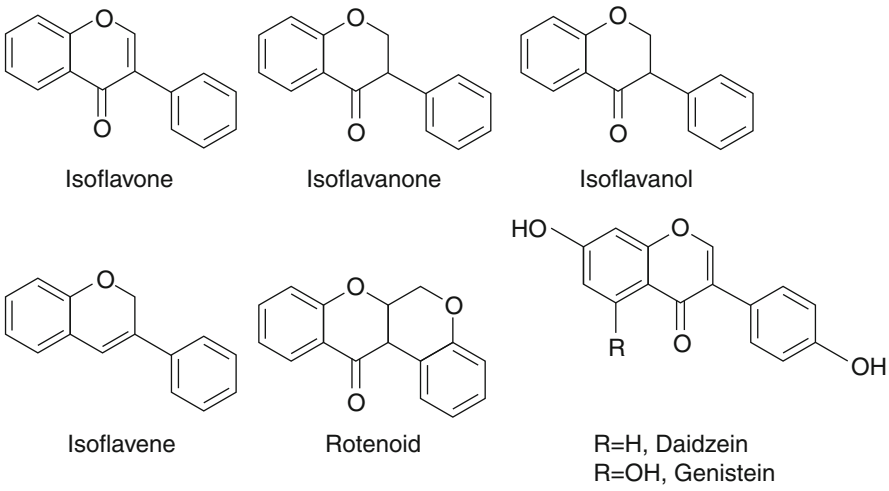


Fig. 10 Chemical structures of isoflavonoids

Though the cancer preventive role of soybeans and its components has been demonstrated by a number of experimental studies, the epidemiological data published so far have not drawn a consistent conclusion on soy intake and cancer risk. A small double-blinded, placebo-controlled study on highly purified genistein and daidzein indicated that they have negative effects on localized prostate cancer.

Epidemiological studies as well as clinical trials showed that Asian women who usually have diets rich in soy food (25–50 mg/day) have better bone health than western women who usually consume less soy food (less than 2 mg/day), characterized by higher bone mineral density and lower rate of bone fracture. In addition, Asian women have significantly lower incidence of hot flashes and other menopausal symptoms compared to western women, which is believed to be due to the effects of soy isoflavones. However, other studies showed that soy intake has no beneficial effect on menopausal symptoms (Rodriguez et al. 2006). High levels of serum cholesterol are associated with cardiovascular diseases. Soybean has been shown to exhibit cholesterol-lowering activity. Isoflavones were believed to be the specific components of soybean that offer protection against cardiovascular diseases by reducing plasma lipid and lipoprotein concentrations, which result in improved flow-mediated arterial dilation and systemic arterial compliance. However, isoflavone supplements were not shown to be effective in reducing cholesterol in two human studies (Nestel et al. 1997; Hodgson et al. 1998).

Anthocyanins

Anthocyanins are known as the largest and most important group of water-soluble vacuolar pigments that are responsible for the pink, red, blue, and purple color of the

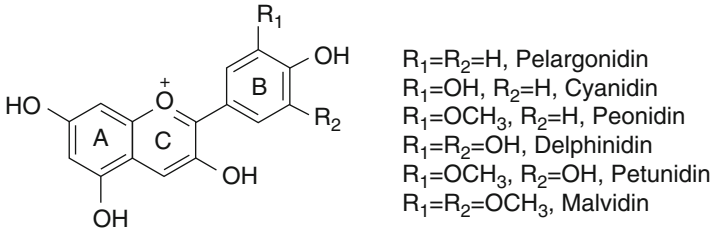


Fig. 11 Chemical structures of anthocyanidins

majority of fruits, flowers, vegetables, and grains (Shahidi and Naczk 2004). Anthocyanins are highly reactive species in plant tissues. Food processing can lead to the conversion of genuine anthocyanins to other molecules, resulting in either loss or destabilization of color and increasing of the range of available hues (Fig. 11).

The basic structures of anthocyanins are anthocyanidins, in which the two aromatic rings A and B are linked by a heterocyclic ring C that possesses oxygen. More than 23 different anthocyanidins have been found with pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin as the most common ones. Anthocyanins in plants mainly exist in the conjugated form as glycosides. More than 500 types of anthocyanins have been identified in plants. Individual anthocyanin varies in the hydroxylation and methoxylation patterns on the B ring; the nature, position, and number of conjugated sugar units; the nature and number of conjugated aliphatic or aromatic acids groups; and the presence or absence of an acyl aromatic group in the molecule. Cyanidins are the most common group of naturally occurring anthocyanins, followed by delphinidins. The substituent groups on the B ring of anthocyanidins and the pH conditions determine severely the color saturation and the stability of anthocyanins. Generally, higher degree of hydroxylation and lower degree of methoxylation of the hydroxyl groups of the aromatic rings result in higher saturated color. Anthocyanins are relatively stable in acidic solutions exhibiting a red color. However, they are unstable under neutral and weakly acidic conditions (Tsao 2010).

The fruit is the major source of dietary anthocyanins in the human diet. Usually, the amount of anthocyanins in the fruit is proportional to the intensity of the color. Strawberries contain about 0.15 mg of anthocyanins/g fresh weight, and cherries contain about 0.45 mg/g. Fruits with high color intensity such as blackcurrants and blackberries contain anthocyanins up to 2–4 mg/g fresh weight. Wine is also rich in anthocyanins that 200–350 mg of anthocyanins can be obtained from 1 l of wine. These anthocyanins are transformed into various complex structures during wine aging. Other food sources of anthocyanins include cereals and leafy and root vegetables (Yildiz 2010).

Berries contain a wide range of phytochemicals, such as flavonoids (e.g., anthocyanins, flavonols, catechins), phenolic acids (e.g., hydroxycinnamic acids), and tannins (e.g., proanthocyanidin, ellagitannins). Berry seed oils, berry oils, berry powders, and standardized berry extracts have been marketed as functional foods

and nutraceuticals. Anthocyanins and anthocyanin-rich berries or derived extracts have been suggested to possess a wide range of health benefits for humans and animals in a growing number of studies. Both in vitro and in vivo studies demonstrated the protective effects of anthocyanins, including antioxidant activity, anti-edema, decreasing capillary permeability, increasing the regeneration of visual purple, improving vision at dusk, anti-inflammatory activity, and anticarcinogenic activity (He and Giusti 2010). Berry extracts have also been shown to protect heart and brain health. However, it must be noted that not a single class of compounds may explain most of the health-promoting effects of consuming fruits and vegetables. Apparently, the phytochemicals contained in fruits and vegetables work collaboratively with other fruit ingredients to benefit our body.

Tannins

Tannins are polyphenols widely distributed with a wide diversity of structures capable of binding and precipitating proteins from aqueous solutions. Tannins are commonly classified into two categories, condensed tannins (also known as proanthocyanidins) and hydrolysable tannins, according to their structures.

Condensed tannins, also known as proanthocyanidins, chiefly comprise a flavan-3-ol unit to form dimers, oligomers, and polymers, up to 50 monomer units (Fig. 12). Proanthocyanidins have complex structures that individual proanthocyanidin varies in the number of flavan-3-ol unit, the location and type of interflavan linkage in the molecule, and the nature and position of substituents on the flavan-3-ol unit. Proanthocyanidins can be classified into several subgroups (e.g., procyanidins, propelargonidins, and prodelphinidins) based on their hydroxylation pattern of A and B rings (Shahidi and Naczk 2003).

