REVIEW

Astonishing Diversity of Natural Surfactants: 5. Biologically Active Glycosides of Aromatic Metabolites

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ABSTRACT: This review article presents 342 aromatic glycosides, isolated from and identified in plants and microorganisms, that demonstrate different biological activities. They are of great interest, especially for the medicinal and/or pharmaceutical industries. These biologically active natural surfactants are good prospects for the future chemical preparation of compounds useful as antioxidant, anticancer, antimicrobial, and antibacterial agents. These glycosidic compounds have been classified into several groups, including simple aromatic compounds, stilbenes, phenylethanoids, phenylpropanoids, naphthalene derivatives, and anthracene derivatives.

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The father of modern medicine was Hippocrates, who lived sometime between 460 and 377 BC. Hippocrates left historical records of pain-relief treatments, including the use of a powder made from the bark and leaves of the willow tree to help heal headaches, pains, and fevers. Since the time of Hippocrates, people have chewed on willow leaves and bark to alleviate pain. About 2,000 years later, aspirin began being manufactured from a compound extracted from the tree. As it turns out, that family of compounds, called phenolic glycosides, also plays a key role in plant health, making many plants tough and disease resistant.

Aromatic compounds, including phenolic compounds, are widely distributed in the plant kingdom (2). These compounds are essential for the growth and reproduction of plants and are produced as a response to defend injured plants against pathogens. In recent years, interest has been growing in aromatic compounds and their presumed role in the prevention of various degenerative diseases, such as cancer and cardiovascular diseases (3–5). The antioxidant activities of aromatic compounds and their possible use in processed foods as natural antioxidants have gained considerable recognition in recent years (3,6,7). Terrestrial vascular plants and their aquatic counterparts contain several types of phenylpropanoid metabolites. In vascular plants, this pathway provides major classes of organic compounds of specialized function and structure. These include neolignans and lignans, structural cell wall polymers (lignins and the aromatic portion of suberins), proanthocyanidins (condensed tannins, i.e., the phenylalanine-derived portion), and related compounds. Without this pathway, the normal growth, development, and survival of both woody and nonwoody plants would not be possible. Indeed, since approximately 10–45% of all vascular plant material is of phenylpropanoid origin, these metabolites constitute a major sink of organic carbon. Many of these molecules can occur in plants in the form of glycosides, which means they have one or more simple sugars, such as glucose, galactose, mannose, xylose, or another sugar attached to them. Not only are thousands of aromatic compounds known, but some of the smaller molecules also can polymerize, or join together to form larger and more complex molecules. Different kinds of molecules might be found in one polymer (8–11).

Phenolic compounds (a molecule containing an aromatic ring that bears one or more hydroxyl groups is referred to as "phenolic") can also be bound to certain proteins, polysaccharides, or lipids (12–18), and as if this were not complex enough, some molecules can have multiple isomers, forms in which their atoms are arranged slightly differently.

Simple and polyphenolic compounds and/or their glycosides of fruits and vegetables may play an important role in physiological functions related to human health (19–26). Different polyphenolics may have varied biological activities, such as having anticancer, anti-inflammatory, cytostatic, cytotoxic, antimitotic, neurotoxic, antiplatelet, antibacterial, antifungal, aggregational, or antiradical activities, as well as antioxidant or cardioprotective activities (3,20,22,24,27–29).

Aromatic glycosides, representative of a large group of natural compounds mainly originating from plant species that can be separated on several groups, including simple aromatic glycosides, stilbene glycosides, phenylethanoid and phenylpropanoid glycosides, naphthalene glycosides, and glycosides of anthracene derivatives (anthraquinones, angucyclines, oxanthrones, and anthrones), as considered in this review article.

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For the previous article in this series, see Reference 1.

Abbreviations: D-GalN, D-galactosamine; EC_{50}, the median effect concentration, being a statistsically derived concentration of a substance that can be expected to cause (i) an adverse reaction in 50% of organisms or (ii) a 50% reduction in growth or in the growth rate of organisms; GI_{50}, the concentration needed to reduce the growth of treated cells to half that of untreated (i.e., control) cells; HUVEC, human umbilical vein endothelial cells; IC_{50}, concentration at which growth or activity is inhibited by 50% (applies to ligand and growth inhibition); K_i, prolyl hydroxylase activity, expressed as mol/mg protein; LLC, Lewis lung carcinoma; LPS, lipopolysaccharide; MIC, minimum inhibitory concentration of an antibiotic that inhibits a bacterium; MPP^+, 1-methyl-4-phenylpyridinium ion; OLE, olive leaf extract; SDG, secoisolariciresinol diglycoside **245**; TNF-α, tumor necrosis factor α.

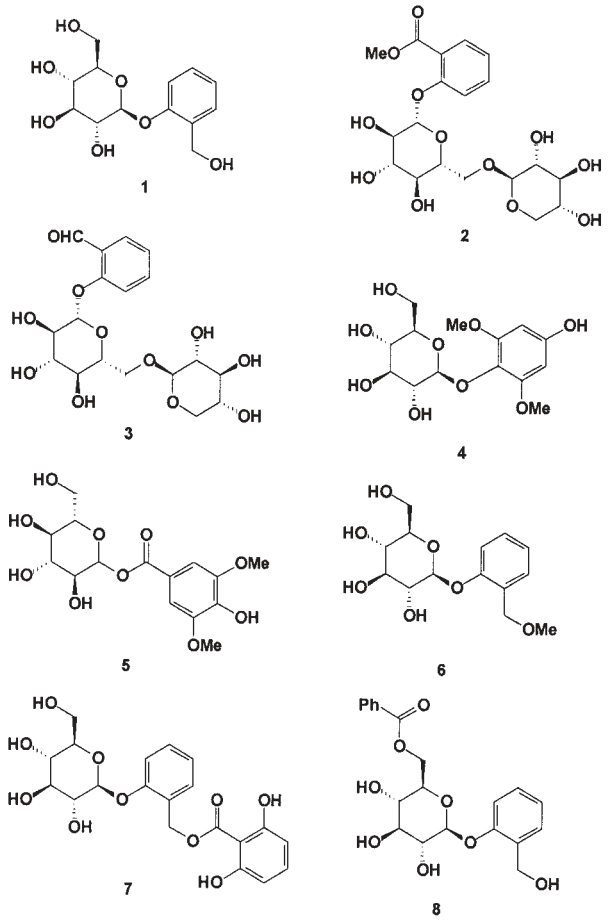
SIMPLE AROMATIC GLYCOSIDES

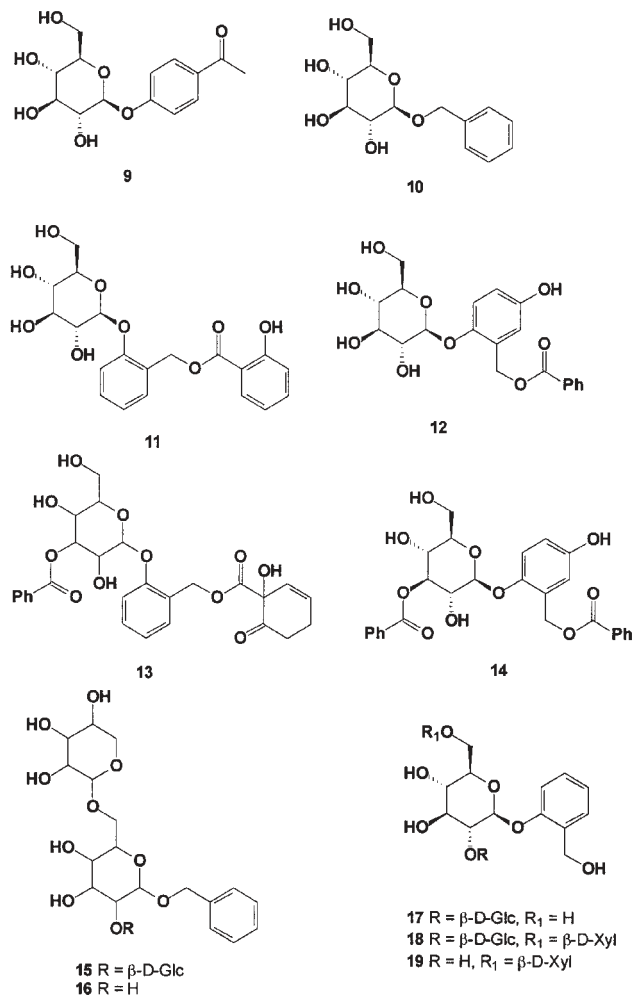
Simple aromatic (including phenolic) glycosides have been isolated mainly from plants, although a few compounds have been isolated from microorganisms. Compounds in this group often also possess alcoholic, aldehydic, and carboxylic acid groups. Medicinal herbs constitute an important source of biologically active compounds, and they have given us a number of important drugs that are mainstays of treatment in synthetic systems of medicine (30–32).

The Egyptians (*ca*. 1500 BC) recorded a collection of recipes for medicines that included a recipe using an infusion of dried myrtle leaves (which contain salicylic acid) to relieve back pain. The effects of aspirin-like substances have been known since the ancient Romans recorded the use of willow bark as a fever fighter. The leaves and bark of the willow tree contain a substance called salicin, **1**, a naturally occurring compound similar to acetylsalicylic acid (aspirin) (33). Aspirin is probably the most successful medicine of all time, and new uses for it continue to be discovered (34–37).

In 1828, Johann Buchner, a professor at Munich University, isolated pure salicin from willow bark (*Salix alba*). Two Italians, Luigi Brugnatelli and Carlo Fontana, had in fact already obtained salicin in 1826, but in a highly impure form. By 1829, Henri Leroux, a French chemist, had improved the extraction procedure to obtain about 30 g from *S. alba* bark. In 1838, Raffaele Piria, an Italian chemist then working at the Sorbonne in Paris, split salicin into a sugar and an aromatic component (salicylaldehyde) and converted the latter, by hydrolysis and oxidation, to an acid of crystallized colorless needles, which he named salicylic acid (38–43). The name salicin was derived from *salix*, which is the Latin word for willow tree. Many well-known drugs have come from studying natural plant compounds such as salicin, the active constituent found in white willow bark. This herb has been used for centuries to ease discomfort associated with the joints and muscles. Occurring as white crystals or powder, salicin has analgesic, antipyretic, disinfectant, and antiseptic properties, and it has been found in a number of plant species: *S. alba, Salix tetresperma, Salix fragilis, Populus nigra, Populus alba, Populus tremula*, and *Filipendula ulmaria* (39–44).

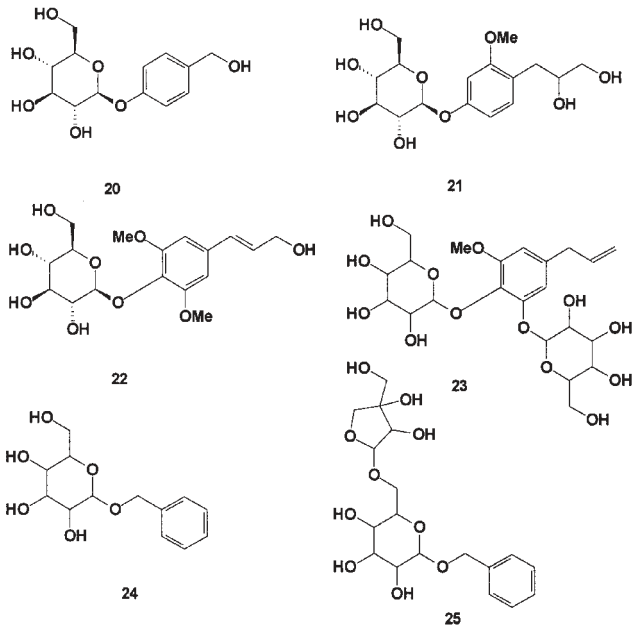
Salicin-related compounds, such as gaultherin **2** (formerly known as monotropitoside or monotropitin), monotropin, and spiraein are some of the known compounds present in plant flora having activity similar to salicin. Gaultherin **2** is a glycoside of methyl salicylate that is present in *Gaultheria procumbens* (wintergreen); it is also known as monotropitoside and is used as a source for the manufacture of salicylic acid (44). Salicin is found in most Salicaceae species, together with other much less abundant glycosides such as populin, tremuloidin, fragilin, glycosmin, picein, salireposide, grandidentatin, triandrin, salicylpopulin (salicyloylpopulin), and salidroside (salicyloylpopulin) (45). Salicylates have long been known as water-soluble compounds derived from a number of plants, particularly willow (*Salix* spp.), meadowsweet (*Spirea* spp. and *F. ulmaria*), sweet birch (*Betula lenta*), white birch (*Betula pendula*), wintergreen (*G. procumbens*), balsam poplar (*Populus balsamifera*), black poplar (*P. nigra*), balm of Gilead (*Populus candicans*), black haw (*Viburnum prunifolium*), and sweet violet (*Viola odorata*), with analgesic, antipyretic and anti-inflammatory properties (46–48). In 1953, Paris and Pointet (49) reported the presence of gaultherin **2** in the bark of *Ostryopsis davidiana*. More recently, Towers *et al*. (50) studied leaf extracts of 22 species of *Gaultheria* after acid or alkali hydrolysis, yielding *p*-hydroxybenzoic, *o*-pyrocatechuic, protocatechuic, gentisic, vanillic, *p*-coumaric, caffeic, and ferulic acids, and found that 13 species contained derivatives of salicylic acid as well; the glycoside gaultherin **2** was isolated from *G. procumbens* and *Gaultheria hispidula*. Gaultheria oil (or wintergreen oil), which consists almost solely of methyl salicylate, was formerly distilled on a commercial scale from the leaves of this species. *Gaultheria procumbens*, also known as teaberry, wintergreen, Canada tea, partridge berry, checkerberry, boxberry, wax cluster, spice berry, mountain tea, deerberry, spicy wintergreen, aromatic wintergreen, chink, ground berry, grouse berry, red pollom, redberry tea, hillberry, and ivory plum, is related to the Northwest native evergreen groundcover *Gaultheria shallon*, which was used by Quinault and Klallum Indians for its medicinal properties as a stimulant, antiseptic, astringent, diuretic, emmenagogue, and aromatic, and was also useful in chronic inflammatory rheumatism, rheumatic fever, sciatica, diabetes, all bladder troubles, scrofula, and skin diseases (51). Spiraein **3**, which contains salicylaldehyde, xylose, and glucose, was first isolated from *F. ulmaria* (52) and was later was found in other plant species, i.e., *Populus tremuloides*, *Salix purpurea*, *S. fragilis, Salix nigricans*, and *Salix rosmarinifolia* (53). Leonuriside A **4** and erigeside C **5** were isolated from the aerial parts of *Acanthus ilicifolius* (54). Two new salicin derivative glucosides, 7-*O*-methylsalicin **6** and 7-*O*-(2,6-dihydroxy-benzoyl)salicin **7**, were isolated from the leaves of *Alangium platanifolium* var. *trilobum* (55). Salicin **1** and populin **8** were isolated from hot-water bark extracts of *Populus tomentosa*, *Populus davidiana*, *Populus euphratica*, and *Populus simonii* (56).





HPLC analysis of the bark of *Salix petiolaris* (*S. gracilis* var. *textoris*), which was collected in November, was shown to contain salicin **1**, populin **8**, picein **9**, salicyloylsalicin **11**, salireposide **12**, grandidentatin, vimalin, tremulacin **13**, and salicyloylsalicin-2-*O*-benzoate **14** (57). Golden root (*Rhodiola rosea*) has been used for many years as an adaptogen in Chinese traditional medicine and was reported by Tolonen *et al*. (58) to have many pharmacological properties; its known phenylpropanoid metabolites, picein **9** and benzyl-*O*-β-glucopyranoside **10**, were recently isolated. Three new glycosides, benzyl alcohol β-D-glucopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→6)]-β-D-glucopyranoside **15**, 2′-*O*-β-D-glucopyranosylsalicin **17**, and 2′-*O*-β-D-glucopyranosyl-6′-*O*-β-D-xylopyranosylsalicin **18**, along with the known benzyl alcohol β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside **16** and 6′-*O*-β-D-xylopyranosyl-salicin **19**, were isolated from the water-soluble fraction of the dried leaves of *Alangium chinense* (59).

