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REVIEW

Astonishing Diversity of Natural Surfactants: 7. Biologically Active Hemi- and Monoterpenoid Glycosides

Valery M. Dembitsky*

Department of Organic Chemistry and School of Pharmacy, Hebrew University, Jerusalem, Israel

ABSTRACT: This review article presents 90 hemi- and 188 monoterpenoid glycosides, isolated and identified from plants and microorganisms, that demonstrate different biological activities. These natural bioactive glycosides are good prospects for future chemical preparations from these compounds as antioxidants and as anticancer, antimicrobial, and antibacterial agents. These glycosidic compounds have been subdivided into several groups, including hemiterpenoids; acyclic, monocyclic, and bicyclic monoterpenoids; and iridoid monoterpenoids.

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Terpenes (terpenoids) are the second-largest group of secondary metabolites (nearly 23,000 are known). They are incredibly diverse in structure and activity, even though they all originally derive from a simple molecule called isoprene. Many terpenes are hydrocarbons, but oxygen-containing compounds such as alcohols, aldehydes, or ketones (terpenoids) are also isolated from natural sources. Their building block is the hydrocarbon isoprene CH_2=C(CH_3)–CH=CH_2. The German chemist Otto Wallach was the first to propose that monoterpenoids were constructed of a linkage of isoprene units (in head-to-tail form) (2). Wallach (born March 27, 1847, in Königsberg, died February 26, 1931, in Göttingen) was awarded a Nobel Prize in Chemistry in 1910. His interest began with the analysis of fragrant essential oils—oils removed from plants by steam distillation, with industrial uses; he then started researching their molecular structure. Wallach succeeded in determining the structure of several terpenes, including limonene, in 1895 (3,4). He showed that terpenes were derived from isoprene, C_5H_8—his "isoprene rule"—and therefore had the general formula $(C_5H_8)_n$.

Such compounds were classified by molecular size in a way that was systematic, but not consistent with the idea of isoprene as the structural unit. Later, Leopold (Lavoslav) Ruzicka (pronounced closely following the French transcription, "Rougitchka"; born on September 3, 1887, in Vukovar, Croatia; died on September 26, 1976, in Zürich, Switzerland) (5,6) formulated a classification system in which he defined monoterpenes as having carbon skeletons with two 5-carbon isoprene units, sesquiterpenes with three isoprenes, and so on. In 1953 his "biogenetic isoprene rule," which was pioneered by Wallach, became the crowning achievement of his lifetime. Ruzicka's main work, started in 1921, involved macrocyclic compounds, higher terpenes, and steroids. He shared the Nobel Prize with Adolf Friedrich Johann Butenandt (1903–1995) in 1939.

The hemiterpene isoprene, which contains five carbons (one isoprene unit, C_5), is a gas emitted into the atmosphere by many plant species. A monoterpene (monoterpenoid) contains 10 carbons (two isoprene units, C_{10}); a sesquiterpene, 15 carbons (three isoprene units, C_{15}); and a diterpene, 20 carbons (four isoprene units, C_{20}). Sesterpenes (five isoprene units, C_{25}) were isolated from insect protective waxes and from fungal sources. Triterpenes (six isoprene units, C_{30}) are important structural components of plant cell membranes. Many plant pigments, including the yellow and red carotenoids, are tetraterpenes (eight isoprene units, C_{40}). Natural rubber is a polyterpene containing more than 40 isoprene units (7,8).