Proanthocyanidins (condensed tannins) are responsible for the astringent character of fruits and beverages and for the bitterness of chocolate through the formation of complexes with salivary proteins. The astringency decreases over the course of maturation and often disappears when the fruit reaches ripeness. Proanthocyanidins occur in high levels in grapes, berries, apples, peanut inner skins, chocolates, pine bark, and cinnamon bark. Grape skins and seeds are particularly rich sources of proanthocyanidins that have received considerable attention from nutritionists, epidemiologists, and general consumers.

The abilities of grape seed proanthocyanidins to protect against lipid peroxidation and DNA fragmentation induced by 12-*o*-tetradeca-noylphorbol-13-acetate (TPA) have been examined in vivo. It showed that grape seed proanthocyanidins have greater ability to decrease the production of reactive oxygen species in the liver and brain tissues of mice as compared to vitamin C and E. Moreover, proanthocyanidins showed a threefold to fourfold greater DNA fragmentation reduction ability than either vitamin C or beta-carotene in both hepatic and brain tissues. All these data support the powerful antioxidant activity of proanthocyanidins, which may be responsible for its cardioprotection, cancer chemoprevention, and lowering cholesterol level (Shi et al. 2003).

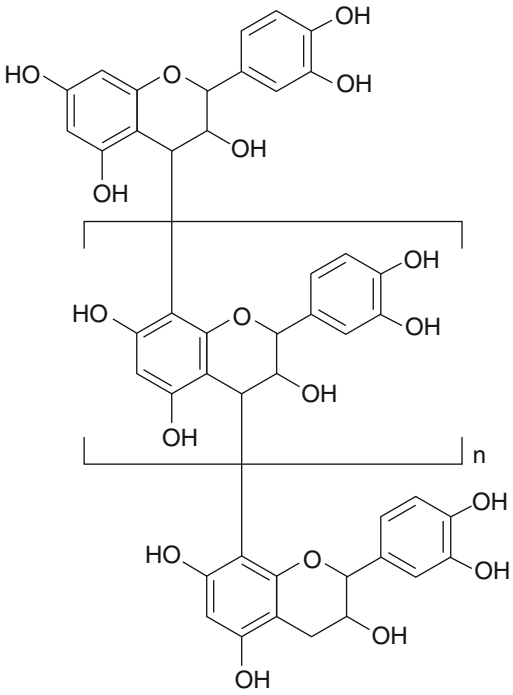


Fig. 12 Chemical structures of condensed tannins

Berries of *Vaccinium* sp. exhibit a wide range of biological activities with potential health benefits for humans and animals. Cranberry and wild blueberry and their derived materials have been shown to prevent bacterial motility-induced urinary tract infections. Proanthocyanidins have been suggested to be responsible for this protective effect due to their ability of preventing bacterial colonization. Proanthocyanidins fraction in wild blueberry has also been shown to prevent chemically induced carcinogenesis in vitro (Bomser et al. 1996).

Cinnamon bark has been widely used as a spice for centuries. In addition to its culinary uses, cinnamon bark has been employed in the form of a traditional herbal medicine for treating various health conditions. The available evidence from in vitro and animal studies suggested the protective effects of cinnamon as an antitumor, anti-inflammatory, antioxidant, antimicrobial, and cholesterol-lowering agent, as a treatment of infectious diseases, and for the prevention of cardiovascular diseases. The well-documented physiological effect of cinnamon is its activity for the treatment of type 2 diabetes (Gruenwald et al. 2010). However, further clinical studies are necessary to draw solid conclusions about these health benefits described above. A wide range of phenolic compounds, particularly, proanthocyanidins occurring in high amount in cinnamon bark, could in part account for the biological function of cinnamon (Mateos-Martín et al. 2012).

Hydrolysable tannins are molecules with a polyol (generally D-glucose) as a central core. Hydrolysable tannins have a more restricted occurrence than

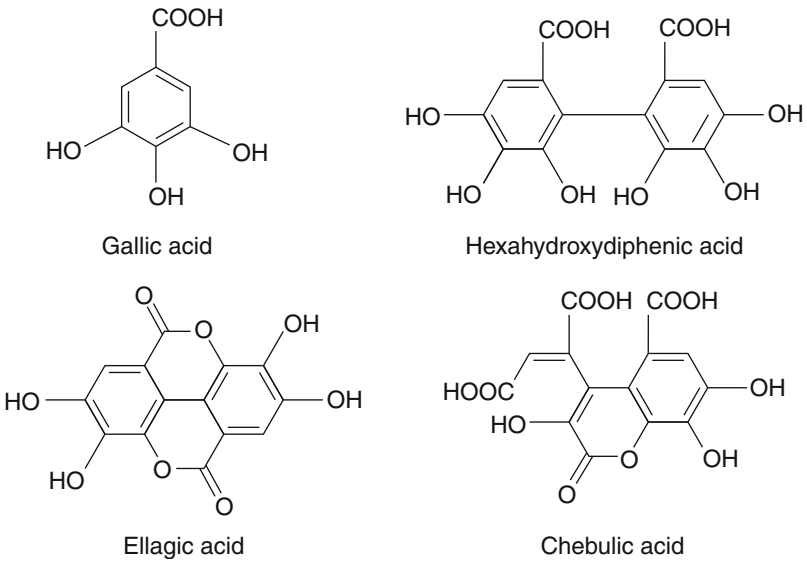


Fig. 13 Phenolic acid residues of hydrolysable tannins

condensed tannins in plants. They are further divided into two subclasses, gallotannins, which involve a glucose esterified to gallic acid, and ellagitannins, which are ellagic acid-derived hexahydroxydiphenic acid (Fig. 13). The distribution of gallotannins is rather limited in nature while ellagitannins are commonly found in many plant families. The profile of hydrolyzable tannins in a plant species is generally stable throughout the year (Amoo 2009).

Pomegranate (*Punica granatum* L.), a rich source of polyphenol compounds, particularly hydrolyzable tannins and anthocyanins, is widely used to process to juice and sauce. The total content of hydrolyzable tannins (e.g., gallagyl tannins, gallotannins, and ellagic acid tannins) and anthocyanins (e.g., pelargonidin, cyaniding, and delphinidin glycosides) in pomegranate juice ranges from 417.3 to 556.6 mg/L and from 161.9 to 387.4 mg/L, respectively. The hydrolyzable tannins have been reported to account for 92 % of the antioxidant activity of the whole fruit. The anthocyanins impart the red color to the fruit and juice. Other phenolic compounds such as catechin, gallocatechin, epicatechin, gallic acid, and caffeic acid have also been detected in pomegranate.

Pomegranate fruit extracts/constituents exhibit several health benefits such as antioxidant, antiatherogenic, antitumor, antiviral, antifungal, antibacterial, free radical scavenging, prevention of heart diseases, and strengthening of the immune system in a growing body of in vitro and in vivo studies. All these protective effects could in part attribute to the diverse phenolic compounds in the pomegranate (Shahidi and Naczk 2003).