Dill (*Anethum graveolens*) has been cultivated in Europe since antiquity and is popular aromatic herb and spice. Its seed also has been used for medicinal purposes to relieve digestive problems and to stimulate milk for nursing mothers. Dill water was believed to have a soothing effect on the digestive system and was given to babies to relieve hiccups and colic, and essential oils from dill have antimicrobial (60,61), antihyperlipidemic, and antihypercholesterolemic activities (62). From the water-soluble fraction of an ethanol extract of dill seed, which has been used as a spice and medicine, 33 compounds were obtained, including the known compound **10** and the new aromatic glucosides **20**–**25** (63).

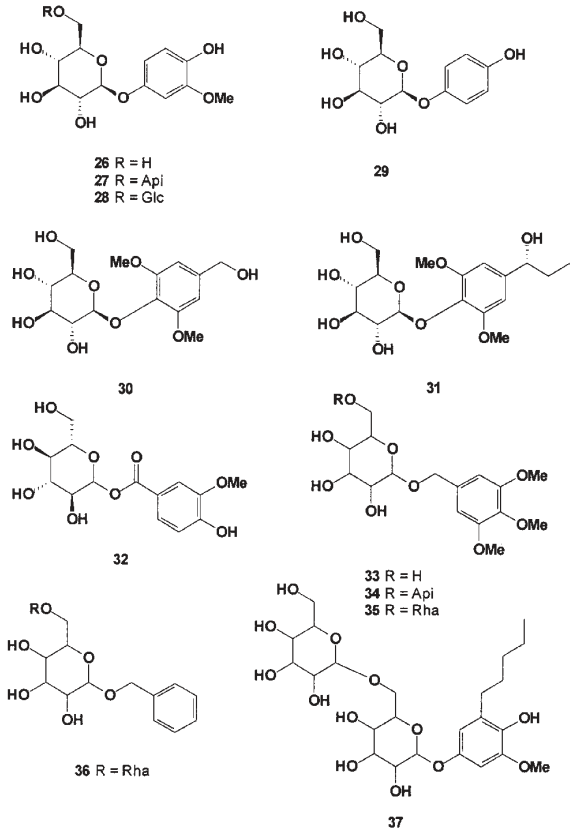


Important crude drugs from the *Atractylodes* plant (Japanese name *jutsu*), *Atractylodes* rhizome [*Atractylodes japonica* and *Atractylodes ovata* (Japanese name *byaku-jutsu*)], and *Atractylodes lancea* rhizome [*A. lancea* and *Atractylodes chinensis* (Japanese name *so-jutsu*)] are used as diuretics and stomachics (64). The new aromatic glycosides **26**–**29** were isolated together with 10 known compounds, including **25**, from the water-soluble fraction of the fresh rhizome of *A. japonica* (65).

Coriander (*Coriandrum sativum*) has one of the longest recorded histories of any of the spices. There is evidence that this native of the Mediterranean and Near East has been in use since 5000 BC. Its seeds have been found in Bronze Age ruins on the Aegean Islands and in the tombs of the pharaohs. Coriander is mentioned in the Ebers Papyrus and in the books of Moses. It was grown in Assyria and Babylon and was used in minced meat dishes, sausages, and stews. The seeds have been used as a drug for indigestion, against worms, and as a component of embrocations for rheumatism and pains in the joints. From the water-soluble portion of a methanol extract of coriander fruits, two new aromatic glycosides, **30** and **31**, were isolated together with the known compounds **4**, **24**, and **25** (66).

The seed of the *Amomum* plant is one of the most ancient and highly valued spices in the world. The seed of *Amomum xanthioides* (Zingiberaceae) also has been used for medicinal purposes; it is prescribed in traditional medicines for stomachic and digestive disorders and contains the simple aromatic glycosides **24** and **32** (67).

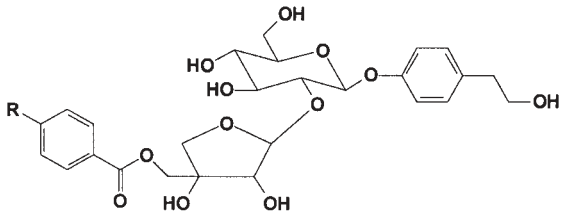
The Aceraceae plant *Acer nikoense* is indigenous to Japan (Japanese name, *megusurinoki*), and its stem bark has been used as a folk medicine for the treatment of hepatic disorders and eye diseases. The new aromatic glycoside nikoenoside **33** and also kelampayoside A **34**, **35**, and **36** were isolated from the stem bark of *A. nikoense* (68).



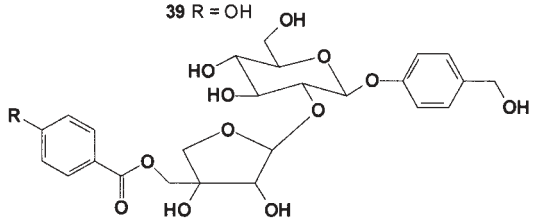
Plants of the genus *Eugenia* showed antidiabetic (69), hypoglycemic (70), and also antibacterial and antifungal activities against gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*), gram-negative bacteria (*Salmonella typhimurium, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Escherichia coli*), and fungal strains (*Candida albicans, Cryptococcus neoformans, Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Rhizopus* sp., *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Microsporum gypseum*) (71). Lambertianoside **37**, a novel phenylglycoside with anti-HIV activity, has been isolated from the aqueous extract of leaves from *Eugenia lambertiana* [HIV EC_{50} (i.e., median effect concentration causing an adverse reaction in 50% of organisms or a 50% reduction in the growth or growth rate of an organism), 3 μg/mL; HIV IC_{50} (i.e., 50% inhibition concentration), 25 μg/mL] (72).

Pumpkin, the fruit of *Cucurbita moschata* (Cucurbitaceae), has been a popular vegetable in cooking since antiquity, and salted, roasted pumpkin seeds are used in several countries as snacks; pumpkin seeds are also an important traditional Chinese medicine used in the treatment of cestodiasis, ascariasis, and schistosomiasis. Pharmacological studies on the seeds have demonstrated hepatoprotective (73) and antitumor activities (74). The new phenolic glycosides cucurbitosides A–E, **38**–**42**, were isolated from the seeds of *C. moschata* (75). The dried stem bark of *Albizzia julibrissin* (Leguminosae) has been used in Chinese herbal medicine to treat insomnia, diuresis, asthenia, ascaricide, and confusion. From the stem bark of *A.*

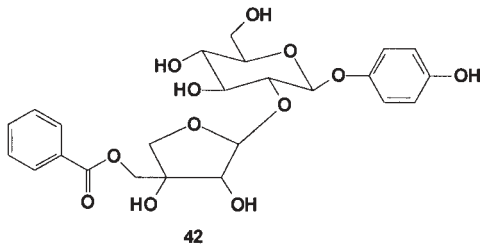
julibrissin, two new phenolic glycosides were isolated, albibrissinosides A **43** and B **44**. Albibrissinoside B **44** showed a strong 1,1-diphenyl-2-picrylhydrazyl radical-scavenging activity, with an IC_{50} value of 10.2 μM (positive control, L-ascorbic acid IC_{50} 10.4 mM), whereas albibrissinoside A **43** showed a weak scavenging activity, with an IC_{50} value of 253 μM (76).



38 R = H
39 R = OH



40 R = H
41 R = OH



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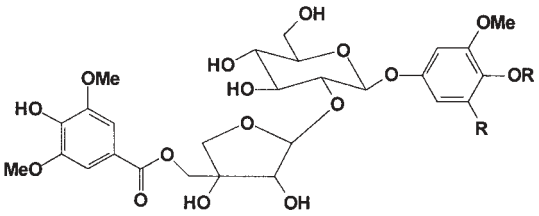
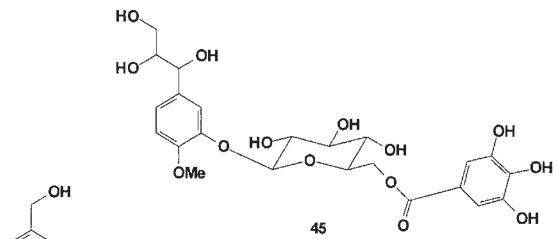


43 R = Me, R_1 = OMe
44 R = R_1 = H

Three new phenolic compounds, 2-methoxy-5-(1′2′3′-trihydroxypropyl)-phenyl-1-*O*-(6″-galloyl)-β-D-glucopyranoside **45**, 2-methoxy-5-hydroxymethyl-phenyl-1-*O*-(6″-galloyl)-β-D-glucopyranoside **46**, and 1-galloyl-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside **47**, were isolated from the leaves of *Baseonema acuminatum* (Asclepiadaceae) (77). The antimicrobial activity of all compounds was evaluated *in vitro* against the bacteria *S. aureus* (two strains), *Bacillus cereus*, *B. subtilis*, *E. coli*, and *Salmonella typhimurium* and against three strains of *C. albicans*. The new compounds **45** and **46** showed antifungal activity against two clinically isolated *C. albicans* strains and against *C. albicans* ATCC 2091 [minimum inhibitory concentration (MIC) values in the range of 25–100 μg/mL]. Compound **47** inhibited only one strain of *C. albicans* at the maximum concentration used. Melilotoside **48** was isolated from *Ephedra nebrodensis* (78). The new phenolic glycosides quercetin β-D-glucopyranosyl 4-*O*-β-D-glucopyranosylcaffeate **49**, methyl 3-*O*-β-D-glucopyranosyl-5-hydroxycinnamate **50**, and β-D-glucopyranosyl 4-*O*-β-D-glucopyranosylbenzoate **51** were isolated from the flowers of *Moricandia arvensis* (79). Compounds **49**–**51** showed antioxidant activity, and **49** proved to possess the most potent radical-scavenging activity.



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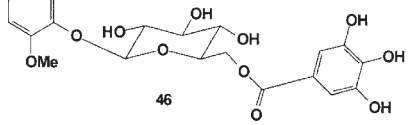

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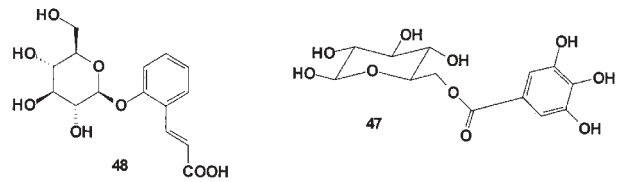

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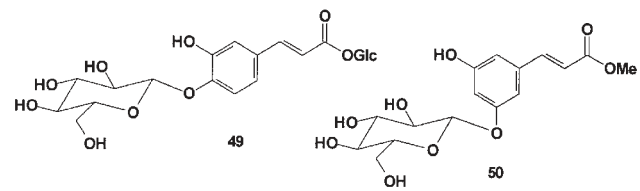

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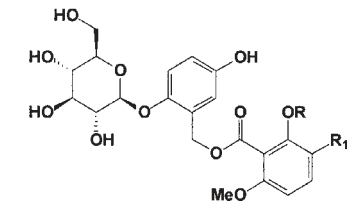
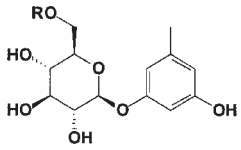
Curculigo orchioides (Amaryllidaceae) is a tiny herbal plant widely distributed in China, India, Malaysia, Japan, and Australia. Its rhizomes have the properties of warming the kidneys, invigorating yang, expelling cold, and eliminating dampness, and are used as the traditional Chinese medicine *xian mao* to cure impotence, enuresis, cold sperm, cold pain of the back and knee, and numbness of the limbs (80). In India, the tuberous roots of this plant are considered to be a tonic, alterative, demulcent, diuretic, and restorative, and are used as a poultice for itching and skin diseases (81). Three phenolic glycosides, curculigosides **52**, B **53**, and C **54**; orcinol glycoside **55**; and anacardoside **56** have been isolated from the rhizomes of *C. orchioid*es and have been described in some recently published papers (81–88).

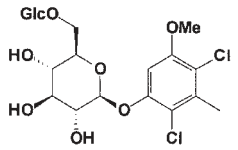
Three rare new chlorophenyl glycosides, curculigin A **57**, B **58**, and C **59**, have been isolated from *C. orchioid*es (82,86). A new chlorine-containing phenoloid named capitulatin A **60** has been isolated from the rhizomes of *Curculigo capitulata* (89).



52 R = Me, R_1 = H
53 R = R_1 = H
54 R = Me, R_1 = OH



55 R = H
56 R = Glc



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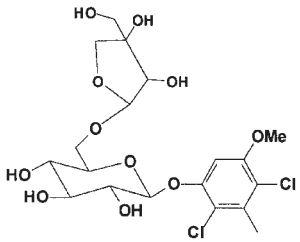

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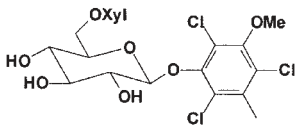

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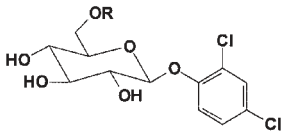
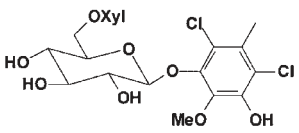


61 R = H
62 R = Malonic acid
63 R = Api



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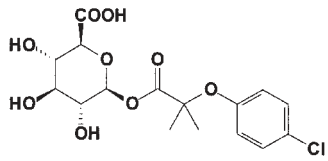
Three chlorophenyl glycosides **61**–**63** were extracted from the tissues of *Lemna minor* exposed to 2,4-dichlorophenol (90). Chlorophenols are an important class of xenobiotics used in a variety of biocides and have been shown to be resistant to microbial degradation. Enzyme-catalyzed hydrolysis with β-glucosidase was found to be ineffective in releasing the β-glucosides with chemical modifications at C-6. The presence of these glucoconjugates confirmed that *L. minor* was capable of xenobiotic uptake and transformation. The products identified suggested that chlorophenols were incorporated into the vacuoles and cell walls of *L. minor* (90). The chlorophenol glucuronides **64** and **65** were isolated from human urine (91). β-(2-Chloroethyl)-D-glucoside **66** was isolated from the green plant *Taraxacum officinale* (92). Chlorophenol glycosides with the common structure **67** can be synthesized by aquatic plants and have been isolated from aquatic environments (93).