Terpenes are largely found in essential oils, and they were known and used in ancient Egypt for various religious aims. The terpene camphor, obtained from the camphor tree (*Cinnamomum camphora* syn. *Laurus camphora*, Lauraceae) was used to reduce fevers, soothe gums, and treat epilepsy. Camphor trees are native to China and Japan and are cultivated for their wood for the extraction of camphor oil. Marco Polo was the first to note that the Chinese used camphor oil as a medicine, scent, and embalming fluid. Camphor crystals have strong antiseptic, stimulant, and antispasmodic properties and are applied externally as unguents or balms as a counterirritant and analgesic liniment to relieve arthritic and rheumatic pains, neuralgia, and back pain. It may also be applied for skin problems such as cold sores and chilblains, and used as a chest rub for bronchitis and other chest infections. Camphor was introduced in Europe from the East by the Arabs around the 11th century. The process of obtaining plant essential oils by fat extraction was known by the early Middle Ages. These compounds have important uses as flavorings and perfumes, as well as intermediates in the production of other commercial products such as solvents and adhesives. Many terpenes play roles as plant hormones and in the chemical defenses of plants against microbial diseases and insect herbivores; many others have important medicinal properties. Many terpenoids and isoprenoids are toxic to insects, and a few are also repellents and toxicants to subterranean termites, although the mechanism of toxicity is not well known.

Iridoids, a widely distributed class of natural monoterpenoids, have shown encouraging biological activities including hepatoprotective, anticancer, immunostimulant, and antileishmanial activities (9,10).

*Address correspondence at Department of Organic Chemistry, P.O. Box 39231, Hebrew University, Jerusalem 91391, Israel.
E-mail: dvalery@cc.huji.ac.il

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

Abbreviations: IPP, isopentenyl diphosphate; MEP, methylerythritol phosphate.

Hemi- and monoterpenoid glycosides are representatives of a water-soluble group isolated from terrestrial and marine plants and organisms. They can be subdivided into several known groups including hemiterpenoids, monoterpenoids (acyclic, monocyclic, and bicyclic), and iridoid monoterpenoids and are presented in this review article.

HEMITERPENOID GLYCOSIDES AND RELATED COMPOUNDS

A small group of terpenes named hemiterpenes are made up of one 5-carbon unit (or from C5 to C9), and are the simplest of all terpenes. Isoprene is emitted from the leaves of many plants, and experimental data have been partly reviewed in some articles (11–15). Hemiterpenes accumulate in plant tissues and can be found in association with other compounds such as alkaloids, coumarins, phenols, and/or flavonoids (16,17).

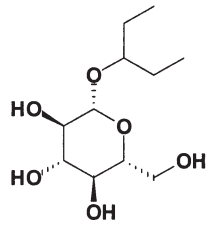
Plants have been shown to use the mevalonate pathway for the biosynthesis of sterols and triterpenes in the cytoplasm and to use the recently discovered deoxyxylulose phosphate pathway for the biosynthesis of a variety of hemiterpenes, monoterpenes, and diterpenes, as well as for the biosynthesis of carotenoids and the phytol side chain of chlorophyll in plastids (18). In higher plants, the five-carbon building blocks of all terpenoids, isopentenyl diphosphate (IPP), and dimethylallyl diphosphate are derived from two independent pathways localized in different cellular compartments (19). The methylerythritol phosphate (MEP, or nonmevalonate) pathway, localized in the plastids, is thought to provide IPP and dimethylallyl diphosphate for hemiterpene, monoterpene, and diterpene biosynthesis, whereas the cytosol-localized mevalonate pathway provides C_5 units for sesquiterpene biosynthesis. It has been shown that only one of the two pathways, the plastid-localized MEP pathway, is active in the formation of volatile terpenes. The MEP pathway provides IPP precursors for both plastidial monoterpene and cytosolic sesquiterpene biosynthesis in the epidermis of snapdragon petals. The trafficking of IPP occurs unidirectionally from the plastids to the cytosol. The MEP pathway operates in a rhythmic manner controlled by the circadian clock, which determines the rhythmicity of terpenoid emission (19). Different Salicaceae species contain from 2 to 8% hemiterpenes of the total volatile oil (20).

Foeniculum vulgare, the common fennel, is a biennial or perennial plant with a whitish, tap-shaped root, the whole herb being smooth and of a deep glaucous green. It inhabits the southern parts of Europe and is naturalized in Japan, Kurdistan, Malaysia, Mexico, Spain, Turkey, and Venezuela. For the medicinal use of its fruit (commonly called seeds), fennel is largely cultivated in the south of France, Saxony, Galicia, and Russia, as well as in India and Persia. Fennel was well known to the ancients and was cultivated by the ancient Romans for its aromatic fruit and succulent, edible shoots.