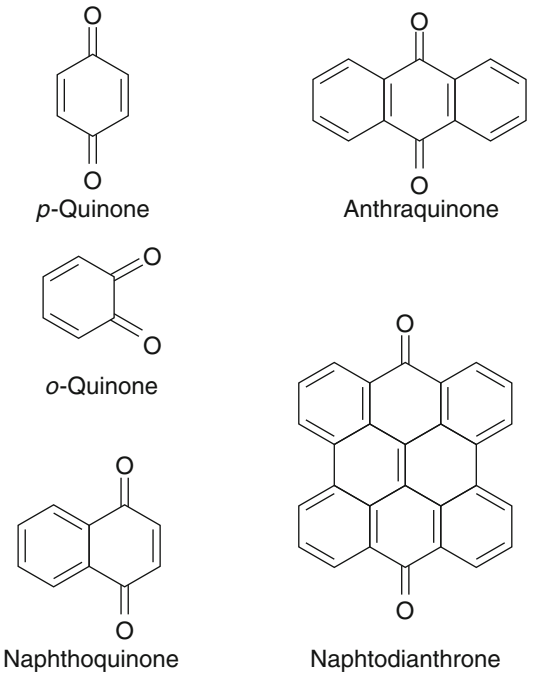


Fig. 14 Skeletal structures of quinines

Quinones

Quinones are kinds of phenolic compounds with a fully conjugated cyclic dione structure, such as that of benzoquinones, derived from aromatic compounds by the conversion of an even number of –CH= groups into –C(=O)– groups with any necessary rearrangement of double bonds. Quinones show a wide range of pharmacological activities, which are the basis for their applications in the broad field of pharmacy and medicine. Plants which are rich in quinones are classically used in industry (dyestuffs) and pharmaceutical (laxatives) practice (Martínez and Bermejo Benito 2005). The most common skeletal structures of quinones found in plants are *p*-quinone, *o*-quinone, anthraquinone, naphthoquinone, and naphtodianthrone (Fig. 14).

Senna leaves are harvested from *Cassia* senna plants, and they are used to make herbal laxatives and tea to treat constipation. The active components in senna are anthraquinone derivatives, namely, rhein, aloe-emodin, chrysophanic acid, and physcion (Fig. 15), which are present both in free and glycoside forms. Sennosides A and B present in senna are the dianthrone derivatives of rhein with two glucose units. The leaves contain maximum sennosides at the time of flowering, and the handpicked pods are superior to black pods with regard to sennoside content. Owning to their chemical structures, the active components in glycoside forms are unabsorbed into the large intestine, where microbial metabolism takes place and the active aglycone is released. The intestinal bacterial flora also accounts for the

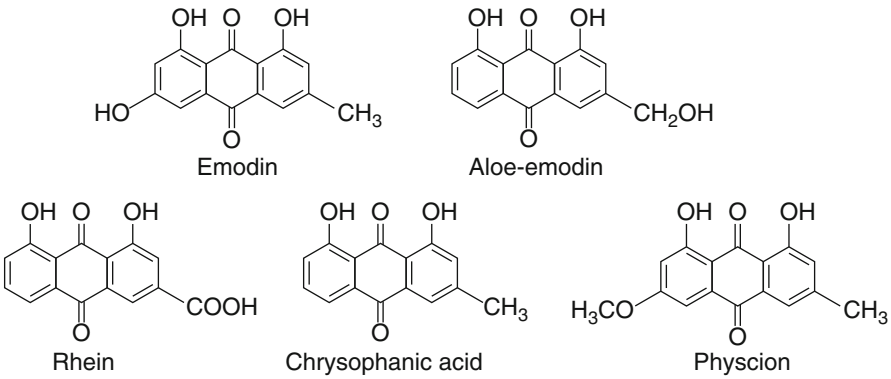


Fig. 15 Chemical structures of emodin, aloe-emodin, rhein, chrysophanic acid, and physcion

reduction of anthraquinone aglycones to the corresponding anthrones. These aglycones exert their laxative effect by damaging epithelial cells, which leads directly and indirectly to changes in absorption, secretion, and motility. The anthranoids are transformed after adsorption mainly into their corresponding glucuronide and sulfate derivatives, which appear in urine and bile (Selvaraj and Chander 2013).

Emodin, an active component present in the root and rhizome of *Rheum palmatum* L., has been shown to exhibit antitumor effects, but the mechanism is not fully understood. Several studies demonstrated that emodin induced cell apoptosis in human lung squamous carcinoma cell line CH27 and cells derived from human colon carcinoma. *Rheum officinale* H. Bn., a Chinese medicinal plant, also contains large amounts of anthraquinones as active compounds (e.g., emodin, chrysophanol, and rhein), which specifically inhibited one of the carcinogenesis-related enzymes (cytochrome P450). Additionally, chrysophanol, emodin, and rhein have been shown to inhibit benzo(α)pyrene-mediated DNA damage in human hepatoma cell line Hep62. In the same way, Kuo et al. (1997) tested four anthraquinones, emodin, emodin-1-glucoside, physcion, and physcion-1-glucoside, purified from another Chinese herb *Polygonum hypoleucum Ohwi* for their effects on antitumor activity in vitro. Emodin, on a percentage basis, was proven to be the most potent one against the various tumor cells proliferation, particularly K562 and Raji cell lines (Martínez and Bermejo Benito 2005).

Aloe-emodin is a natural anthraquinone from *Aloe vera* L. leaves that has been reported to exhibit anti-neuroectodermal tumor activity both in vitro and in vivo. Aloe-emodin has been demonstrated to be nontoxic for normal cells, but to possess potent neuroectodermal tumor cell selective cytotoxicity. Taking into account of its unique cytotoxicity profile and mode of action, aloe-emodin might represent a conceptually new lead antitumor drug. Aloe-emodin also significantly inhibited the growth of Merkel carcinoma cell, a free-floating cell line that was established from a metastasis of a Merkel cell carcinoma patient, and was characterized by

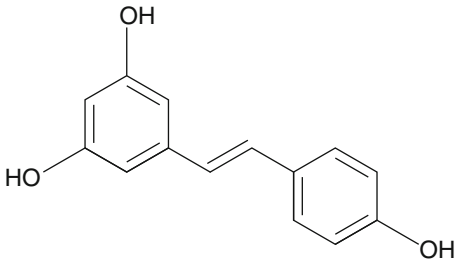


Fig. 16 Chemical structures of resveratrol

immunocytochemical methods using antibodies against the neuroendocrine and epithelial antigens. Aloe-emodin merits further investigation as a potential agent for treating these tumors (Wasserman et al. 2002).

Stilbenes

Stilbenes are a group of phenolic compounds that share a similar chemical structure to flavonoids, in which the two aromatic rings A and B are linked by a methylene bridge. Stilbenes are present in low quantities in the human diet. *Trans*-resveratrol (Fig. 16), mostly present in glycosylated forms, is one of the most recognized stilbenes. Cranberries and grapes contain the amounts of resveratrol between 0.16 and 3.54 mg/kg fresh weight, which contribute to the high concentration of resveratrol in red wine between 0.1 and 14.3 mg/L. Resveratrol is present in peanuts in a relative lower amount between 0.02 and 1.92 mg/kg (Lim and Koffas 2010).

Resveratrol is a potent antioxidant and thereby may play a role in the chemopreventive effects. Resveratrol has been shown to increase the plasma level of antioxidants and reduce the extent of lipid peroxidation in vivo, which may reduce the risk of coronary heart disease and myocardial infarction. Red wine has been reported to inhibit human LDL oxidation in vitro (Teissedre et al. 1996); this protective effect of red wine may be attributed to wine phenolics. In vitro and in vivo studies indicate that resveratrol can suppress platelet aggregation which is one of the major contributors to the atherosclerosis process. Resveratrol has also been shown to reduce the atherosclerotic plaques formation and restores flow-mediated dilation in vivo. These results may partly explain the mechanisms of resveratrol's cardioprotective effects.

Resveratrol has also been reported to inhibit carcinogenesis at the initiation, promotion, and progression stage in both in vitro and animal studies, such as prostate cancer, lung metastases, skin tumors, and colorectal cancer. Several mechanisms have been proposed on the cancer-prevention activity of resveratrol: resveratrol can inhibit the enzymatic activity of cyclooxygenase to inhibit the arachidonic pathway, in which tumor stimulator prostaglandins are produced; resveratrol can induce cell cycle arrest and apoptosis; and resveratrol can inhibit the preneoplastic lesion development to slow down the carcinogenic progression.