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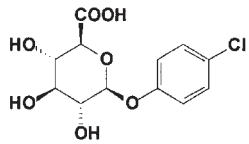

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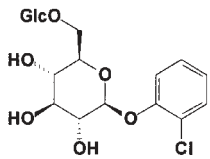

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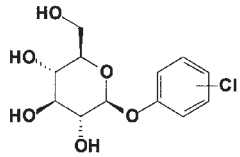
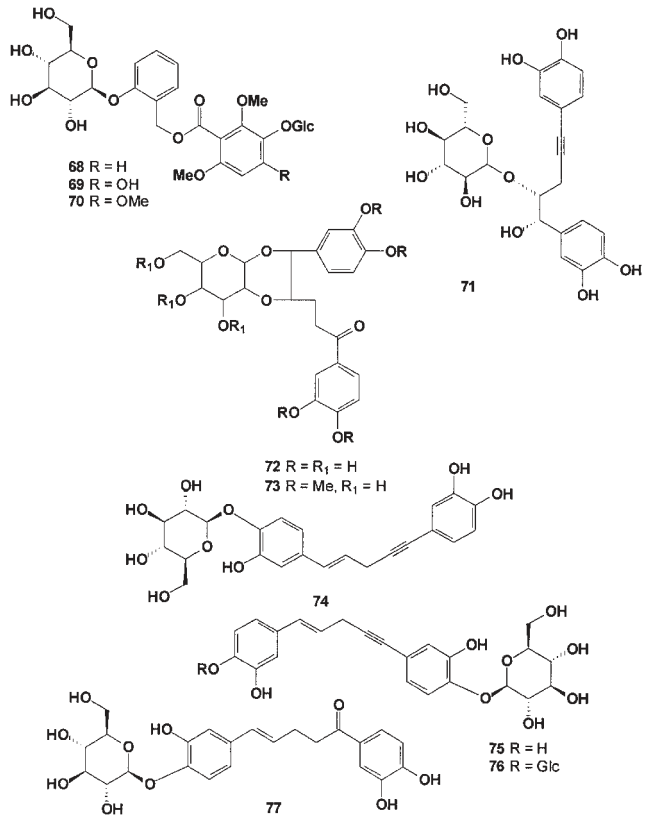
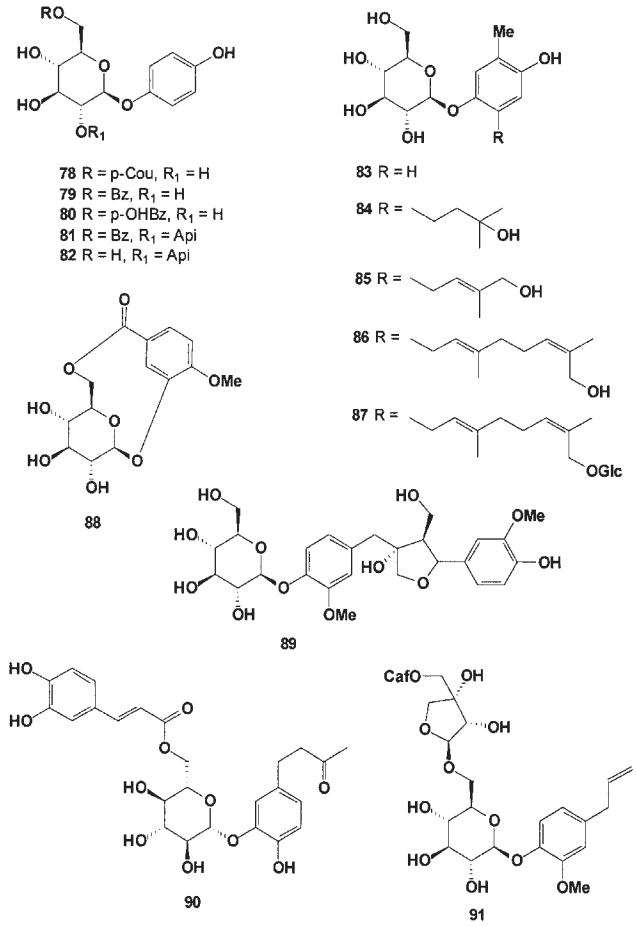


67

From the rhizomes of *Curculigo pilosa*, two benzylbenzoate diglucosides, piloside A **68** and B **69**; the *O*-methyl derivative **70**; nyasicoside **71**; and a glucosyl-fused norlignan, pilosidine **72**, previously obtained only as the tetra-*O*-methyl derivative **73**, were isolated. Pilosidine **72** showed a facilitating effect on adrenaline-evoked contractions in rabbit aorta (85). Nyasicoside **71** also was found in the rhizomes of *C. capitulata* (94). A monoglucoside, shipamanine **77**, and the related compounds obtuside A **74**, obtuside B **75**, and hypoxoside **76** were isolated from the rhizomes of *Hypoxis obtusa* (95,96). Shipamanine **77** and hypoxoside **76** showed antiviral, antitumoral, and analgesic activities.





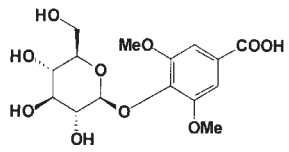
The poisonous perennial shrub *Breynia officinalis* (Euphorbiaceae) grows in Okinawa, Taiwan, and southern China. It is administered orally as a remedy for healing wounds and edema, as an ointment, for syphilis, and for intestinal hemorrhage due to overwork (97). The novel phenolic glycosides **78**–**82** have been isolated from the leaves of *B. officinalis* collected on Okinawa Island (98).

The herbaceous plant *Pyrola japonica* (Pyrolaceae) is widespread in Korea, Japan, and China; the leaves are used as a detoxicant for the bites of snakes, insects, and dogs, and as a drug to cure yellowish and bloody sputum (99). Five new phenolic glycosides, **83**–**87**, were isolated from the whole plants of *P. japonica* (100), and a new cyclic compound, jujuphenoside **88**, was isolated from the seeds of *Ziziphus jujuba* var. *spinosa* (101).

Three active glycosides (including sinenoside 1 **89**), which afford protection to red blood cell membranes to resist hemolysis induced by the peroxyl radical initiator 2,2′-azo-bis-(2-amidinopropane) dihydrochloride, were isolated from *Ligustrum sinense* (102). Dracunculifoside K **90** and N **91**, and 10 other glycosides were isolated from the aerial part of *Baccharis dracunculifolia* (Compositae); these compounds have an (*E*)-caffeoyl group like dracunculifosides A–J, which were reported previously (103).

Syringic acid 4-β-D-glucoside **92** was isolated from the aerial part of *Erigeron breviscapus* (104), and a lignan, glycoside (−)-secoisolariciresinol-*O*-α-L-rhamnopyranoside **93**, was isolated from the aerial parts of *Rubus amabilis* (105). Dictamnoside A **94** was isolated from the whole herb of *E. breviscapus* (106).

Four erythro-anethole glycol monoglucosides, **95**–**98**, and two new glycosides of *p*-hydroxyphenylpropylene glycol were isolated from the methanolic extract of the seed of *Foeniculum vulgare* (Umbelliferae). This is the first report of the isolation of all four *O*-β-D-glucopyranosides, which have the glucosyl unit attached to the hydroxy group of the erythro-glycol function of individual stereoisomeric aglycons (107).



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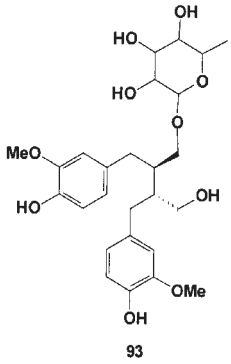

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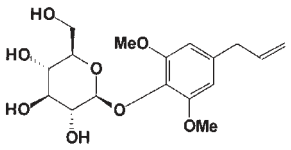

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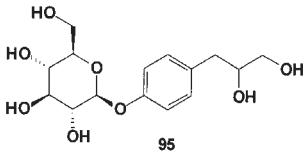

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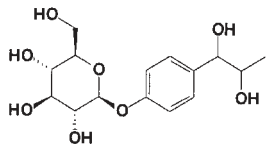

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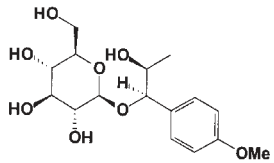

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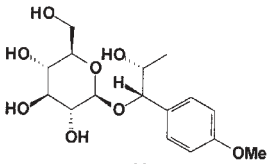
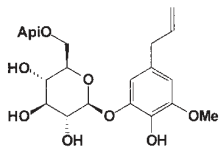


98

Aromatic glycosides, named hovetrichoside G **99** and F **100**, shashenoside I **101**, arillanin F **102**, and kelampayoside A **103**, have been isolated from the bark of *Hovenia trichocarea* (108).

The HIV-inhibitory activity of the extract was traced to polymeric tannins, whereas 2-hydroxy-3-*O*-β-D-glucopyranosyl-benzoic acid **104** was inactive in the National Cancer Institute's primary anti-HIV screening. This glycoside was isolated from *Geniostoma antherotrichum* (109).

The unusual compound (7*S*,8*S*)-3,5,8-trihydroxy-7-(4-hydroxyphenyl)-bicyclo[4.2.0]-octa-1,3,5-trien-2-yl-β-D-glucopyranoside **105** was isolated from an aqueous extract of *Polygonum multiflorum* (110).



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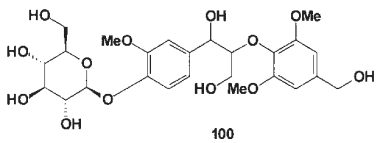

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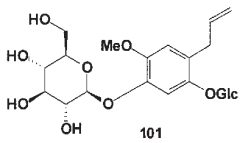

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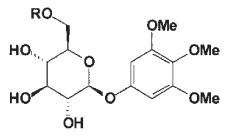
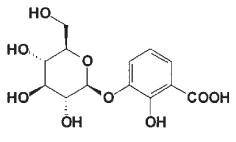


102 R = Xyl
103 R = Api



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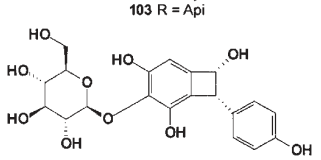


105

Many other simple aromatic glycosides with biological activities have been isolated from plant species, and readers of *Lipids* can find additional interesting information in a number of review articles (111–122).

STILBENES

Stilbenes—or 1,2-diphenylethylenes, of which more than 300 are known—are biologically active compounds that have shown different activities, such as nitric oxide production inhibition and antibacterial, antifungal, antioxidant, anti-inflammatory, anticancer, and antimalarial activities (123–128). These compounds and/or their glycosides also have attracted much attention for their biological effects, including antioxidant cyclooxygenase-I and -II inhibitory (129), antiplatelet-aggregation (130), antifungal (131), tyrosinase-inhibitory (132), anti-HIV-1, and cytotoxic effects (133), which play an important role in photochemical reactions (134,135). They have been found in many families of higher plants but mainly in Vitaceae, Gnetaceae, Polygonaceae, Liliaceae, Moraceae, and Cyperaceae. According to the National Library of Medicine (National Center for Biotechnology Information, Bethesda, MD), more than 28,000 research papers have been published on the activities of stilbenes and related compounds.

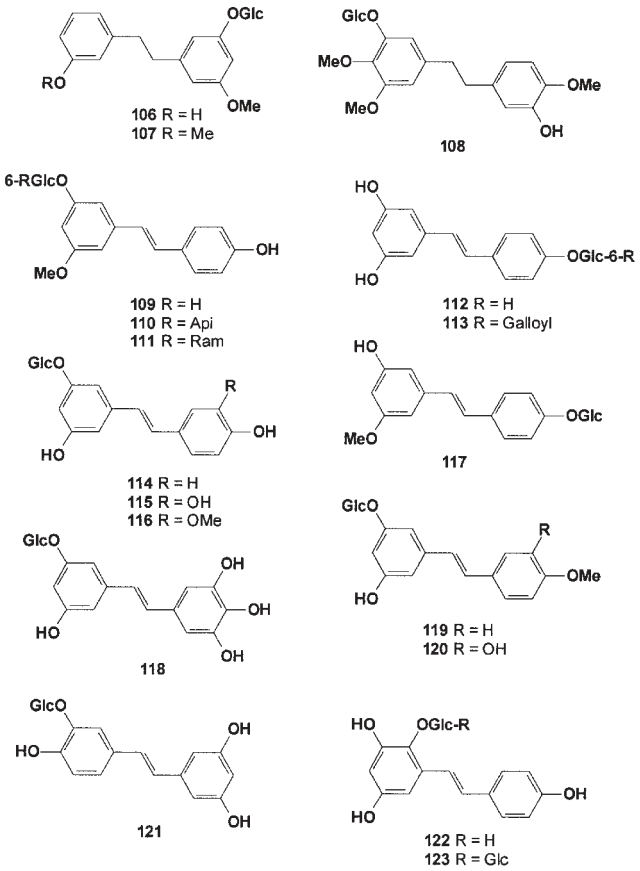
Two novel bibenzyl glucosides, together with their known aglycons batatasin III **106** and 3′-*O*-methylbatatasin III **107**, were isolated from the tubers of *Pleione bulbocodioides* (136); icariside A6 **108** also was isolated from the aerial parts of *Epimedium grandiflorum* var. *thunbergianum* as a minor constituent (137).

The tree *Acer mono* (*A. truncatum* subsp. *mono,* Aceraceae), known as *gorosoe* in Korean, is widely distributed in Korea, China, and Japan. The leaves of *A. mono* have been used in Korean folk medicine for hemostasis, and the roots have been used for the treatment of arthralgia and cataclasis. The sap of *A. mono* has been used to treat difficulty in urination, constipation, other gastroenteric disorders, gout, and neuralgia (138). Two new stilbene glycosides, **109** and **110**, were isolated from the leaves of *A. mono* along with seven known compounds. Compounds **109** and **110** showed significant hepatoprotective activities (97.3% protection against toxicity induced by H_2O_2 at 50 μg/mL) in primary cultures of rat hepatocytes (139). Compounds **109** and **111**, isolated from the stem bark extract of *Boswellia papyrifera* (140), exhibited significant inhibition of phosphodiesterase I and xanthine oxidase (140).

Resveratroloside **112**, a well-known stilbene glycoside, is widely distributed in grapes and wines (141). The highest contents of resveratrol and resveratrol glycoside **112** were observed in wines made with the mourvedre, pinot, and cabernet sauvignon varieties; the lowest were in those made with gamay, cabernet franc, or grenache (141). It has also been found in many other plant species (142). Resveratroloside **112** exhibited relatively higher cytotoxic activities against human oral squamous cell carcinoma and salivary gland tumor cell lines than against normal human gingival fibroblasts (143). Other pharmacological activities of resveratrol and their glycosides have

recently been reviewed (144). 4′-*O*-β-D-(6″-*O*-Galloyl)-glucopyranoside **113** was isolated from the Japanese rhubarb, *shinshu daio* (145). *Trans*-piceid **114**, *trans*-astringin **115**, isorhapontigenin 3-*O*-β-D-glucoside **116**, and pinostilbenoside **117** were isolated from the bark of some *Pinaceae* species (146). Compounds **115** and **116** also were found in the Colorado blue spruce (*Picea pungens*) and Engelmann spruce (*Picea engelmannii*) (147). Resveratroloside **112** and pinostilbenoside **117** were found in the inner bark of *Pinus sibirica* (148). Hydroxystilbene glycoside **111** was isolated from the roots of the Italian tree *Terminalia sericea* (149), and **118** was isolated from the Australian *Eucalyptus sideroxylon* (149). Deoxyrhaponticin **119**, rhaponticoside **120**, piceatannol 3′-*O*-β-D-glucopyranoside **121**, and compound **117** were obtained from an extract of the rhizomes of *Rheum rhaponticum* (150).

trans-Piceid **114** and compound **122** were found in grapes and wine (151). Kimura and Okuda (151) studied the effects of stilbene glucosides, which were isolated from medicinal plants and grapes, on tumor growth and lung metastasis in mice bearing highly metastatic Lewis lung carcinoma (LLC) tumors, and also the inhibitory effects of stilbene glucosides on the differentiation of human umbilical vein endothelial cells (HUVEC). Piceid **114** inhibited the DNA synthesis in LLC cells at a concentration of 1000 μM, but not at lower concentrations (10–100 μM). 2,3,5,4′-Tetrahydroxystilbene-2-*O*-D-glucoside **122** also inhibited DNA synthesis in LLC cells (IC_{50}, 81 μM). In addition, both stilbene glucosides inhibited the formation of capillary-like tube networks (angiogenesis) of HUVEC at concentrations of 100–1000 μM. It was suggested that the antitumor and antimetastatic activities of the stilbene glucosides piceid and 2,3,5,4′-tetrahydroxystilbene-2-*O*-D-glucoside **122** might be due to the inhibition of DNA synthesis in LLC cells and angiogenesis of HUVEC. The pharmacological effect of stilbene glycoside **122** on two kinds of cell models of amentia imitation was observed; the protective mechanism of stilbene glycoside, the main effective component of the tuber fleeceflower root on nerve cells, was explored; and a basis was provided for clarification of the efficacy of a Chinese drug compound from the tuber fleeceflower root (152). The results indicated that stilbene glycoside **122** significantly promoted cell viability and reduced cell membrane damage in β-amyloid 25–35 and H_2O_2, treating nerve cells. This drug may antagonize the cell damage initially induced by hydrogen peroxide and prevent subsequent toxicity of the amyloid β-protein in nerve cells. This nerve protection of the drug will be the basis for treating Alzheimer's disease and other neurodegenerative diseases.

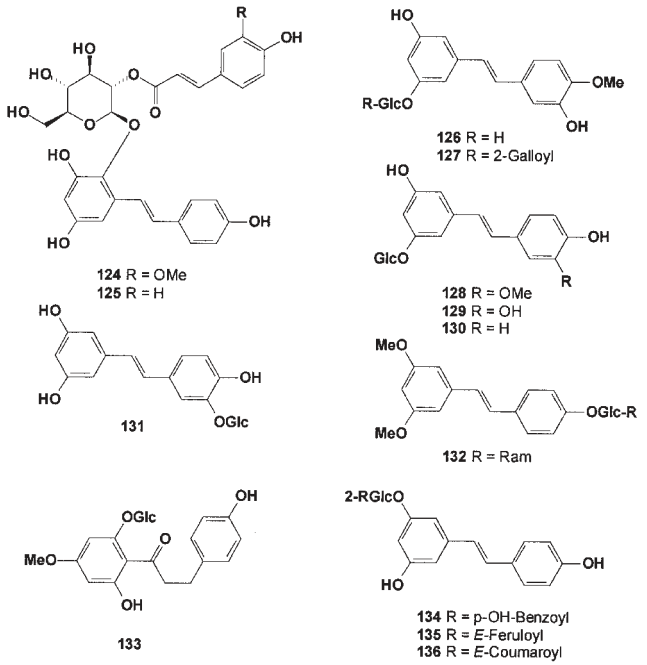


The tetrahydroxystilbene glycosides **122**–**125** were isolated from *P. multiflorum* (153). These isolated tetrahydroxystilbene glucosides are used to prepare drug and/or health-care foods for the prevention and treatment of cerebrovascular and cardiovascular diseases.