The *F. vulgare* fruit extract exhibited anti-inflammatory, analgesic, and antioxidant activities (21) and showed acaricidal activities against *Dermatophagoides farinae* and *D. pteronyssinus* (22) as well as antimicrobial activity against some phytopathogenic bacterial species (*Pseudomonas syringae, P. cichorii, P. viridiflava, P. corrugate, P. tolaasii, P. reactans, P. agarici, Erwinia carotovora* subsp. *carotovora, Agrobacterium tumefaciens, Burkholderia gladioli* pv. *agaricicola,* and *Xanthomonas campestris*) (23). Some hemiterpenoid glycosides (**1–9)** were obtained from the water-soluble fraction of the methanol extract of the fennel fruit (*F. vulgare*, Umbelliferae) (24).

A new hemiterpene glucoside, (2*E*)-4-hydroxy-2-methyl-2-butenyl β-D-glucopyranoside **10**, was isolated from Italian populations of *Ornithogalum montanum* (Liliaceae) (25). Four new nonbasic hemiterpenoid glucosides, woorenosides VI **12**, VII **13**, VIII **11**, and IX **14**; the nonglycosidic woorenosides X and XI; and a new acetylated flavone glycoside, woorenoside XII, were isolated from the fresh rhizomes of *Coptis japonica* var. *dissecta* (26). (*S*)-2-Methylbutan-1-yl-β-D-glucopyranoside **15** was isolated in a yield of 0.01% from the leaves of *Bystropogon plumosus* (Lamiaceae) endemic to the Canaries (27). The essential oil of some species of the genus *Bystropogon—B. plumosus*, *B. origanifolius* var. *palmensis*, *B. wildpretii*, *B. maderensis*, and *B. canariensis* var. *smithianus*—showed antimicrobial and antifungal activities (28). A new hemiterpenoic acid glycoside named securiterpenoside **16** was isolated from the Chinese medicinal plant *Securidaca inappendiculata* (Polygalaceae), whose bark is used for bathing and shampooing the hair (29).

Two new hemiterpene glycosides were isolated from wine of the grape *Vitis vinifera* cv. Gewurztraminer and were identified by MS and NMR spectroscopy as *O*-β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosides of 3-methyl-3-butenol **17** and of 3-methyl-2-butenol **18** (30). Two hemiterpene glycosides, (2*Z*)-3-hydroxy-1-methyl-1-propenyl-β-D-glucopyranoside **19** and (2*Z*)-3-hydroxy-2-methyl-1-propenyl-β-D-glucopyranoside **20**, were identified in a water-soluble extract obtained from Riesling grapevine leaves and purified by HPLC (31).



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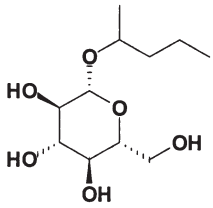

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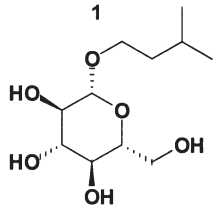

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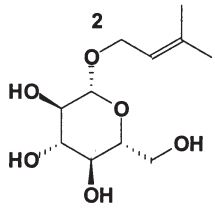

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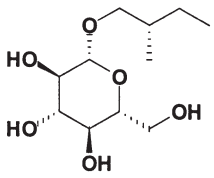

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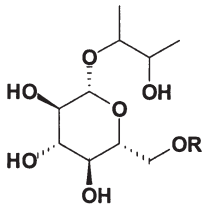
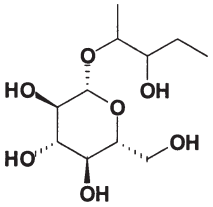


6 R = H
7 R = Api



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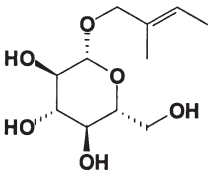

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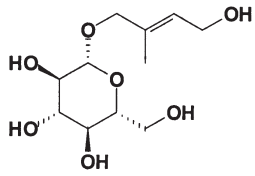