Caloric restriction has been thought to be the only way to extend life span since the 1930s. Resveratrol, a potent sirtuin activator, has antiaging and life-prolonging potentials. The biological effect is achieved by the activation of the NAD+−dependent deacetylase sirtuin, which contributes a lot to calorie restriction, thereby extending the life span. Other health benefits of resveratrol such as neuroprotective, antidiabetic, anti-inflammatory, and antiviral activity have also been described both in vitro and in vivo (Fernández-Mar et al. 2012).

Alkaloids

Alkaloids are a group of diverse low-molecular-weight compounds with nitrogenous bases (usually heterocyclic), which make them have potent bioactivity and bitter taste. Chemically, alkaloids are often constituted by one or more rings of carbon atoms with a nitrogen atom inside the ring, and most of them are derived from amino acids. However, its origin from different plant families or different groups of alkaloids makes the position of the nitrogen atom in the carbon ring vary, which leads to diverse structures and functions of the alkaloid family. Up to date, more than 10,000 naturally occurring alkaloids have been discovered from over 300 different plant species. Alkaloids are also isolated from animals, fungi, and bacteria. With the application of different purification and structural elucidation techniques, the structure and biological activity of natural alkaloids are becoming well known; some of them are utilized as pharmaceuticals, stimulants, narcotics, and poisons (Wink et al. 1998). Owing to the fact that alkaloids have a great structural diversity and without uniform classification, here we only highlight the six groups of most common alkaloids, including indole alkaloids, pyrrolidine alkaloids, tropane alkaloids, quinolone alkaloids, isoquinoline alkaloids, and izidine alkaloids.

The group of indole alkaloids is considered as the largest class of alkaloids, which contains more than 1,500 natural products that are traditionally used as medicinal agents. Chemically, indole alkaloids contain a structural moiety of indole (Fig. 17), and many of them also have the isoprene groups. The amino acid tryptophan is the biochemical precursor of all indole alkaloid syntheses (Lewis 2006).

Pyrrolidine alkaloid is a group of alkaloids consisting of 80 natural compounds, and most of them are derived from ornithine and lysine by adding acetate/malonate units. The basic unit is the five-membered carbon rings containing the nitrogen atom. The simple pyrrolidine alkaloid structures can be exemplified by hygrine and cuscohygrine (Fig. 18) isolated from plant Solanaceae. These simple pyrrolidine units can be further derived to other series of alkaloids by condensing with other compounds. Tropane alkaloid is a group of alkaloids that contains a tropane ring and is often esterified with a variety of acids, such as acetic acid, atropic acid, isobutyric acid, isovaleric acid, propanoic acid, tiglic acid, tropic acid, and 2-methylbutyric acid. Most of them occur naturally in species of Solanaceae, Convolvulaceae, and Erythroxylaceae.

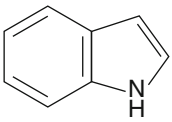


Fig. 17 Chemical structural of indole

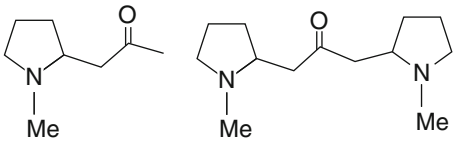


Fig. 18 Pyrrolidine alkaloids

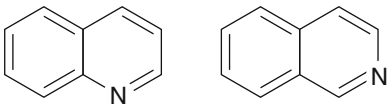


Fig. 19 Quinoline and isoquinoline

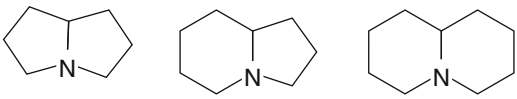


Fig. 20 Skeleton of izidine alkaloids

Quinoline and isoquinoline are the compounds with benzo-fused pyridines (Fig. 19). Quinoline forms part of the structure of quinine which has a 6-MeO substituent and a side chain attached to C_4 of it. Isoquinolines are the alkaloids that are mainly distributed in Papaveraceae (poppy family) and Berberidaceae (barberry family). Isoquinoline has a wide range of biochemical effects; they are usually considered as bioactive ingredients in herbal medicines. For example, they can be used as painkiller, inhibit the growth of cancer cells and bacteria, and stimulate bone marrow leucocytes as well as myocardial contractility.

Izidine alkaloids include some 500 compounds containing a pyrrolizidine, indolizidine, or quinolizidine skeleton (Fig. 20).

A necine base (the hydroxylated pyrrolizidine, Fig. 21) is the basic structure of the pyrrolizidine alkaloids, which could be derived to a series of alkaloids by esterifying with a carboxylic acid either as a monoester, a diester, or a cyclic diester with a dicarboxylic acid. The fourth class of these alkaloids is the *N*-oxides of the above structures. Most of these alkaloids show liver toxic effects.

In the nutraceutical industry, only a few of alkaloids are widely applied, such as the bioactive alkaloids that are isolated from yohimbe, bitter orange, golden seal, caffeine, and ephedra.

Yohimbine (Fig. 22) is an active indole alkaloid with sexual stimulant and aphrodisiac effects found naturally in *Pausinystalia yohimbe* (K. Schumann,

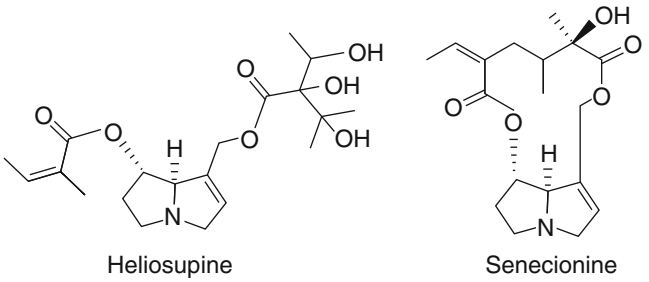
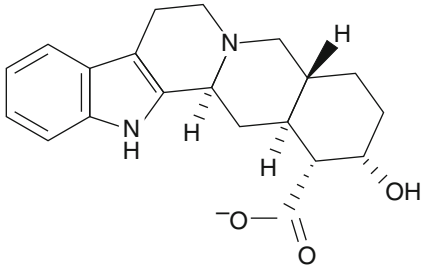


Fig. 21 Pyrrolizidine alkaloids

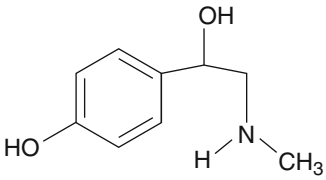
Fig. 22 Chemical structure of yohimbine



Yohimbe). It can increase blood flow to the penis by affecting the central nervous system, specifically stimulating the lower spinal cord region where the sexual responses are conveyed. In the United States, yohimbine in the hydrochloride form has been used to treat the erectile dysfunction as a prescription medicine. The commercial dietary supplements of yohimbe bark with different purity are also widely sold for the treatment of sexual dysfunction and enhancement of sexual satisfaction. However, there are lots of side effects related to the consumption of yohimbine as reported, such as elevated systolic blood pressure and heart rate as well as anxiety, headache, and increased urinary output. So, the patients who have high blood pressure or CVD should avoid the usage of yohimbine; ordinary people should also use it under the supervision of medical doctors (Drewes et al. 2003).