Stilbenes isolated from the rhizomes of the Korean rhubarb *Rheum undulatum* and related compounds were investigated for their antiallergenic activities (154). Thus, the effects of substitutes on the aromatic rings of stilbenes have indicated that stilbenes substituted with methoxyl groups at the 3-, 5-, and 40-positions exhibit higher activity than those with hydroxyl groups. Moreover, the activity is dramatically decreased when there is no substitute on aromatic rings. Substitution of the glycoside moiety on the ring dramatically decreases the activity, which can be observed from the inhibitory activities of rhaponticin [**126**, IC_{50} > 100 (9.4) μM], and rhaponticin 2-*O*-gallate (**127**, 45.6 μM), isorhapontin (**128**, 23.5 μM), and piceatannol 30-*O*-β-D-glucopyranoside (**131**, −7.1 μM) compared with

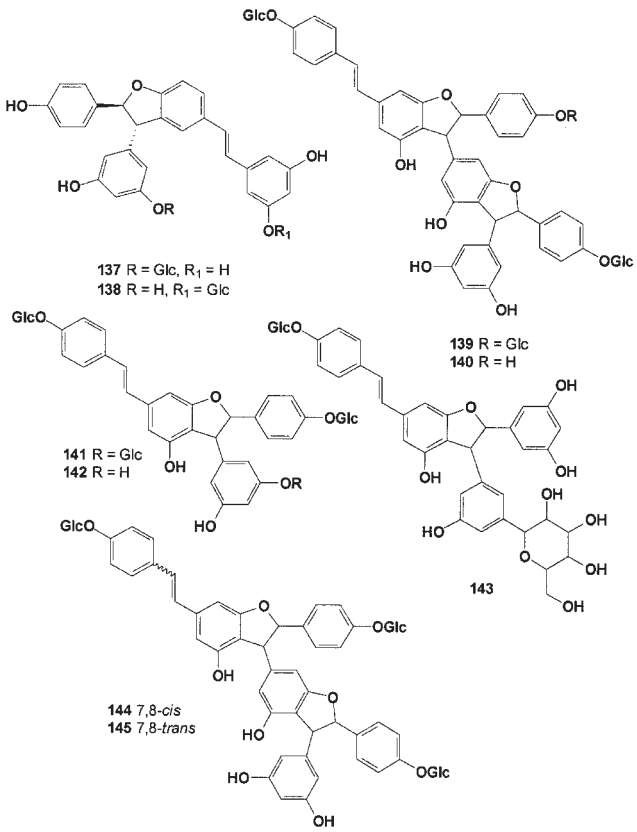
nonglycosidic compounds such as rhapontigenin (11 μM), isorhapontigenin (12 μM), and piceatannol (24 μM). The results revealed that 3,5,40-trimethylpiceatannol exhibited the most potent inhibition against β-hexosaminidase release as a marker of degranulation in RBL-2H3 cells (IC_{50} 2.1 μM), followed by trimethylresveratrol (IC_{50} 5.1 μM). Glycosides **128–130** also were found in extracts from the root bark of *Picea abies* (155). The stilbenes rutinoside **132** and dihydrochalcone glucoside **133** were isolated from *Guibourtia tessmanii* (156).

Species of the Dipterocarpaceae family are a rich source of polyphenols, particularly resveratrol oligomers, and they show various biological activities such as being cytotoxic, antiviral, and anti-inflammatory (157). Resveratrol glycosides **134–136**, together with known compounds, were isolated from the acetone-soluble part of the stem of *Upuna borneensis* (Dipterocarpaceae) (157).



Two new stilbene dimer glucosides, resveratrol (*E*)-dehydrodimer 11-*O*-β-D-glucopyranoside **137** and resveratrol (*E*)-dehydrodimer 11′-*O*-β-D-glucopyranoside **138**, were isolated from grape *Vitis vinifera* cell cultures (158). The structures and stereochemistry of the new compounds were determined on the basis of spectroscopic data analysis. Compounds **137** and **138** are dimers that belong to a new type of oligostilbene formed from a resveratrol unit and a resveratrol glucoside unit. Compound **137** exhibited nonspecific inhibitory activity against cyclooxygenase-I and -II, with an IC_{50} value of 5 μM.

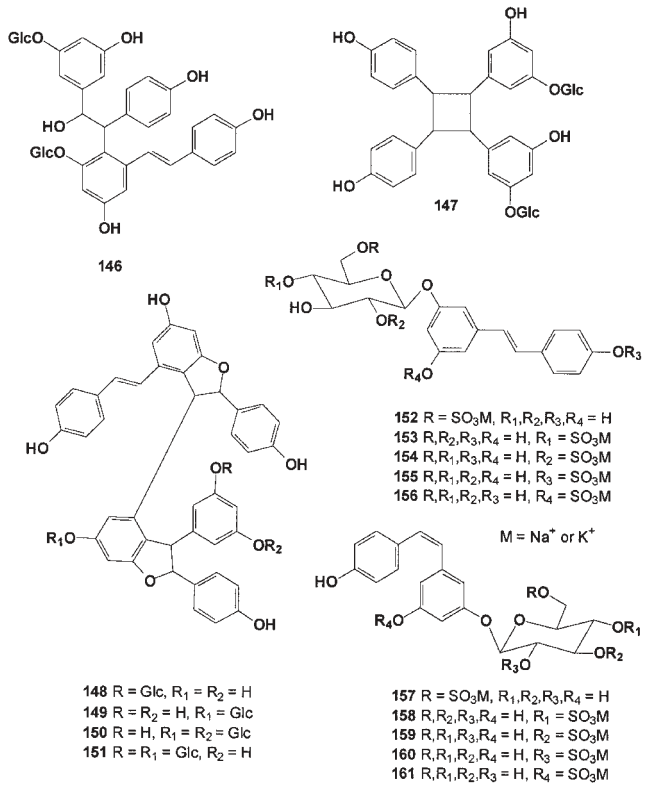
The genus *Gnetum* (Gnetaceae) is known to contain abundant stilbene derivatives that have interesting biological activities, such as inducing apoptosis in colon cancer (159) and reducing blood sugar (160), revealing the importance of plants containing stilbenoids as resources for the development of new drugs. The new stilbene glucosides gnemonosides F **139**, G **140**, H **141**, I **142**, and J **143** were isolated from the liana stems of *Gnetum gnemonoides* and *Gnetum africanum*, along with nine known stilbenoids (161). Other stilbene derivatives, gnemonols K and L (resveratrol trimers), M (isorhapontigenin dimer), and gnemonoside K (glucoside of resveratrol trimer, *cis*-**144** and *trans*-**145** isomers), together with known stilbenoids and a lignan, were isolated from the methanol-soluble parts of the root of *Gnetum gnemon* (Gnetaceae). The antioxidant activity of the nonglycoside stilbenoids on lipid peroxide inhibition and superoxide scavenging activity were reported previously (162).



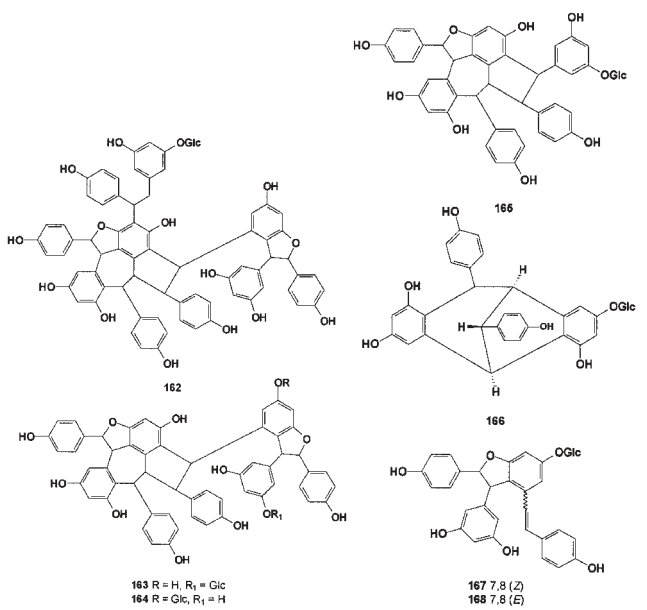
Two dimeric stilbene glycosides, **146** and **147**, were isolated from the root of *Polygonum cuspidatum* (163). One of these glycosides **147**, possesses a novel four-membered ring. Both compounds exhibited strong inhibition of lipid peroxidation but showed no cytotoxic DNA-cleavage activities and no inhibition of protein tyrosine phosphatase 1B.

New glycosides of the stilbene trimers foeniculosides I **148**, II **149**, III **150**, and IV **151** were isolated from *Foeniculum fructus* (seed of *F. vulgare*), along with the known stilbene trimers miyabenol C and *cis*-miyabenol C (164).

The rare, naturally occurring stilbene glycoside sulfates **152–161** were isolated from an aquatic extract of the root of *P. cuspidatum* (165).



A lowland forest tree, *Upuna borneensis* (Dipterocarpaceae), is a monotypic genus distributed in Malaysia (Borneo, including Sabah, Sarawak, and Brunei) (166). Four new stilbene glucosides, upunosides A **162**, B **165**, C **166**, and D **167**, were isolated from the stem of *U. borneensis* (Dipterocarpaceae), together with three known glucosides, vaticaside B **163,** vaticaside C **164**, and paucifloroside A **168**. Upunoside A **162** is the first natural instance of a glucoside of a resveratrol pentamer, and its aglycone has a dibenzo-fused bicyclo[5.3.0]octadiene and two dihydrobenzofuran moieties (167).



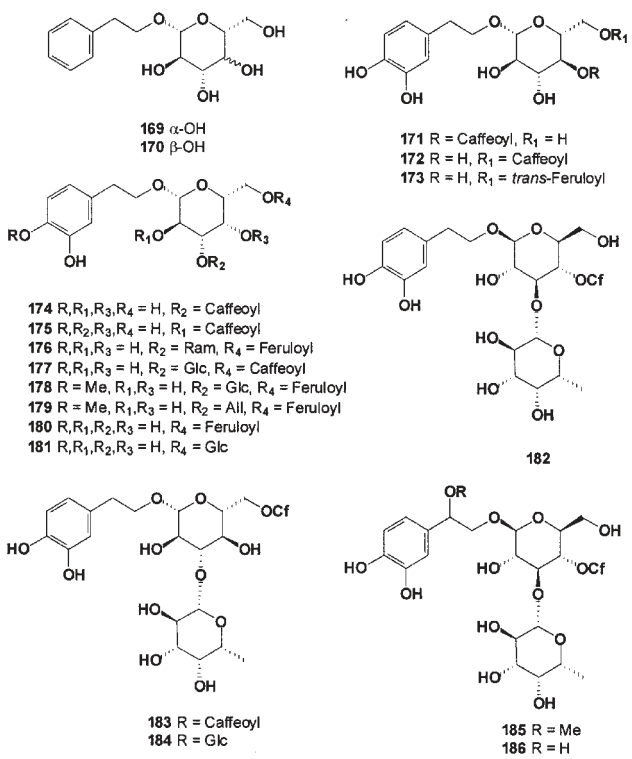
PHENYLETHANOID GLYCOSIDES

Phenylethanoid glycosides are a group of water-soluble natural compounds widely distributed in medicinal plants but also found in other plant species (168–170). Structurally, these metabolites are characterized by benzoic acid derivatives and phenylethyl moieties attached to a β-glucopyranose (apiose, galactose, rhamnose, or xylose) through ester and glycosidic linkages, respectively. More recently, phenylethanoid derivatives attached by an ether and/or ester bond to iridoid glucosides have been found. Phenylethanoid glycosides have been isolated from the aerial parts, leaves, stems, fruit, flowers, roots, and bark of plants or the whole plant; they have been found in the plant families Acanthaceae, Alangiaceae, Asteraceae, Berberidaceae, Bignoniaceae, Buddejaceae, Crassulaceae, Lamiaceae, Magnoliaceae, Oleaceae, Orobanchaceae, Plantaginaceae, Scrophulariaceae, and Verbenaceae (170).

Phenethyl β-D-glucopyranoside **169** and phenethyl β-D-galactopyranoside **170** are simple among the identified phenylethanoid glycosides. Phenethyl β-D-glucopyranoside **169** was found in the flowers of *Rosa gallica* (171), and **170** was obtained by fermentation of phenethyl alcohol and the β-galactosidase of *E. coli* (172). Calceolarioside A **171** and B **172** were isolated from the aerial parts of *Calceolaria hypericina* (173). Calceolarioside B **172** and osmanthuside E **173** were isolated from the aerial parts of *Scutellaria galericulata* (Lamiaceae) and showed antimicrobial activity against two gram-positive bacteria, two gram-negative bacteria, and three yeast-like fungi. Among the glycosides, only calceolarioside B **172** and martynoside seemed to possess antifungal activity; both had high MIC values except against the *C. albicans* strain (174). Plantainosides A–F **174**–**179** were isolated from an aqueous extract of the whole plant *Plantago asiatica*, together with eight known phenylethanoid glycosides (175), and the phenylethanoid glycosides **174** and **175** showed antioxidant activity. Calceolarioside A **171**, plantainoside A **174**, and forsythoside A **180** were isolated from *Forsythia suspense* (176). Compounds **171** and **174** were isolated from the genus for the first time, and compound **180** showed immune-enhancing activity in mice (176). Scroside D **181** was isolated from the roots of *Picrorhiza scrophulariiflora* (Scrophulariaceae) (177) and also showed antioxidant activity.

Acteoside **182** (also known as kusaginin, NSC 603831, TJC 160, and verbascoside) is a very active phenylethanoid glycoside that has been isolated from many plant species (170). Acteoside **182** and isoacteoside **183** (isoverbascoside) were isolated from the southwestern Indian paintbrush, *Castilleja linariaefolia* (178). The extracts displayed *in vivo* activity against murine P-388 lymphocytic leukemia (178), and the pure glycosides acteoside **182** (ED_{50} 2.6 μg/mL) and isoacteoside **183** (ED_{50} 10 μg/mL) showed high cytotoxic activity against the murine P-388 cell line. Acteoside **182** and angoroside A **184** showed strong anti-inflammatory activity *in vitro* (179). Acteoside **182** reduced the risk of atherosclerosis, not only by protecting LDL from oxidative modification but also by its free radical-scavenging properties (180); it also inhibited

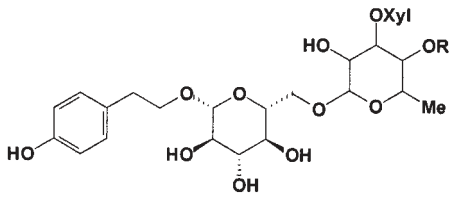
human leukocyte elastase (181) and lipopolysaccharide-inducible nitric oxide synthase *in vitro* (182). Acteoside **182** inhibited the telomerase activity (12.5–27 mg/mL) of the human gastric adenocarcinoma cell MKN45 (183). Acteoside **182** and isoacteoside **183** showed antiproliferative activities against B16F10 cells [acteoside, GI_{50} (concentration needed to reduce the growth of treated cells to half that of untreated cells) 8 μM; isoacteoside, GI_{50} 8 μM] and their methanolysis products (methyl caffeate GI_{50} 26 μM; 3,4-dihydroxyphenethyl alcohol GI_{50} 8 μM; 3,4-dihydroxyphenethyl glucoside GI_{50} 10 μM; desrhamnosyl acteoside GI_{50} 6 μM; and desrhamnosyl isoacteoside GI_{50} 6 μM), suggesting that the 3,4-dihydroxyphenethyl alcohol group might be more responsible for the activities of acteoside and isoacteoside than the caffeoyl group (184). Acteoside showed no apparent effect on the marked elevation of serum tumor necrosis factor α (TNF-α), but it partially prevented *in vitro* TNF-α-induced cell death (100 ng/mL) in D-galactoseamine (D-GalN)-sensitized hepatocytes (0.5 mM) at concentrations of 50, 100, and 200 μM. These results indicated that D-GalN/lipopolysaccharide (LPS)-induced hepatic apoptosis can be blocked by an exogenous antioxidant, suggesting the involvement of reactive oxygen intermediates in TNF-α-dependent hepatic apoptosis (185). Acteosides also showed an inhibitory effect on histamine- and bradykinin-induced contractions of guinea pig ileum (186). Campneoside I **185** and II **186** were isolated from a butanol extract of *Paulownia tomentosa* stems and showed antibacterial activity against *S. aureus* (SG511, 285, and 503), *Streptococcus pyogenes* (A308 and A77), and *Streptococcus faecium* MD8b (187). The most active compound of the extract was identified as campneoside I **185**, which had an MIC value of 150 μg/mL against *Streptococcus* and *Staphylococcus* species. From such antibacterial activity, the methoxy group of campneoside I was postulated to be the essential element for the antibacterial activity (187). The protective effect of campneoside II **185**, isolated from *Cistanche tubulosa*, on the apoptosis of neurons induced by the neurotoxin 1-methyl-4-phenylpyridinium ion (MPP^+) was reported (188).