In traditional Chinese medicine, bitter orange can be used for treating a variety of clinical symptoms, including indigestion, diarrhea, dysentery, and constipation, and as an expectorant (Blumenthal 2004; Stohs and Shara 2007). At present, manufacturers like to advertise the extract of *Citrus aurantium* (bitter orange) for weight management and weight loss as well as enhancing sports performance. The main functional compound contained in the extract of bitter orange is *p*-synephrine, which is a protoalkaloidal constituent. Chemically, *p*-synephrine is derived from phenylethanolamine by attaching the hydroxyl group in the para position on the benzene ring of the molecule (Fig. 23). It has been suggested that the synephrine alkaloids extracted from *C. aurantium* are sympathomimetic agents containing both α- and β-adrenergic receptor agonists; these adrenergic agonists can lead to reducing gut motility. Through this signaling pathway, synephrine alkaloids could

Fig. 23 Chemical structure of *p*-synephrine



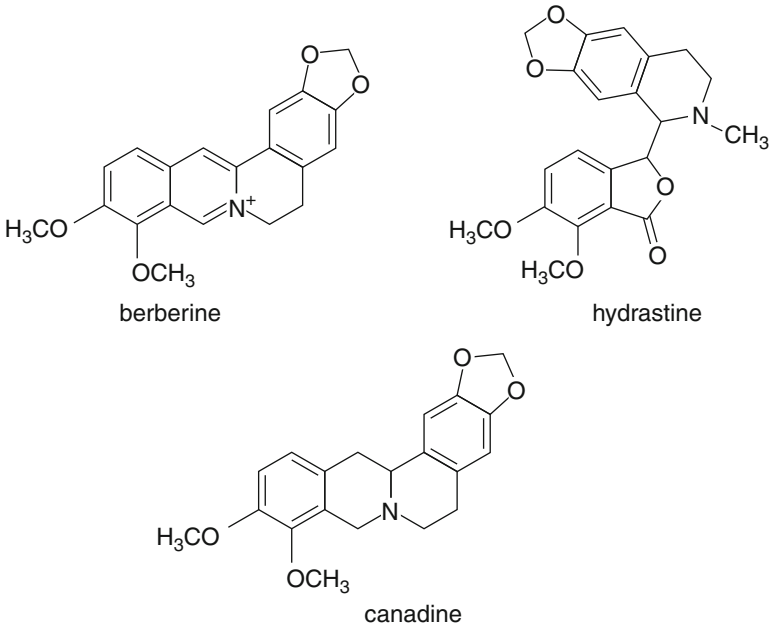


Fig. 24 Structures of three main goldenseal constituents

potentially decrease food intake by keeping the sensation of satiety and increase the burning of energy stored in our body (Haaz et al. 2006).

Goldenseal (*Hydrastis canadensi*) is a native North American plant, which contains a high amount of isoquinoline alkaloids and has been widely used to treat gastrointestinal disturbances, eye infections, and inflammation in a variety of regions for a long history (Upton 2001). The extracts of goldenseal root have been known to have antibacterial, immunostimulant, antimicrobial, and anticancer properties for a long time, all because of these three major alkaloids found in the extracts, berberine, hydrastine, and canadine (Fig. 24). In particular, berberine, the most active and abundant compound in this plant, exhibits multiple pharmacological activities (Brown et al. 2008). Nowadays, goldenseal is available in a wide array as herbal products and has been occupying great international market share. According to the American Herbal Products Association (AHPA), over 90 % of manufacturers sell goldenseal-containing products, and it can create more than $50 million profit annually in the United States alone.

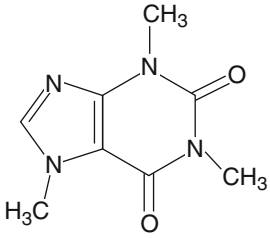


Fig. 25 Chemical structure of caffeine

Caffeine (Fig. 25) is the most abundant purine alkaloid in the coffee plant, and it also belongs to a group of methylxanthines and methyl uric acids derived from purine nucleotides. Caffeine is well known as a stimulator of wakefulness and to enhance concentration and minimize the sensation of fatigue (Heckman et al. 2010). This kind of popularity was due to the active promotion of caffeine products by manufacturers. It gives people a wrong impression that caffeine only has benefit without any side effects. However, scientific studies suggested that high levels of caffeine consumption may have adverse effects on fertility and increase risk of restriction to fetal growth during pregnancy. The recommendation of caffeine consumption limit for women trying to become pregnant is $<$300 mg per day (Kuczkowski 2009). In addition, pregnant women are advised to drink no more than two cups of coffee or four cups of tea per day (Heckman et al. 2010). Regarding the health risks caused by caffeine, many countries should start to establish the regulatory boundaries around caffeine-containing products.

In the food market, caffeine is a common ingredient of lots of beverages (e.g., coffee, tea, cola); energy drinks are the typical commercial beverages that contain variable amounts of caffeine and other ingredients (e.g., guarana, taurine, sugar derivatives). The caffeine content inside those beverages could range between 50 and 505 mg per container (Reissig et al. 2009). In the pharmacy, caffeine can also be sold as over-the-counter cold preparations, stimulants, analgesics, and appetite suppressants (Barone and Roberts 1996).

Ephedra is the evergreen shrub-like plant that mainly grows in Central Asia and Mongolia. Ephedrine (Fig. 26) is the principal active compound isolated from various plants in the genus *Ephedra* (family Ephedraceae), which can powerfully stimulate the nervous system and heart by increasing the activity of adrenergic receptors. Chemically, ephedrine has similar molecular structure with phenylpropanolamine and methamphetamine as well as epinephrine (adrenaline), as it has a phenethylamine skeleton as its basic structure. In the market, it was used to sell in hydrochloride or sulfate salt form.

As a traditional medicine in China and India, ephedra has been used for a long time to treat colds, fever, flu, headaches, asthma, wheezing, and nasal congestion. In the recent time, manufacturers have applied the ephedra as an ingredient in dietary supplements for weight loss purpose. In the herbal market, consumers could find capsules, tablets, tinctures, and teas containing dried stems and leaves of the ephedra plant. It has also been suggested that using ephedrine or ephedrine plus

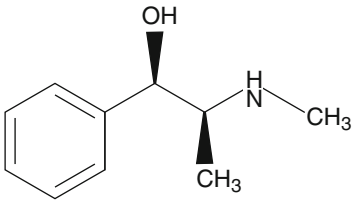


Fig. 26 Chemical structure of ephedrine

caffeine could significantly induce weight loss over a relatively short time (less than or equal to 6 months). However, there has no study that assessed their long-term effects (greater than 6 months). According to the US Food and Drug Administration (FDA), except for short-term weight loss, ephedra could greatly increase the risk of heart problems and stroke. The reasons are still unclear. In 2004, the FDA banned the US sale of dietary supplements containing ephedra. However, ephedra can still be used as traditional Chinese herbal remedies or sold as herbal teas in certain countries (Woolf et al. 2005).

Terpenes

The terpenes or isoprenoids isolated from plant source mostly are the secondary metabolites associated with plant growth and development. Terpenes are considered as the most diverse class of metabolites while there had been over 30,000 types of terpenes discovered. Chemically, isoprene which has the molecular formula C_5H_8 is the basic unit form for terpenes, so that the basic molecular formulas of terpenes could be showed as $(C_5H_8)_n$ where n is the number of linked isoprene units. This is called the isoprene rule or the *C5 rule*. Since the isoprene units may form linear chains by being linked together "head to tail" or form rings, terpenes contain varied compounds with diverse structure (Fig. 27). That is why people classify terpenes according to their molecular formula, such as monoterpenes, C10; sesquiterpenes, C15; diterpenes, C20; sesterterpenes, C25; triterpenes, C30; and so on (Dewick 2001).