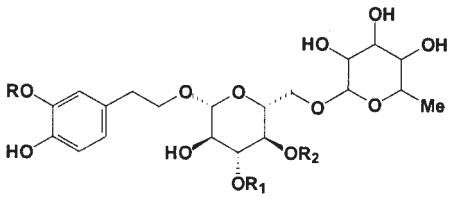
A series of biologically active phenylethanoid trisaccharides with α-L-rhamnose attached to the C-6′ of glucose **187**–**197** have been isolated from some *Mussatia* species (189–192). Mussatiosides I **188**, II **190**, and III **193** showed inhibitory action on ADP-induced rat platelet aggregation (192). The order of activity was: **188** > **190** > **193**. This antiplatelet effect is likely related to the reported inhibition of cAMP-phosphodiesterase.

Two new phenylethanoid glycosides with cytotoxic activity, 1-*O*-3,4-dimethoxy-phenylethyl-4-*O*-3,4-dimethoxy cinnamoyl-6-*O*-cinnamoyl-β-D-glucopyranose **198** and 1-*O*-3,4-dimethoxyphenylethyl-4-*O*-3,4-dimethoxy cinnamoyl-β-D-glucopyranose **199**, have been isolated from the acetone extract of

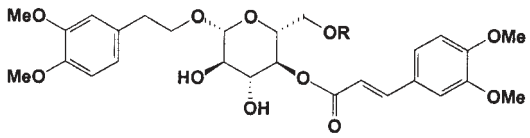
Psidium guaijava seeds (193). The biological assay of an acetone extract and two isolated compounds showed that the extract had moderate inhibitory activity against both Ehrlich ascites carcinoma (EAC) cells and leukemia P-388 (180% and ED_{50} 1/4 14:6), whereas the two new isolated compounds **198** and **199** showed high inhibitory activity against EAC (220 and 240%) and low activity against leukemia P-388 (ED_{50} 1/4 17:3 and 16:1).



187 R = H
188 R = Cinnamoyl
189 R = Coumaroyl
190 R = Di-Me-Caffeonyl
191 R = Feruloyl
192 R = Coumaroyl
193 R = Me-Coumaroyl
194 R = Vanilloyl

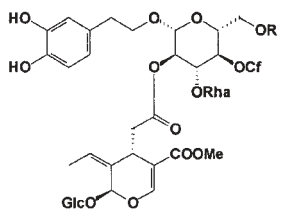


195 R = H, R_1 = Api, R_2 = Cf
196 R = Me, R_1 = Api, R_2 = Fr
197 R = H, R_1 = Glc, R_2 = Cf

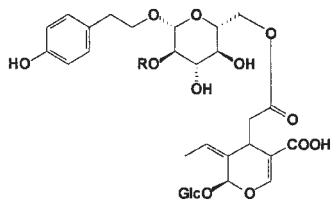


198 R = Cinnamoyl
199 R = H

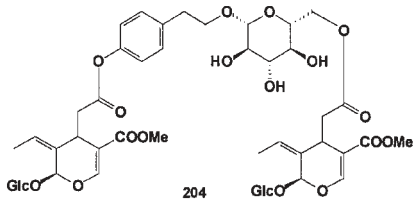
Types of phenylethanoid glycosides linked with iridoids or secoiridoid glucosides have been isolated from plants. Oleoacteoside **200** was isolated from *Syringa reticulata* (194,195), *Jasminum polyanthum* (196,197), and *Picconia excelsa* (198). Oleoechinacoside **201** was isolated from *S. reticulata* (194), and nuzhenide **202** was isolated from the leaves of *S. reticulata* (199). The esterglucoside **203** was found in *Ligustrum japonicum* (200). The unusual polyglucosidic metabolite **204** was isolated from embryos of the American ash (*Fraxinus americana*) (201).



200 R = H
201 R = Glc



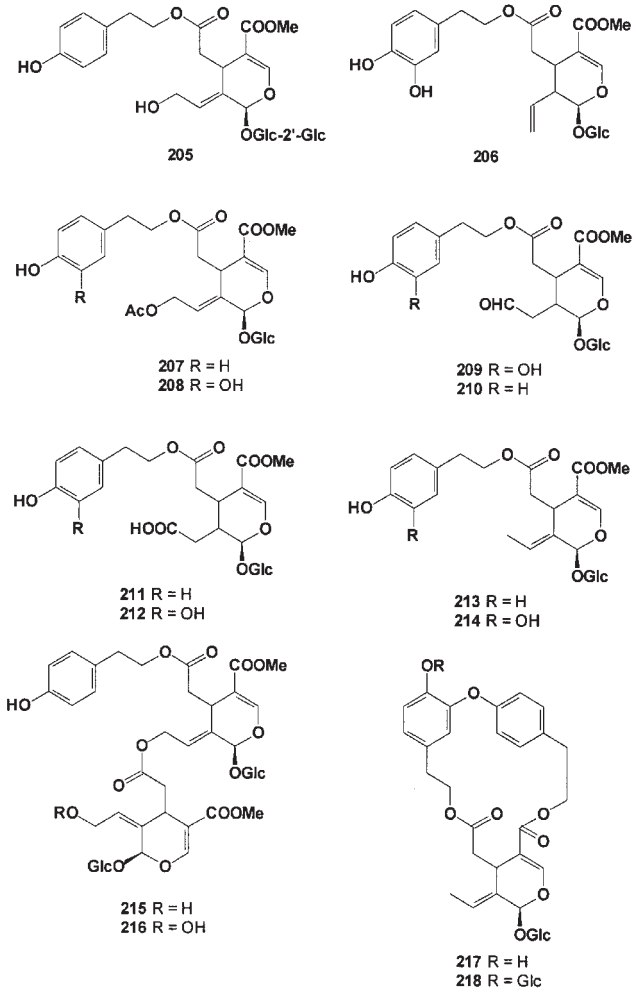
202 R = H
203 R = Oleosyl



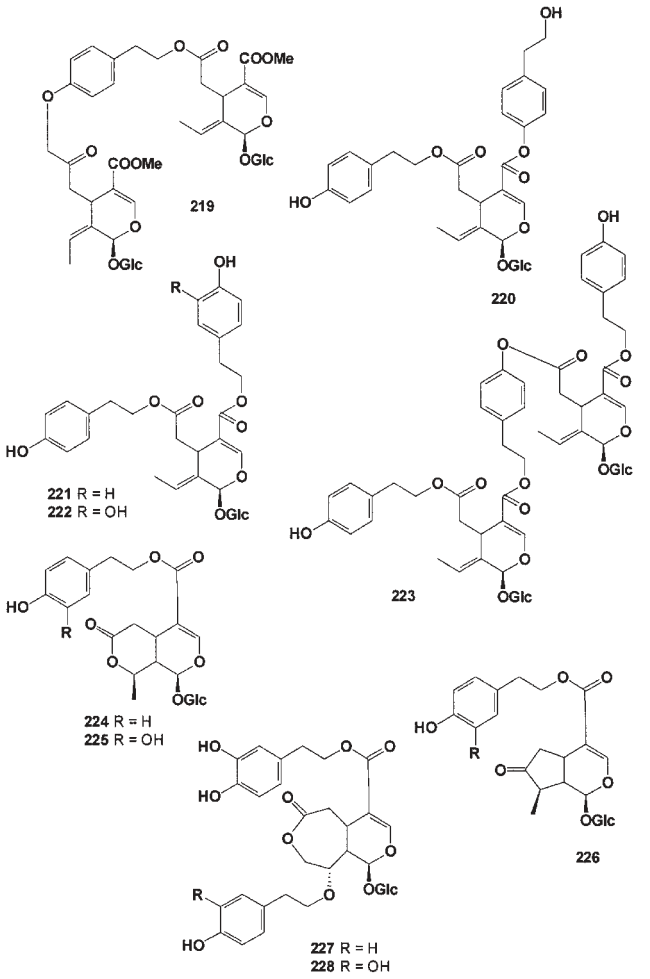
204

Phenylethanoid derivatives attached by ether and/or ester bonds with iridoid and/or secoiridoid glucosides have been isolated from the Oleaceae family (202). A new secoiridoid glycoside named hiiragilide **205** was isolated from the leaves of *Osmanthus ilicifolius* (203). Oleuroside **206** was isolated from *Olea europaea* (204) and from tissues of the novel olive cultivar Hardy's Mammoth (205,206). The antiviral activity of olive leaf extract (OLE), containing oleuroside **206**, hydroxytyrosol, oleuropein, and verbascoside, was reported recently (207). Also, OLE was shown to inhibit acute infection and cell-to-cell transmission of HIV-1, as assayed by syncytia formation using uninfected MT2 cells co-cultured with HIV-1-infected H9 T-lymphocytes. OLE also inhibited HIV-1 replication, as assayed by the expression of p24 in infected H9 cells. These anti-HIV effects of OLE are dose dependent, with an EC_{50} of 0.2 μg/mL (207). 10-Acetoxyligstroside **207** and 10-acetoxy-oleuropein **208** were found in an extract of the bark of *Osmanthus asiaticus* (208). Ligustaloside A **209** and ligustaloside B **210** were isolated from the leaves of *Ligustrum lucidum* (Oleaceae) (209) and *Ligustrum vulgare* (210). Kikuchi and Yamauchi (211) found a corresponding pair of compounds, ligstrosidic acid **211** and oleuropeinic acid **212**, in the fruit of *Ligustrum japonica* and *L. lucidum*. Ligstroside **213** and the cytotoxic compound oleuropein **214** were isolated from the stem bark of *Syringa velutina* (212). Oleuropein **214** showed the most potent cytotoxic effect on several tumor cell lines (P-388, L-1210, SNU-5, and HL-60) among eight isolated compounds. Three new secoiridoid glucosides, jasamplexosides A **215**, B **216**, and C (like B, but with the additional part of a secoiridoid glucoside; structure not shown), were isolated from the crude drug *niu du teng*, the leaves and stems of *Jasminum amplexicaule* (213). An unusual cyclic secoiridoid glucoside, insularoside **217**, was isolated

from *Fraxinus insularis* (214), and fraxuhdoside **218** was isolated from the bark of *Fraxinus uhdei* (215).



A minor iridoid named austromoside **219** was found in *Osmanthus austrocaledonica* (216), and fraxiformoside **220** was isolated from *Fraxinus formosana* (217) and *Fraxinus malacophylla* (218). Framoside **221**, which has anti-inflammatory activity, was isolated from *Fraxinus* species (219); neooleuropein **222** was isolated from *Fraxinus chinensis* (220); and fraximalacoside **223** was isolated from *F. malacophylla* (218). Lilacoside **224** and fliederoside **225** were isolated from *Syringa vulgaris* (221). In 1970, syringopicroside **226** was isolated from *S. vulgaris* (222) and more recently was found in many *Syringa* species (223). A unique series of seven-membered lactones exemplified by jasmolactone C **227** and D **228** were isolated from the aerial part of *Jasminum multiflorum* (224,225). The structures of these compounds, which contain a novel bicyclic 2-oxo-oxepano[4,5-c]pyran ring system, were tested for pharmacological activity, and **227** and **228** were found to possess coronary vasodilating and cardiotropic activities (224).



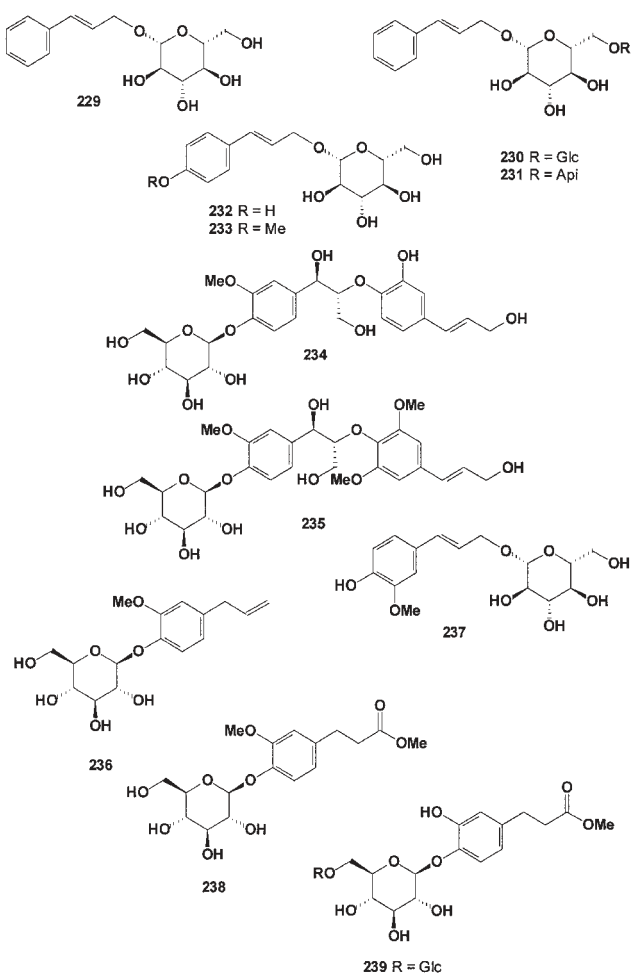
PHENYLPROPANOID GLYCOSIDES

Phenylpropanoids and phenylethanoid glycosides are a large class of water-soluble natural metabolites widely distributed in plant species (226–231). Phenylpropanoids can conveniently be treated as a group of aromatic compounds consisting of the derivatives of phenylpropanols and/or benzoic acids (caffeic, cinnamic, coumaric, ferulic, sinapic, and others), including their glycosides (see also the Simple Aromatic Glycosides section). More complex phenylpropanoid glycosides are compounds based on phenylethanes (see the Phenylethanoid Glycosides section). Phenylpropanoid compounds have a wide array of important functions in plants. They serve in the interaction of plants with their biotic and abiotic environments, mediate certain aspects of plant growth and development, and are important structural components of the secondary cell wall. Phenylethanoid glycosides have been isolated from the aerial parts of plants, leaves, stems, fruit, flowers, roots, bark, and/or whole plant; they are found in the plant families Araliaceae,

Bignoniaceae, Crassulaceae, Labiatae, Lamiaceae, Oleaceae, Polygonaceae, Scrophulariaceae, Smilacaceae, Verbenaceae, and several others.