In the nutraceutical industry, the most popular terpenes belong to the group of monoterpenes, sesquiterpenes, and tetraterpenes. For example, the monoterpene from thyme oil, parthenolide contained in feverfew, valerenic acid from valerian, lutein, and lycopene are considered as bioactive compounds in different products. Thymol (2-isopropyl-5-methylphenol, IPMP) belongs to the monoterpene group and is biosynthetically derived from cymene, isomeric with carvacrol. It can be extracted from *Thymus vulgaris* (common thyme) or various other kinds of plants as well as in oil of thyme. Purified thymol is a white crystalline substance with strong antiseptic properties and pleasant aromatic odor. In foods, thyme is used as a flavoring agent.

Thymol contains a phenolic structure (Fig. 28), which makes it to have the antimicrobial activity against bacterial strains including *Staphylococcus aureus* and *Aeromonas hydrophila*. The phenolic structure of thymol can inhibit the growth and

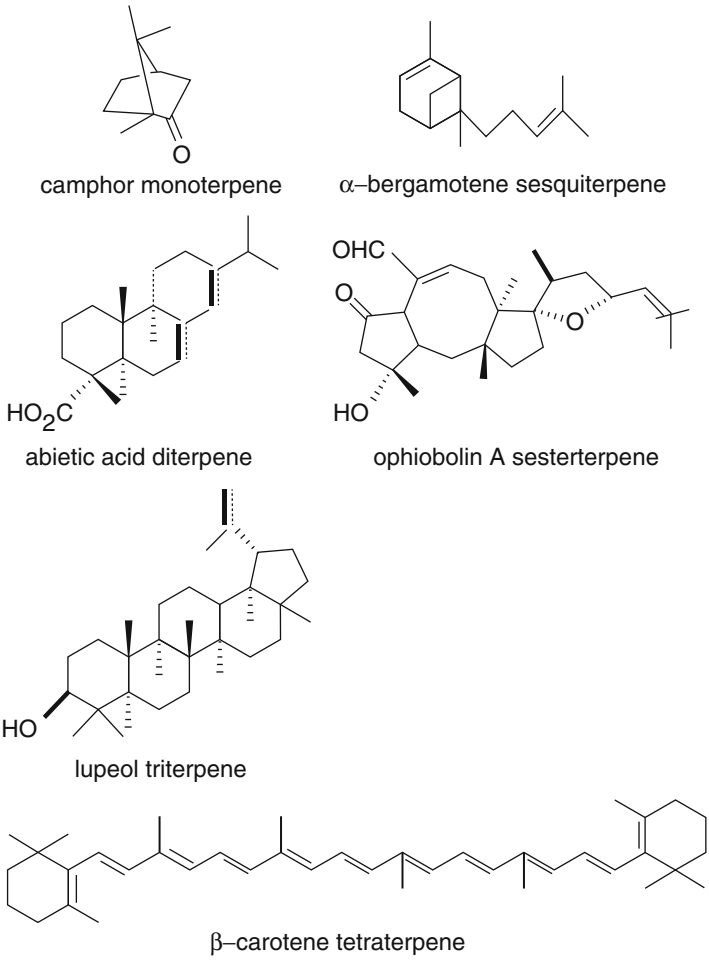
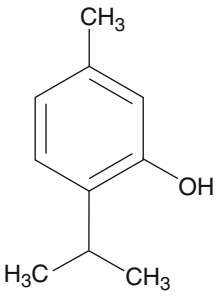


Fig. 27 Typical types of terpenes

Fig. 28 Chemical structure of thymol



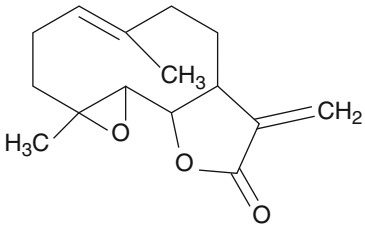


Fig. 29 Chemical structure of parthenolide

lactate production of bacteria as well as decrease their cellular glucose uptake. For medical use, thymol in alcohol solutions or in dusting powder could be used to treat ringworm infections, hookworm infections, and tinea. When combined with chlorhexidine, thymol could be more effective to reduce gingivitis and plaque. It also can be used as an anesthetic. In addition, thymol can be applied as an antiseptic in mouthwash, a preservative in halothane, an ingredient in perfumes as well as in cosmetics, soaps, and toothpastes (Dorman and Deans 2000).

Feverfew (*Tanacetum parthenium*) is a plant that originates from southeastern Europe, but is now widespread throughout Australia, Europe, and North America. In ancient times, feverfew was used to treat menstrual cramps or reduce inflammation; however, at present, it is widely used for preventing migraine headaches by relieving spasms in smooth muscle tissue, and the effectiveness and safety have been proven by several scientific studies. In the market, feverfew supplements are available as tablets, capsules, or liquid extracts, in which at least 0.2 % parthenolide should be contained. Parthenolide (Fig. 29) is a naturally occurring metabolite isolated from feverfew and belongs to the sesquiterpene lactone group. The purified parthenolide is a colorless, bitter-tasting lipophilic compound. Parthenolide was demonstrated to reduce migraine headaches in animal models by decreasing the initial excessive intracranial arterial constriction and directly inhibiting the contraction of vascular smooth muscle. It is also suggested that parthenolide can induce cancer cell apoptosis by inhibiting STAT- and NF-κB-mediated anti-apoptotic gene transcription and directly bind with pattern recognition receptor NOD2. In addition, parthenolide is known to reduce inflammation through the inhibition of NF-κB signaling pathway (Smolinski and Pestka 2005).

Valerian (*Valeriana officinalis*) is a perennial plant with a distinctive odor native to Asia, Europe, and North America. At present, valerian is widely applied as a mild sedative and sleep aid for insomnia and nervous tension. However, there is no conclusive evidence from clinical studies that could prove the efficacy of valerian in treating sleep disorders. In the market, valerian supplements are available as capsules or tablets which are usually made from its roots, stolons, and rhizomes. There are also herbal teas or tinctures available in the market made with dried roots of valerian. The active constituents of valerian remained unclear; it is suggested that the biochemical activity may result from interactions among multiple constituents instead of any single compound. Valerenic acids and its derivatives (Fig. 30) are terpenoids that are isolated from valerian, which belongs to the sesquiterpenoid group. In animal studies, the sedative properties of valerenic acids and its

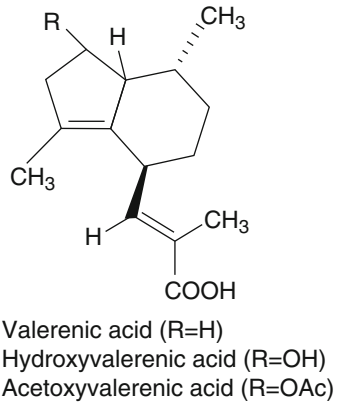


Fig. 30 Chemical structure of valerenic acid and their derivatives

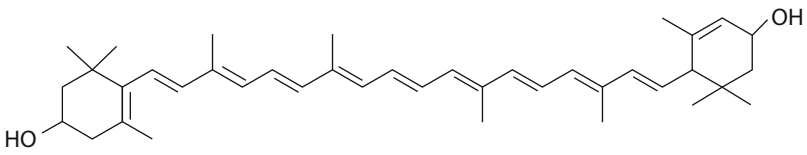


Fig. 31 Chemical structure of lutein

derivatives have been proven. The mechanism behind a valerian extract causing sedation is due to the increased amount of gamma-amino butyric acid (GABA) in the synaptic cleft, which inhibits neurotransmission (Khom et al. 2007; Trauner et al. 2008).