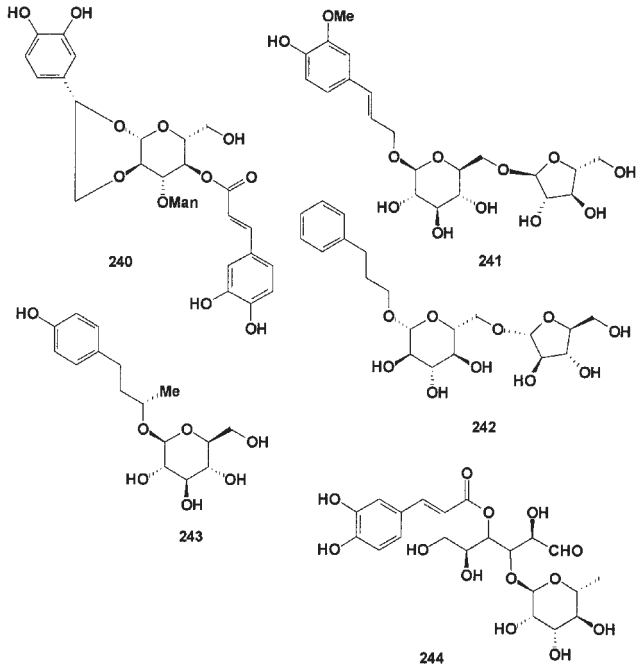
The natural phenylpropanoid glycosides isolated from plants showed activities such as being antitumoral, antiviral, anti-inflammatory, antibacterial, antiatherosclerotic, antiplatelet aggregational, antihypertensive, antifatigue, analgesic, hepatoprotective, immunosuppressive, protective of sex and learning behavior, protective of neurodegeneration, reverse transformative of tumor cells, inhibitive of telomerase and capable of shortening the telomere length in tumor cells, having effects on enzymes and cytokines, antioxidative, free radical scavenging, and quickly repairing oxidatively damaged DNA, among others (227).

Simple phenylpropanoid glycosides such as rosin **229**, rosavin **230**, rosarin **231**, triandrin **232**, and vimalin **233** have been isolated from different plant species belonging to the Crassulacea, Liliaceae, and Salicaceae families (226,227). The biologically active substances rosin **229**, rosavin **230**, rosarin **231**, and tyrosol, which are mainly found in plant rhizomes, have demonstrated therapeutic effects (232). These active components affected the central nervous system by increasing the ability to concentrate and mental and physical power; they were efficient in improving asthenic states and the general resistance of the cells and the organism against harmful outer influences. They also prevented the heart system from stress and arrhythmias, and they possessed some antioxidant activities. Some data confirm that the *Rhodiola rosea* preparations stopped the growth of malignant tumors and metastases in the liver (232). Rosin **229**, rosarin **231**, rosavin **231**, and rosiridin isolated from *R. rosea* showed neurotropic activity in mice (233). Citrusin A **234**, B **235**, C **236**, D **237**, E **238**, and F **239** have been isolated from citrus fruit peels, e.g., from the lemon, unshiu, and kinkan (234,235), and after *in vivo* injection of the compounds indicated above into stroke-prone spontaneously hypotensive rats, they were found to lower the blood pressure (236,237).



A new phenylpropanoid glycoside, crenatoside **240**, as well as the known phenylpropanoid, acteoside **182**, have been isolated from the aerial parts of *Orobanche crenata* (238). Two new phenylpropanoid glycosides, junipercomnoside E **241** and F **242**, were isolated from the aerial parts of *Juniperus communis* var.

depressa (239); betuloside **243** was isolated from *Betula alba* (240); and cistanoside F **244** was isolated from the stem bark of *Acanthopanax trifoliatus* (241).



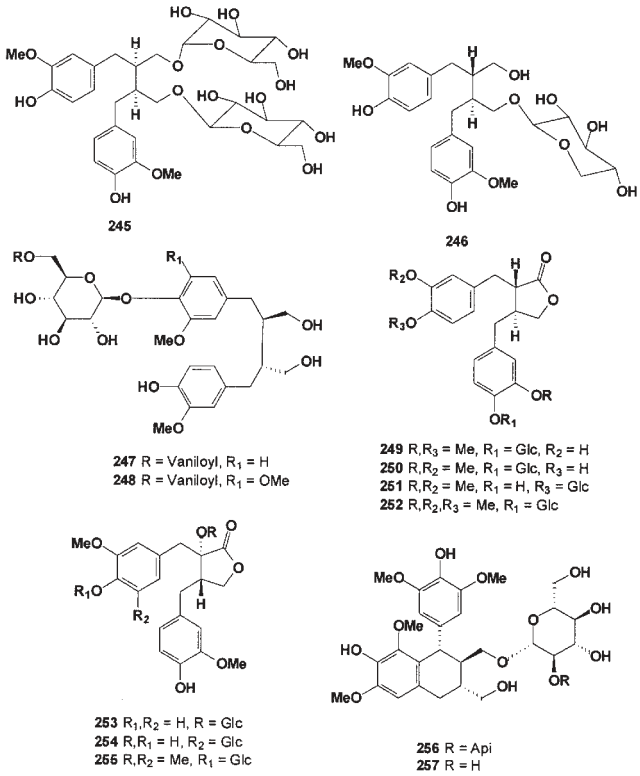
LIGNAN GLYCOSIDES

Lignans are natural bis-phenylpropanoids having a large spectrum of biological activities, and they are widely distributed in the plant kingdom. They are present in small amounts in most unrefined grains such as barley, buckwheat, millet, and oats; legumes such as soybeans; and some vegetables (242–244). Sometimes lignans are referred to as phytoestrogens. However, this term is misleading, as it suggests that lignans may act just like the hormone estrogen in the body. The richest source of lignans is flaxseed, which contains high levels of the lignan precursor secoisolariciresinol diglycoside **245** (SDG). Plant lignans are polyphenolic substances derived from phenylalanine *via* the dimerization of substituted cinnamic alcohols (242). Mammalian lignans are lignans derived from plant lignans. For example, following ingestion, SDG is converted to the aglycone secoisolariciresinol, which is then metabolized to the mammalian lignans enterolactone and enterodiol (245). Most of the effects of oral SDG are mediated by enterolactone and enterodiol (246). SDG has estrogenic and antioxidant activities, and also has antitumor, antiestrogenic, anticarcinogenic, antiatherogenic, and antidiabetic activities (247–249). Similar structures have the glycosides (−)-secoisolariciresinol-*O*-α-L-rhamnopyranoside **93** (105) and (+)-secoisolariciresinol 9-*O*-β-D-xylopyranoside **246** (isolated from the leaves of *Laurus nobilis*) (250). The underground parts of *Glehnia littoralis* (Umbelliferae) contain two new lignan glycosides named glehlinosides A **247** and B **248** (251).

Styraxlignolides C **249**, D**250**, E **251**, and F **252**, butyrolactone lignan glucosides with antioxidant activity, were isolated from the stem bark of *Styrax japonica* (252). Styraxlignolides C **249**, D **250**, and E **251** exhibited weak radical-scavenging activity in the 1,1-diphenyl-2-picrylhydrazyl assay, with IC_{50} values of 380, 278, and 194 μM, respectively.

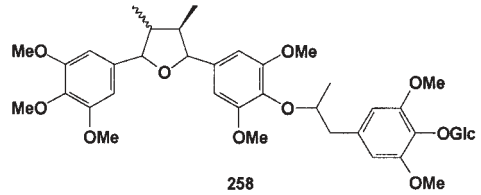
Lignans having a diarylhydroxybutyrolactone skeleton, i.e., nortrachelogenin 8′-*O*-β-D-glucopyranoside **253**, nortrachelogenin 5′-*C*-β-D-glucopyranoside **254**, and nortracheloside **255**, were found in a water-soluble extract of the leaves and stems of *Trachelospermum jasminoides* (253).

The root of *Strobilanthes cusia* (Acanthaceae), popularly known as *da-ching-yeh*, has commonly been used in traditional Chinese medicine. It is used to treat influenza, epidemic cerebrospinal meningitis, encephalitis B, viral pneumonia, mumps, and severe acute respiratory syndrome. A new lignan glycoside, **256**, and the known (+)-9-*O*-β-D-glucopyranosyl lyoniresinol **257** were found in *S. cusia* roots. The isolated compounds **256** and **257** were examined for anti-herpes simplex virus type-1 activity and showed moderate activity (253a).



Bonaspectin C **258** and bonaspectin D **259**, isolated from the aerial parts of *Bonamia spectabilis* (Convolvulaceae), led to the isolation of four minor THF-type sesquilignans (254). Bonaspectin C 4″-*O*-glucoside **258**, its aglycon, and bonaspectin D 4″-*O*-glucoside **259** revealed the highest antiplasmodial activities against *Plasmodium falciparum* [IC_{50} values of 0.98 and 5.1 μM/mL (chloroquine-sensitive strain of *P. falciparum*), and 1.3 and 2.9 μM/mL (chloroquine-resistant clone of *P. falciparum*), respectively]. The cytotoxicity of **258** was estimated by a proliferation assay using the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay against human endothelial cells (ECV-304). A new lignan glucoside, the first 7,9′-monoepoxytetrahydrofuran-type

lignan, named tibeticoside **260**, was isolated from the medicinal plant (roots, stems, and leaves) *Lancea tibetica* (255). Two lignan diglucosides, **261** and **262**, were identified from extracts of germinated sesame seeds (256). The lignan glycoside arctiin **263** is widely distributed in the Compositae family and is used as a chemotaxonomic marker for this family (257). This lignan showed neuroprotective activity against glutamate-induced toxicity in primary cultures of rat cortical cells (258).



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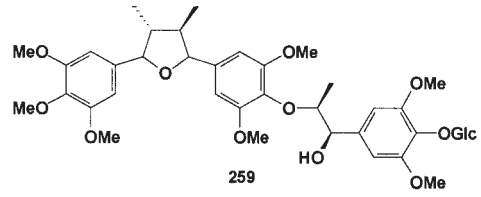

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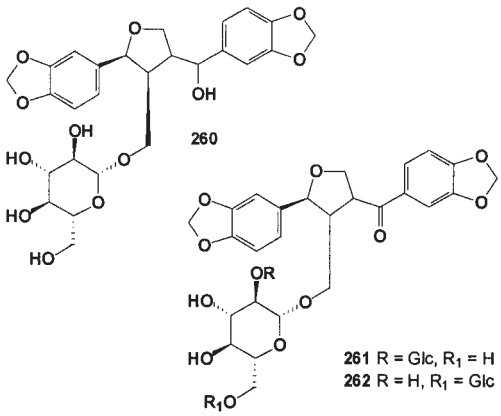
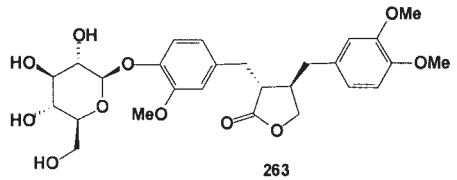
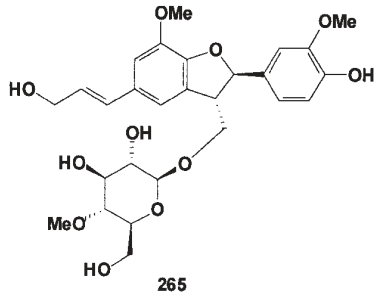




The neolignan glucosides tortosides B **264**, D **265**, and E **266** were isolated from *Pedicularis torta* (259,260). The new lariciresinol-based lignan bis-glucosides, 7*S*,8*R*,8′*R*-(−)-lariciresinol-4,4′-bis-*O*-β-D-glucopyranoside **267** and 7*S*,8*R*,8′*R*-(−)-5-methoxylariciresinol-4,4′-bis-*O*-β-D-glucopyranoside **268** were isolated from the *n*-butanol extract of *Galium sinaicum* roots (261). The two lignan glucosides **267** and **268** were subjected to a cytotoxicity bioassay against the P-388 leukemia cell line, and the tested compounds exhibited weak *in vitro* cytotoxic activity, with IC_{50} values of 100 and 42.0 μg/mL, respectively.

The new neolignan glycosides named dichotomosides A **269**, B **270**, C **271**, and D **272** were isolated from a Chinese natural medicine, the roots of *Stellaria dichotoma* var. *lanceolata* (262). Among them, dichotomoside D **272** inhibited the release of β-hexosaminidase (IC_{50} 64 μM) as well as TNF-α and interleukin-4 (IC_{50} 16, 34 μM) in RBL-2H3 cells.

264



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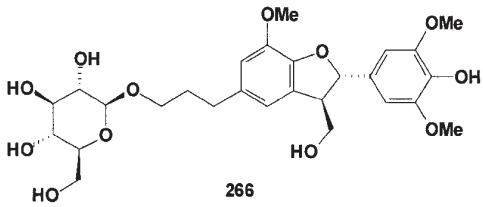

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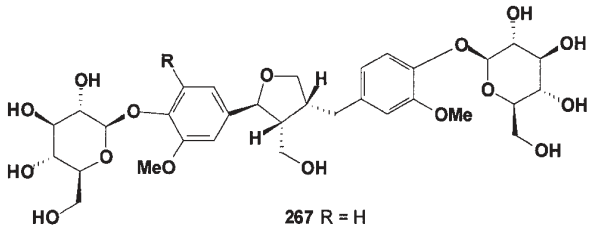
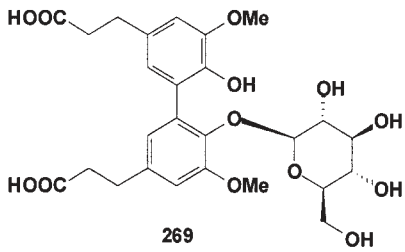


267 R = H
268 R = OMe



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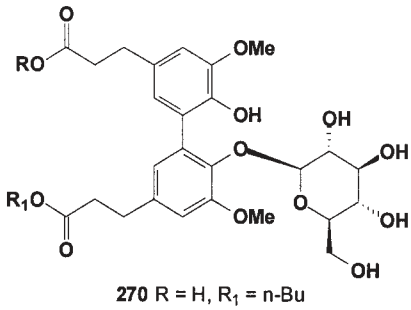
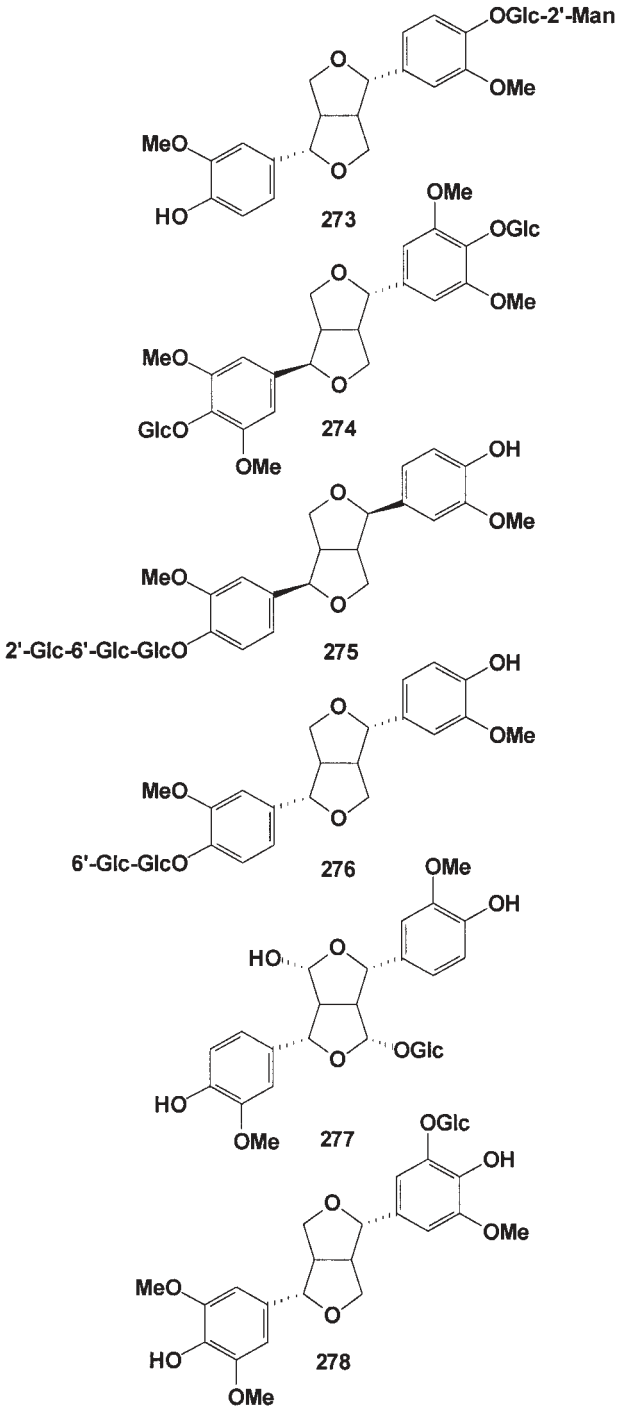