Lutein (Fig. 31) is a xanthophyll belonging to the carotenoid group, which can protect our eyes from the acquired ocular diseases, such as age-related macular degeneration and cataracts. In the eye, lutein can accumulate in the retina and protect it from phototoxic damage by acting as a blue light filter and as an antioxidant. Nowadays, many manufacturers like to add the xanthophyll carotenoids to their multiple vitamin formulas and promote them as the essential nutrients which could greatly benefit your health and your lifestyle. Some companies even develop special eye vitamins containing large amount of lutein and other xanthophyll carotenoids. In manufacturing, marigold flowers are the dominant source of lutein for many lutein supplements. Also, dark green and leafy vegetables such as kale, spinach, and yellow carrots are the major source of lutein we can acquire from food. However, there is no scientific agreement as how much lutein should be taken daily for adequate eye and vision protection; some study shows that dietary intake levels of 6–10 mg/day result in positive effects, while over-consumption of lutein could lead to the bronzing of the skin (Schalch and Weber 1994).

Lycopene is a natural carotenoid predominantly synthesized by plants, which can protect the plants from photosensitization by absorbing visible lights during photosynthesis. Red fruits and vegetables such as apricots, tomato, pink guava, pink

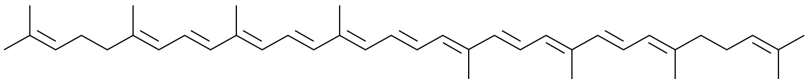


Fig. 32 Chemical structure of lycopene

grapefruit, watermelon, and papaya are the rich sources of lycopene. Especially, tomatoes and their based product are the most common sources of lycopene, which account for more than 85 % of consumption of lycopene in North America (Mangels et al. 1993). Chemically, lycopene is a linear hydrocarbon chain containing 11 conjugated and 2 nonconjugated double bonds (Fig. 32). Under the induction of thermo-energy or light or during chemical reactions, the bonds of lycopene can undergo isomerization from *trans*- to mono- or poly-*cis* isomers (Olson 1989).

As an efficient antioxidant, lycopene can neutralize oxygen-derived free radicals by breaking the double bonds between the carbon atoms. Since many degenerative diseases are caused by the oxidative damage from these free radicals, such as cancer, cardiovascular diseases, cataracts, and premature aging, many manufacturers like to develop dietary supplement products containing tomato lycopene and advertise them as "strong antioxidants that can maintain healthy status."

In the market, lycopene is commonly available in oil-based softgel form, and it can be mixed with other formulations or just by itself. Tomato extracts are also a wide-selling and popular lycopene supplement due to its lycopene content. Also, there is no reported side effect for excessive intake of lycopene except it may cause the bronzing of the skin.

Saponins

Saponins are the bioactive compounds that predominately originate from plants and generally occur as polycyclic triterpenes or steroids with glycosides. Due to their chemical characteristics, saponins have lyobipolar properties, so that they can interact with cell membranes and have the ability to decrease the surface tension of aqueous solutions. Chemically, saponin can be divided into two groups, the triterpenoidal saponins and the steroidal saponins. Steroidal saponins contain 27 carbon atoms which form their core structures, such as spirostan (Fig. 33). However, in nature, (25*R*)-spirostan derivatives ("isosaponins") and (25*S*)-spirostan derivatives ("real" saponins or neosaponins) are the most commonly occurring saponins, which have the A/B/C/D ring structures linked together in the order of *cis-trans-trans* (5β derivatives) or *trans-trans-trans* (5α derivatives). Triterpenoidal saponins or their nor-derivatives contain 30 carbon atoms which form their core structures, such as tetracyclic dammarans and pentacyclic oleanans (Fig. 34). There are also other triterpenoidal saponins, i.e., lupan, oleanan, ursan, and hopan, which have the A/B/C/D ring structures linked together in the order of *trans-trans-trans-cis* (lupan derivatives) or *trans-trans-trans-trans* (oleanan and

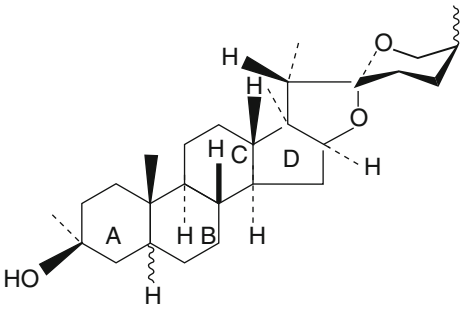


Fig. 33 Core structure of spirostan

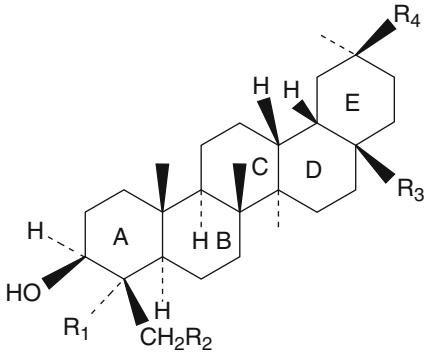


Fig. 34 Core structure of triterpenoid sapogenin with arrangement of rings ABCDE

ursan derivatives), while in dammaran derivatives, the ring order is in *trans-trans-trans* (Hostettmann and Marston 2005).

Black cohosh (*Actaea racemosa* and *Cimicifuga racemosa*) is a perennial plant native to North America and is widely used for the treatment of night sweats, hot flashes, or other menopausal symptoms. The representative triterpene glycosides isolated from black cohosh are actein, cimigenol-3-*O*-arabinoside, cimigenol-3-*O*-xyloside, 23-epi-26-deoxyactein (*syn*-27-deoxyactein), and acetylshengmanol-3-*O*-xyloside (Fig. 35). However, the active compounds of black cohosh still remained unclear. In the market, black cohosh is usually sold as herbal supplement, which is made from roots and rhizomes. The commercial products of black cohosh supplements usually contain 1 mg of total triterpene saponins (using 26-deoxyactein as a standard) per 20-mg dose of extract (Jacobson et al. 2001).

Since the triterpene glycosides found in black cohosh have similar structure with estrogens, they may alter the effects of other chemicals with estrogen-like properties. Even though there is no scientific conclusion that black cohosh has significant effects on estrogen receptors in human, the combination of black cohosh with estrogen should be warned. Regarding the treatment of menopausal symptoms with black cohosh, there are no conclusive scientific results that can prove whether black cohosh is effective to menopausal symptoms since the results from different studies are mixed. Also, most of the studies related to black cohosh are in short

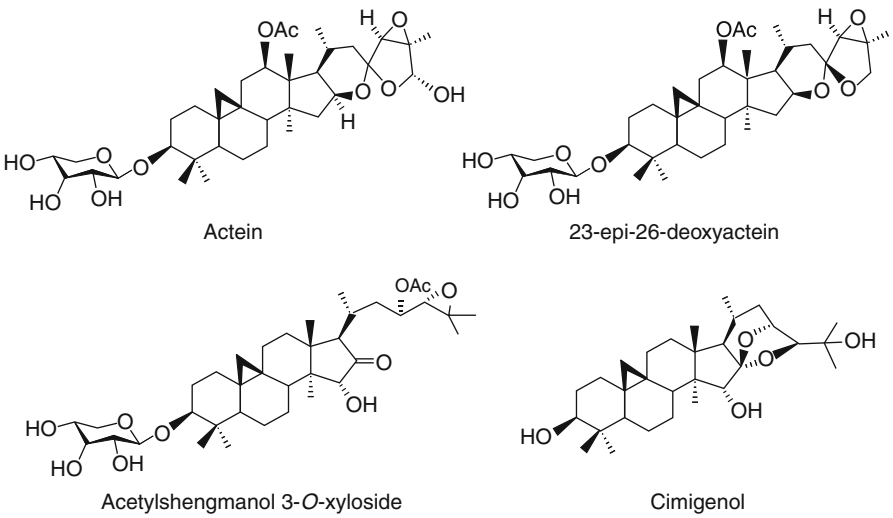


Fig. 35 Chemical structures of major triterpene glycosides found in black cohosh

term; there is lack of long-term study about the safety and effectiveness of the usage of black cohosh. The side effects of using black cohosh have been reported before, even though there are no conclusive scientific evidences that show that it may cause liver damage. However, a warning label should be added on black cohosh products and state that this product could induce harmful effects to your liver and should be used under the supervision of your doctor. So, further studies about the active compounds, mechanism, and potential effects of black cohosh on menopausal symptoms are still needed (Jacobson et al. 2001).