270 R = H, R_1 = n-Bu
271 R = n-Bu, R_1 = H
272 R, R1 = n-Bu

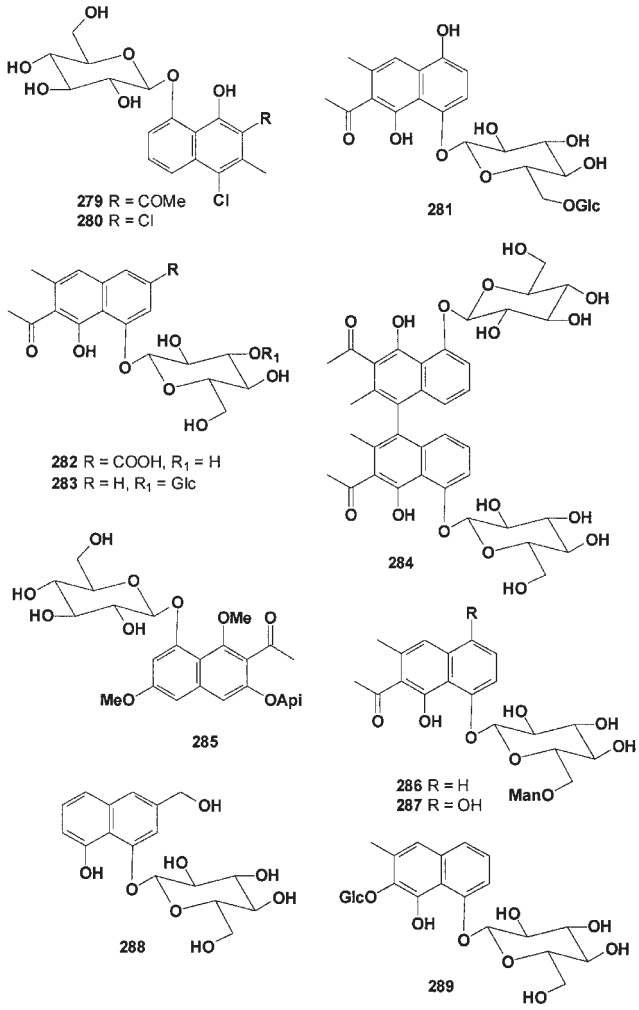
A novel lignan glycoside, hibiscuside **273**, which exhibited good antioxidant activity and strongly inhibited lipid peroxidation in rat liver microsomes, was isolated from the roots of *Hibiscus* species (263). Also, a new lignan named eleutheroside E **274** was extracted from the stem bark of *Acanthopanax trifoliatus* (241). A water-soluble natural antioxidant, pinoresinol glycoside **275**, was isolated from sesame seeds (264). Pinoresinol glycoside **275** prevented the oxidation of linoleic acid *in vitro* in an aqeous solution and that of rabbit red cell ghost membranes by *tert*-butyl hydroperoxide (264). A new lignan, triglucoside **276**, was isolated from sesame seeds; this compound had branched (1→2)- and (1→6)-glucosidic linkages and showed antioxidative activity (265). A new furofuran lignan from *Lactuca indica*, lactucaside **277**, showed significant antidiabetic activity (266). *Coptis japonica* (Ranunculaceae) is known to possess several biological activities, such as anti-inflammatory effects. Pinoresinol glycoside **275** and syringaresinol glycoside **278**, which were isolated from the rhizomes of *C. japonica*, were tested to evaluate their *in vitro* anti-inflammatory effects. Pinoresinol glycoside **275** and isolariciresinol showed higher inhibitory effects on TNF-α production than syringaresinol glycoside **278**, whereas syringaresinol glycoside **278** strongly suppressed lymphocyte proliferation (267). For more information on lignans, neolignans, and related compounds, readers are referred to several review articles (242–244,268).



GLYCOSIDES OF NAPHTHALENE DERIVATIVES

Naphthalene, the fused-ring aromatic hydrocarbon, was first isolated by crystallization from the naphthalene fraction of coal tar, which still remains its major source (269,270). It was also found in combustion processes, including the combustion of refuse, tobacco smoke, coal tar pitch fumes, and oil spills. Most of the naphthalene derivatives found in nature are naphthoquinones, which may arise through the polyketide, terpenoid, or shikimate pathways or a mixture of these (271,272).

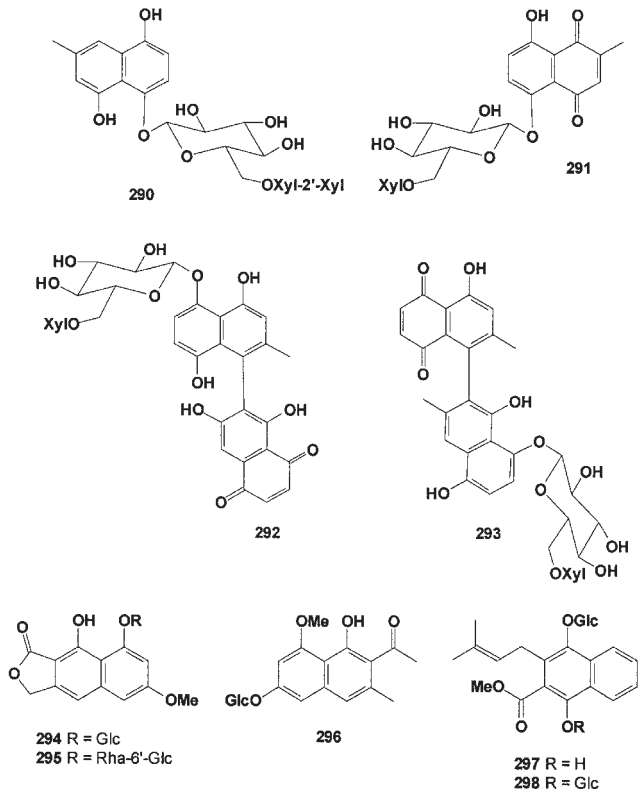
The genus *Rumex* (Polygonaceae) is represented by 25 species in the flora of Turkey (273). The roots of *R. patientia* are used as a purgative and tonic in traditional medicine, and its leaves are commonly used as a green vegetable called *labada* or *develik*. Nine *Rumex* species, including *R. patientia*, have been attributed to the Chinese herbal medicine *yangti*, which has been used as a hemostatic and antifungal agent. Two new chlorinated naphthalene derivatives, patientosides A **279** and B **280**, were isolated from the roots of *R. patientia* (274). Daylily flowers are used as an important ingredient in traditional Asian cuisine and are also valued for their reputed medicinal effects. A new naphthalene glycoside, stelladerol **281**, has been isolated from edible daylily (*Hemerocallis*) flowers (275). This isolated compound was tested for antioxidant and cyclooxygenase inhibitory activities and was found to possess strong antioxidant properties, inhibiting lipid oxidation by 94.6% (10 μM) in an *in vitro* assay. Also from this plant, three new naphthalene glycosides, rumexoside **282**, rumexoside **283**, and labadoside **284** were identified (276). A new naphthalene glycoside, cassitoroside **285**, was isolated from the seeds of *Cassia tora* (277). One new naphthalene glycoside, 5-hydroxydianellin **286**, and a known naphthalene glycoside, dianellin **287**, were isolated from roots of the daylily *Hemerocallis fulva* 'Kwanzo' Kaempfer (278). Diospyrosonaphthoside **288** was isolated from an ethanolic extract of the stem bark of *Diospyros angustifolia* (279), and plicataloside **289**, an *O*,*O*-diglycosylated naphthalene derivative, was isolated from *Aloe plicatilis* (280).



The twigs of *Diospyros lycioides*, a plant commonly known as muthala, are frequently used as chewing sticks by the rural and urban people in Namibia for cleaning the teeth. Studies showed that a methanol extract of *D. lycioides* inhibited the growth of selected oral pathogens. Subsequent bioassay-guided

fractionation led to the isolation of four novel bioactive naphthalene glycosides, diospyrosides A **290**, B **291**, C **292**, and D **293** (281). These compounds inhibited the growth of oral cariogenic bacteria (*Streptococcus mutans* and *Streptococcus sanguis*) and periodontal pathogens (*Porphyromonas gingivalis* and *Prevotella intermedia*) at MIC values ranging from 0.019 to 1.25 mg/mL.

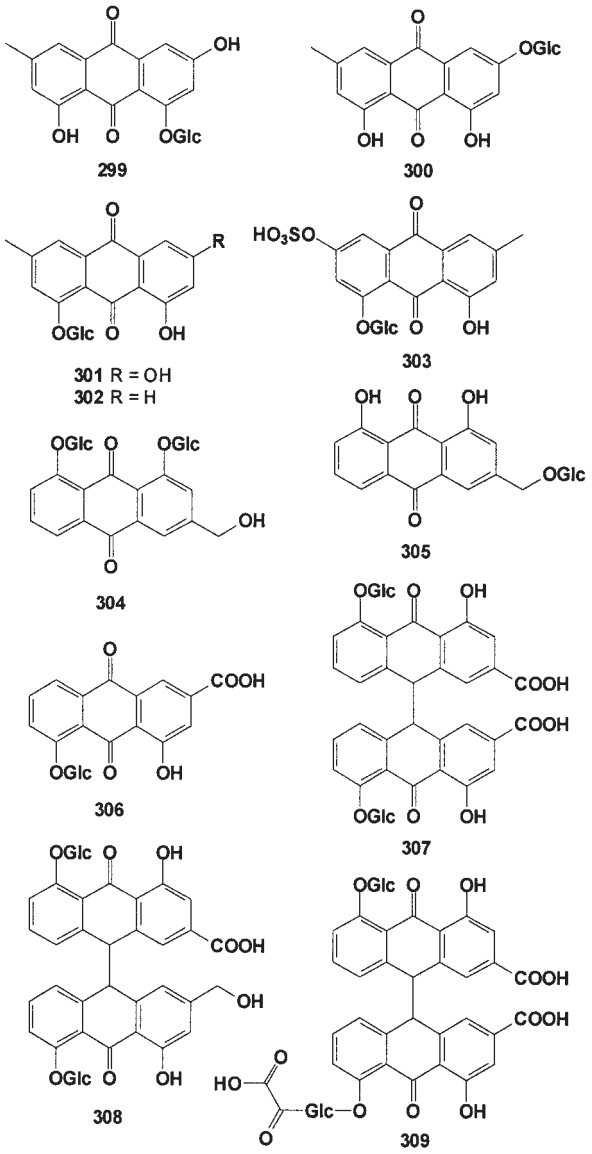
Lactonic 6-methoxysorigenin 8-*O*-β-D-glucopyranoside **294** was isolated from the cortex of *Rhamnus catharticus* (282), and **295** was isolated from *Rhamnus nakaharai* (283). From the leaves and pods of *Cassia senna* and *C. angustifolia*, the new tinnevellin glucoside **296** was isolated (284). The monoglucoside **297** and diglucoside **298** of 2-naphthalenecarboxylic acid were isolated and characterized from the roots of *Rubia ustulata* (285).



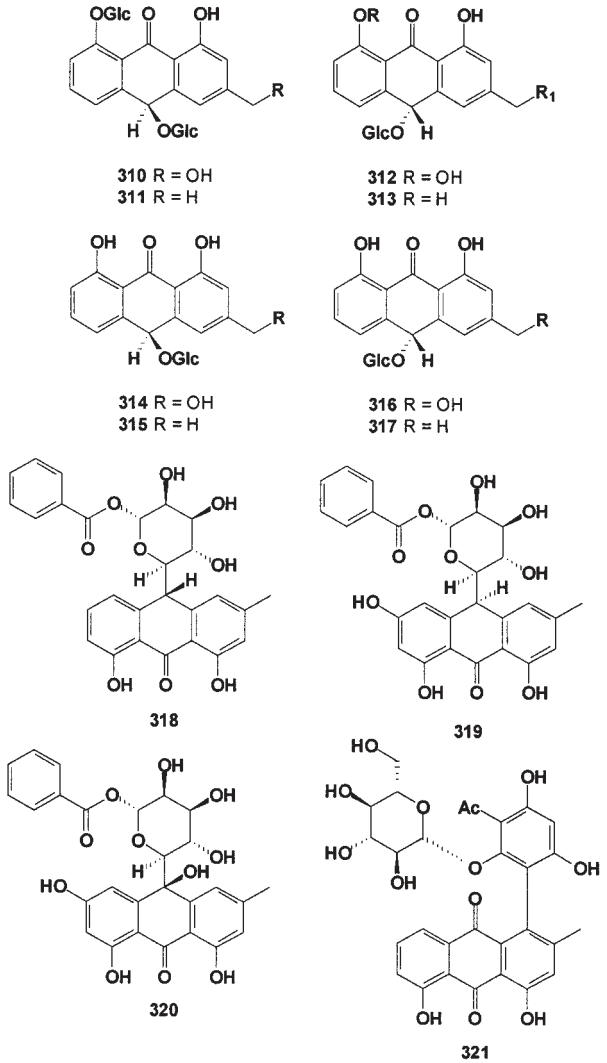
GLYCOSIDES OF ANTHRACENE DERIVATIVES

Glycosides of anthracene derivatives are widely distributed in the plant kingdom, and many of them have shown anticancer, antiviral, antimicrobial, and other biological activities (286–290). Different anthracene glycosides have been isolated from an aromatic bark called cassia (also known as cinnamon, bastard cinnamon, Chinese cinnamon, *Cassia lignea*, cassia bark, *Cassia aromaticum*, or Canton cassia). Over 400 species of cassia are known. Most are indigenous to North, Central, and South America and Africa, but they are now also found in the tropical and subtropical regions of all continents except Europe. Some are native to South Asia, particularly India and Ceylon, and are now widely cultivated in the tropics; others are considered ornamental trees in southern Florida, the West Indies, and Central and South America. The dried unripe fruit, or Chinese cassia buds, have the odor and taste of the bark and are rather like small cloves in appearance. They have been known as a spice in Europe since the Middle Ages and were probably used in preparing a spiced wine called hippocras. Now they are used in confectionery and in making potpourris.

Emodin is perhaps the most nearly ubiquitous natural anthraquinone, occurring in several higher plants, in fungi, and in lichens. In higher plants, it is chiefly present in glycoconjugates. Emodin and chrysophanol frequently occur together in plants such as *Cassia tora, Rumex japonicus, Rhamnus purshiana, Polygonum multiflorum,* and *P. cuspidatum* (291). Emodins 1-*O*-**299** and 3-*O*-**300** were isolated from the Chinese cassia species (292); 8-*O*-β-glucopyranoside **301** was isolated from *C. tora, R. japonicus, R. purshiana, P. multiflorum,* and *P. cuspidatum*; and chrysophanol-8-*O*-β-glucoside **302** was found in *R. japonicus* (291). Emodin (IC_{50} 3.3 μM) is an inhibitor of the growth factor-signaling enzyme phosphatidylinositol-3-kinase (293). A rare sulfated emodin glucoside, emodin 8-*O*-β-D-glucopyranosyl-6-*O*-sulfate **303**, was isolated from the roots of the Nepalese medicinal plant *Rheum emodi* (294). Aloe-emodin diglucoside **304** and aloe-emodin ω-*O*-β-D-glucopyranoside **305** were isolated from Chinese cassia species (292). Emodin 8-*O*-β-glucopyranoside **301**, chrysophanol-8-*O*-β-glucoside **302**, and rhein-8-β-D-glucoside **306**, as well as sennoside A **307**, were isolated from *Rheum palmatum* and *R. tanguticum* (295). Sennoside A **307**, sennoside C **308**, and sennoside E **309** were isolated from *R. palmatum* and *R. tanguticum* species (295).



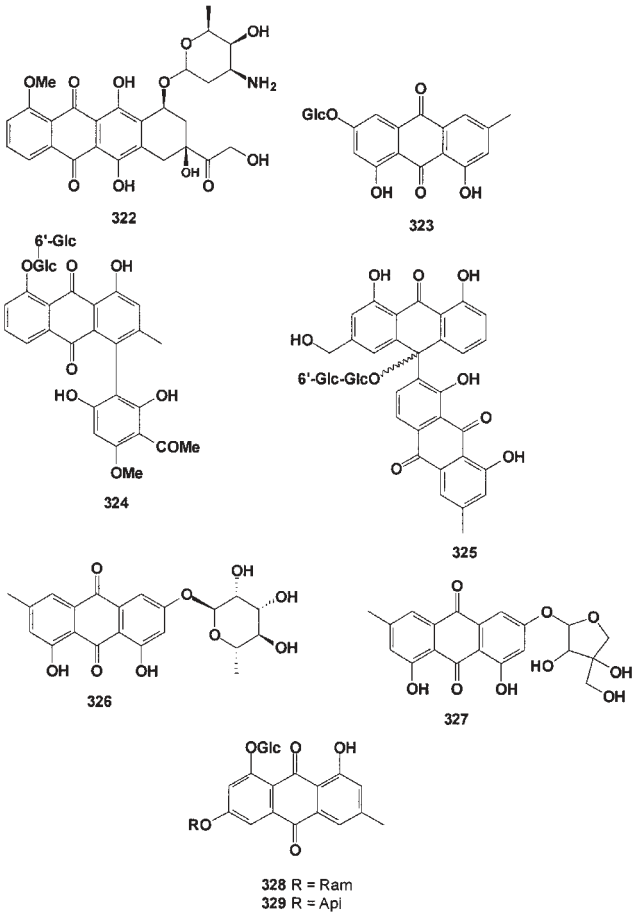
Cascara sagrada is the common name for *Rhamnus purshiana* (family Rhamnaceae), a short shrubby tree native to the Pacific Northwest in the United States. The dried bark of this tree, also called cascara sagrada, is the source of several anthraquinone laxative drugs, a class of laxatives used by many people throughout the world (296). Dried cascara sagrada bark contains approximately 7–10% hydroxyanthraquinone glycosides (297,298). Hydroxyanthraquinone glycosides are hydroxyanthracene derivatives with hydroxyl groups at the C-1 and C-8 positions and sugar groups at the hydroxyl groups (*O*-glycosides) or at the C-10 position (*C*-glycosides) (296,299). Not less than 60% of this 7–10% consists of cascarosides, expressed as cascaroside A **310**. There are four forms of cascarosides: A **310**, B **312**, C **311**, and D **313**. Cascarosides A **310** and B **312** are diastereoisomers, as are cascarosides C **311** and D **313**. Additional constituents of the dried cascara sagrada bark are the diasteroisomers of barbaloin **314** and **316** and chrysaloin **315** and **317**. Barbaloin stimulates the growth of *Eubacterium* species strain BAR (300). The anthraquinones emodin **299** and barbaloin **314** showed antiviral activity, but only emodin was a virucidal agent (301). A new cytotoxic 10-epiuveoside, **318**, was isolated from the root bark of *Picramnia antidesma* (302), along with picramnioside E **319** and mayoside B **320**. One new anthraquinone glycoside, *M*-4′-demethylknipholone-2′-*O*-β-D-glucopyranoside **321**, was found in the methanolic extract of the Australian medicinal plant *Bulbine capitata* (303).



Doxorubicin **322**, an anthraquinone glycoside, is currently one of the clinically most important antineoplastic drugs. In pharmacokinetic studies of doxorubicin **322**, capillary blood sampling was recommended, especially for pediatric patients, to avoid the sometimes traumatic venous blood sampling procedure (304). A new anthraquinone glycoside, emodin-6-*O*-β-D-glucopyranoside **323**, and the earlier isolated chrysophanol-8-*O*-β-glucoside **302**, together with seven known phenolic compounds, have been isolated from the roots of *Rumex patientia*. The cytotoxic effects and radical-scavenging properties of the isolated compounds have been demonstrated (305). The medicinal plant *Bulbine narcissifolia* is used by the Basotho, Griqua, and Whites of southern Africa for wound healing and as a mild purgative. Extraction of the powered root has yielded acetosyringone, chrysophanol,

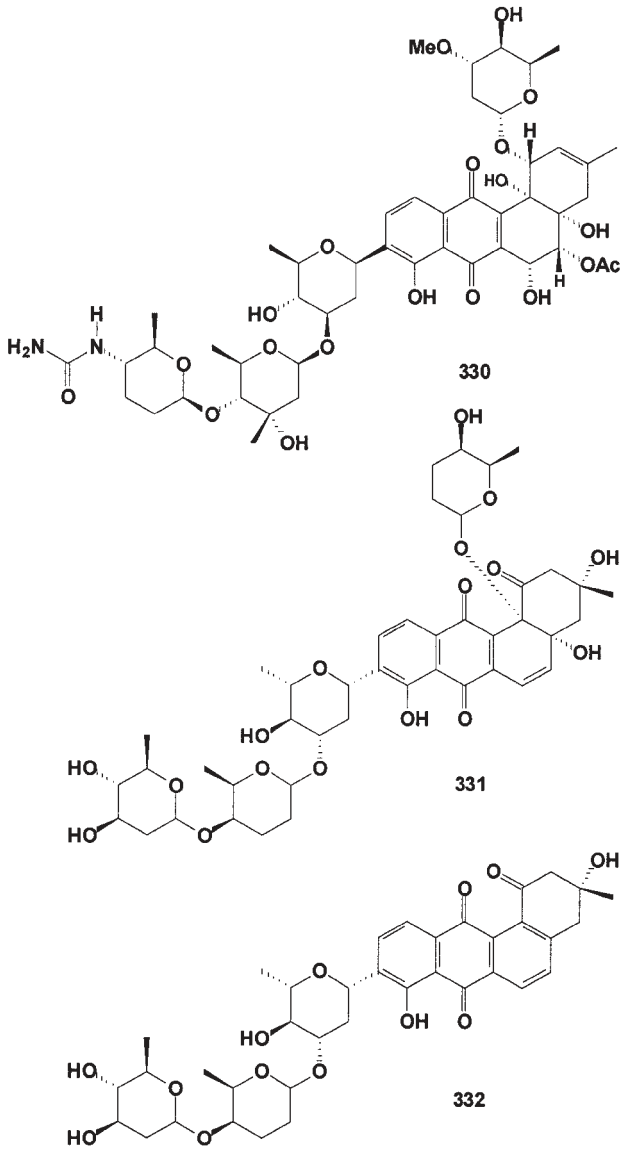
knipholone, isoknipholone, 10,7′-bichrysophanol, and chrysalodin in addition to two new anthraquinone glycosides, knipholone-8-*O*-β-D-gentiobioside **324** and chrysalodin-10-β-D-gentiobioside **325**. NMR spectroscopy was used to elucidate the structures of **324** and **325** and to show that **324** binds weakly to DNA (306).

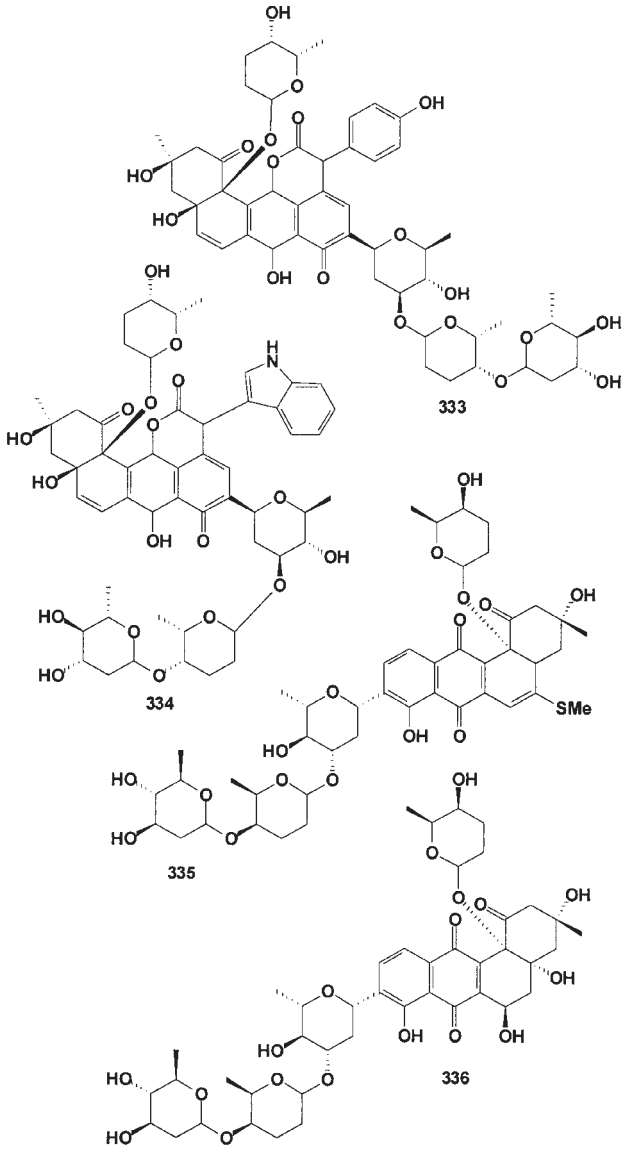
Frangulin A **326** (also known as emodin-L-rhamnoside, franguloside, or rhamnoxanthin) was discovered in 1907 by Tunman (307) in the bark of *Rhamnus frangula* (alder buckthorn); later, in 1909 the German chemist Schmidt (308), and again in 1913 the Russian scientist Krasovskii (309) found the compound in other *Rhamnus* species. More recently, biologically active frangulin A **326**, frangulin B **327**, glucofrangulin A **328**, and glucofrangulin B **329** have been isolated from *Rhamnus* and *Hypericum* species (310–312). Emodin **299** and frangulin B **326** showed significant antiplatelet effects (313); frangulin B **326** also showed potent inhibitory effects on TNF-α formation in LPS/interferon-γ-stimulated murine microglial cell line N9 (314).



An angucycline series compound, P371 A1 **330**, from *Streptomyces* sp. P371, was established as having a novel structure comprising an ureido group at one of the four sugar units (315). Compound **330** exhibited inhibitory activity against pentagastrin-stimulated acid secretion as well as protective activities against HCl/ethanol- and indomethacin-induced gastric lesions.

The colored urdamycins A **331**, B **332**, C **333**, D **334**, E **335**, and F **336** are six new angucycline antibiotics produced from the *Streptomyces fradiae* strain Tu 2717 (316,317). They are biologically active against gram-positive bacteria and stem cells of murine L1210 leukemia. The urdamycins are glycosides and differ in their aglycones, which can be liberated by acidic hydrolysis in addition to the sugars D-olivose and L-rhodinose.

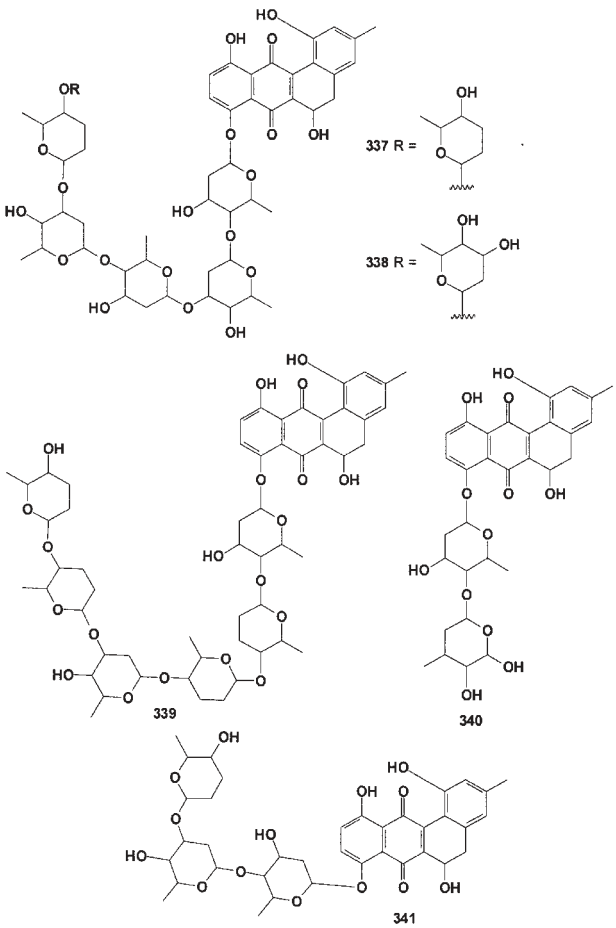


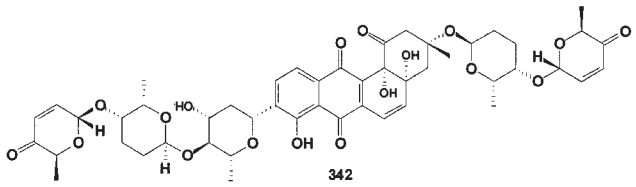


The antibiotic landomycins A **337**, B **338**, C **339**, D **340**, and E **341** are produced by species of streptomycetes (318–320). Streptomycetes, which are the producers of different polyketide antibiotics, can be divided into four groups based on their sensitivity to landomycins A and E: (i) *Streptomyces glaucescens* Tu49, producer of tetracenomycin, and *Streptomyces aureofaciens* 019, producer of chlortetracycline, belong to the most landomycin-sensitive strains. (ii) *Streptomyces cyanogenus* S136, producer of landomycin A, and *Streptomyces lividans* TK24, producer of actinorhodin, are sensitive to mean and high doses of landomycin E (more than 60–80 μg/mL). (iii) *Streptomyces globisporus* 1912 (producer of landomycin E), *S. cyanogenus* S136, *S. fradiae* Tu2717 (producer of urdamycins), and *Streptomyces coelicolor* A3(2) (producer of actinorhodin) have moderate sensitivity to all doses of both antibiotics, but strain S136 is sensitive only to low doses. (iv) Resistance to landomycins A and E was observed in strain *Streptomyces olivaceus* Tu2353, producer of elloramycin. In all these experiments, landomycin E showed lethal activity one to two orders higher than landomycin A, whose molecule is composed of the same aglycon landomycenone A but a longer polysaccharide chain, which probably hampers the penetration of the antibiotic through the cell membrane (319).

A derivative of anthraquinone glycoside, P-1894B **342**, is a potent prolyl hydroxylase inhibitor produced by *Streptomyces albogriseolus* subspecies no. 1894; it inhibited 50% of the activity of purified chick embryo prolyl hydroxylase at a concentration of 2.2×10^{-6} M (321). The inhibition was noncompetitive with respect to Pro-Pro-Gly, with a K_i (prolyl hydroxylase activity, expressed in mol/mg protein) of 1.8×10^{-6} M. When excess amounts of Fe^{2+} or ascorbate were added to the reaction mixture, the inhibition was slightly reversed. Compound **342**, at a dose of 0.15 mg/kg, reduced the hydroxylation of peptidylproline and caused a significant inhibition of collagen biosynthesis in the uterus of the immature rat when stimulated by the administration of 17-β-estradiol.

Biological activities, structures, and other information about glycosides of the anthracene derivatives anthraquinones, angucyclines, oxanthrones, anthranols, and anthrones can be found in several review articles (322–326).





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SUMMARY

Aromatic natural products have been used for thousands of years, and they are the basis of modern medicines. However, the same yardstick used for modern medicines should not be used to compare natural materials. Modern medicines work very quickly, they are concentrated, they are single components, the results are dramatic, and the risks of side effects are very real. The last couple of decades has seen a tremendous increase in interest in the biological properties of aromatic products as a means of identifying novel small compounds that could have potential in clinical medicine. To that end, stilbenes, lignans, naphthalene-like compounds, and anthracene-like compounds have been of particular interest because of their presence in diet constituents and because of the reported beneficial effects on diverse biological processes and disease conditions. The human diet contains an array of aromatic compounds (phytochemicals) with antioxidant activities capable of coping with reactive oxygen species, thus preventing oxidative stress. Of all the different phenolics, lignans, which are alkylphenolic compounds, constitute the largest class of polyphenols; they have proved to be one of the most powerful antioxidants present in the diet. The latest research has focused on understanding the role played by these dietary metabolites in disease prevention, suggesting a new role for "ancient" food items such as tea, cocoa, grapes (wine), and natural oils as functional foods.

As far as the economic importance of plant aromatic compounds is concerned, different types of medicinal plants are used to treat various ailments pertaining to the nervous system, circulatory system, neuromuscular system, skeletal system, skin, and gastrointestinal system, and are used as immunosuppressives, in oral hygiene, and for the reproductive system. Plant aromatics also find a use as antiviral agents, as metabolic probes, in taxonomy, in genetics, in biotechnology, and in commerce.

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