Centella asiatica (CA) is a medicinal herb containing high amounts of triterpenoid saponins which are the primary active constituents of CA. Taking *Centella asiatica* orally can treat the venous insufficiency and varicose veins since the CA can strengthen the walls of veins and stimulate the circulation. Asiaticosides are the major triterpene saponins responsible for the wound healing by increasing collagen formation and angiogenesis. Chemically, asiaticoside has a trisaccharide moiety which is linked with aglycone asiatic acid, madasiatic acid, and madecassoside (Fig. 36). Other than inducing the collagen synthesis, asiaticoside can further heal the wounds by increasing the tensile strength of the newly formed skin. However, there is also a study suggesting that asiaticoside could provoke hypertrophy in scars while inhibiting inflammation (Srivastava et al. 1997). Centelloside is a sugar-free triterpene saponin that is present in fresh plants, which can be used to treat venous hypertension (Heydari et al. 2007). In the market, *Centella asiatica* supplements are available as herbal teas or tablets, which are promoted as the reliever of anxiety, stress, and hypertension. Active constituents isolated from *Centella asiatica* are also widely applied in the area of skin care, which have been advertised as the healer of wounds, burns, and vein ulcers.

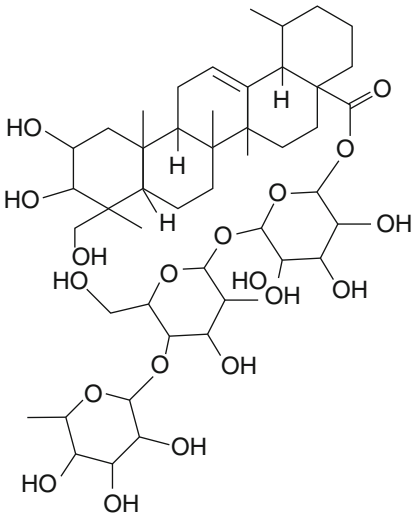
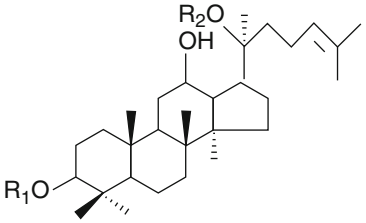


Fig. 36 Chemical structure of asiaticosides

However, the amount of active compounds of *Centella asiatica* is varied among the supplements, as well as in cosmetics.

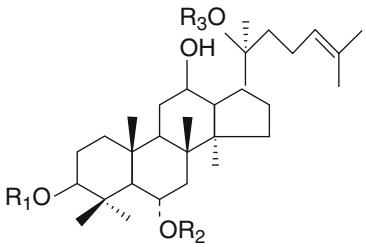
American ginseng (*Panax quinquefolius*) and Asian ginseng (*Panax ginseng* C.A. Meyer) are the two major species of ginseng, which are well known for their preventive and therapeutic properties. Ginsenosides are the primary active ingredients of ginseng and belong to triterpene saponins. About 40 different types of naturally occurring ginsenosides have been found, and they were classified into two groups based on their chemical structure, the panaxatriol and the panaxadiol. In the panaxatriol group, there are ginsenosides Re, Rf, Rg_1, Rg_2, and Rh_1, while in the panaxadiol group, there are ginsenosides Rb_1, Rb_2, Rb_3, Rc, Rd, Rg_3, and Rh_2 (Fig. 37). Generally, Rg_1, Re, Rb_1, Rc, Rb_2, and Rd account for over 90 % of the total ginsenosides, and their ratio is varied among different species of ginseng. Studies have shown that pharmacological activities and therapeutic effects of ginseng could be affected by the ratio of different ginsenosides. For example, panaxatriol group can enhance memory whereas the panaxadiol group does not have this kind of function (Yun 2001). Through chemical analysis, the profiles of the American ginseng have only minor differences with Asian ginseng; only minor differences were found. For example, 24(R)-pseudoginsenoside F_{11} but not ginsenosides $Rf_{1\ and\ 2}$ and Rg_2 was obtained from North American ginseng. However, ginsenoside Rf and lower levels of ginsenoside Rg_2 have been isolated from Asian ginseng.

In China, ginseng roots are used in traditional medicinal therapies for over thousands of years and famous for their magical therapeutic effects. At present, manufacturers like to add the ginsenosides into supplements to generate the herbal supplement improving health status or to produce functional food for preventive benefits. Due to the different ginsenosides contained in ginseng, there are lots of biological activities that have been researched and reported, such as antioxidant



Protopanaxadiol-type

	R1	R2
Rb1	O-G-G	O-G-G
Rb2	O-G-G	O-G-Ap
Rb3	O-G-G	O-G-X
Rc	O-G-G	O-G-Af
Rd	O-G-G	O-G
Rg3	O-G-G	O-H
Rh2	O-G-G	O-H
Aglycone(PD)	O-H	O-H



Protopanaxatriol-type

	R1	R2	R3
Re	O-H	O-G-R	O-G
Rf	O-H	O-G-G	O-H
Rg1	O-H	O-G	O-G
Rg2	O-H	O-G-R	O-H
Rh1	O-H	O-G	O-H
Aglycone(PT)	O-H	O-H	O-H

Fig. 37 Representative ginseng saponins

properties, anticancer effects, acceleration of metabolism, boosting immune system, and enhancing central nervous system. However, there are no conclusive doses of ginseng that should be taken daily to get the positive effects. Some studies suggested that for general preventive effects, 200–400 mg of Panax ginseng should be taken daily, whereas other studies show that 40 mg of Panax ginseng in a multivitamin could be enough (Jia and Zhao 2009).

Conclusion and Future Directions

Nowadays, people start to be concerned with their health status when they aged, so the function and safety of dietary supplements are getting more and more attention. There are more than 60 % of the American population and over 300 million people worldwide taking dietary supplements every day to maintain health. Especially, the botanical dietary supplements are isolated from natural plants holding more attention than others, and they have occupied an important and ever-growing portion of the market. In this chapter, we give the general and specialized reader a comprehensive insight into the most recent findings of some dietary supplement functional foods, which may contain simple phenolics, coumarins, lignans, flavonoids, isoflavonoids, anthocyanins, tannins, quinones, stilbenes, alkaloids, terpenes, and saponins that originated from plant sources.

Even though natural compounds can provide health-essential and health-improving nutrients, they can be toxic to our body or be transformed to toxic

compounds by our system. The safety, efficacy, or working mechanisms of large amount of botanical natural compounds remain unclear, but it does not stop the use and the sales of botanical supplements continue to expand rapidly in our market. That is why further research is needed to optimize the process of isolating these bioactive substances from their respective sources so as to improve the purity and quality of extracted bioactive compounds. Besides, clinical trials, which can generate reliable data on both the efficacy and the safety of these bioactive compounds on treating/preventing certain disease, are essential before widely applying them on the market.

Cross-References

- ▶ Chemical Composition of Beverages and Drinks
- ▶ Chemical Composition of Cereals and Their Products
- ▶ Chemical Composition of Vegetables and Their Products
- ▶ Plant-Associated Natural Food Toxins

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