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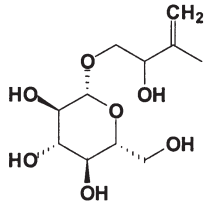

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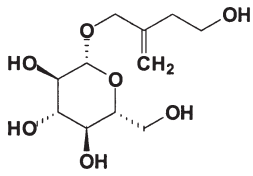

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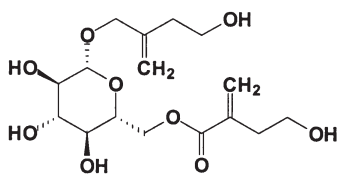

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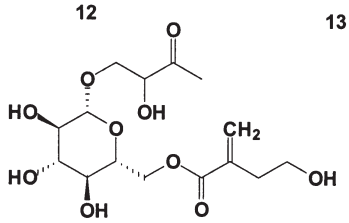

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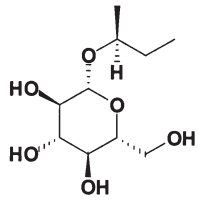

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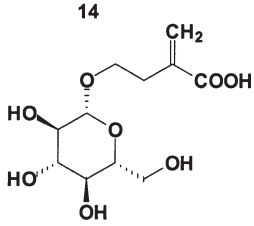

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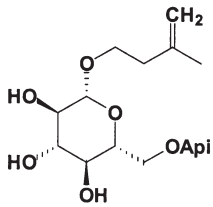

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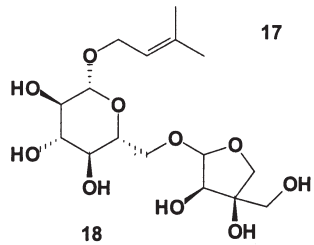
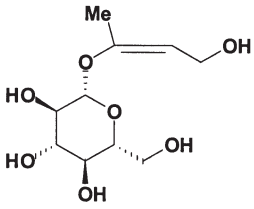


18

Ilex (holly) is a genus of about 400 species of flowering plants in the family Aquifoliaceae. *Ilex* is the old Latin name for holly (*Ilex aquifolium*) or the aohada holly (*Ilex macropoda*) now being used in medicine (32). Extracts from species of the genus *Ilex* showed proteasome inhibitor activity (33) and were capable of inhibiting advanced glycation end products (34). Phytochemical studies of *I. macropoda* led to the isolation of four new hemiterpene glycosides—(2*E*)-4-hydroxy-2-(hydroxymethyl)-2-butenyl β-D-glucopyranoside **21**, aohadaglycoside A **22**, aohadaglycoside B **23**, and aohadaglycoside C **24**—identified from a bark extract (35).



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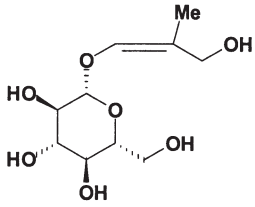

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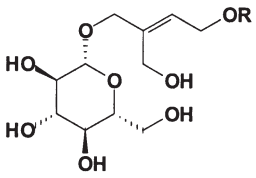
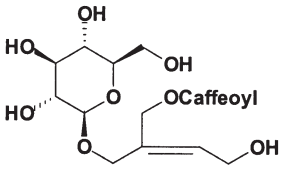


21 R = H
22 R = Caffeoyl



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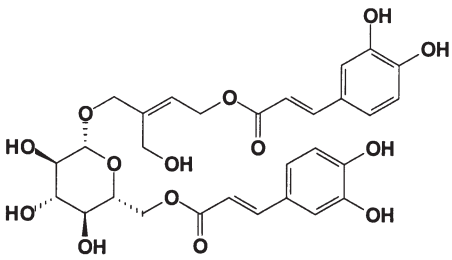

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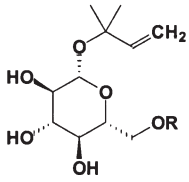
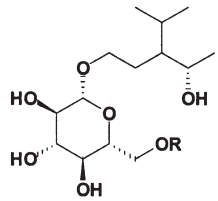
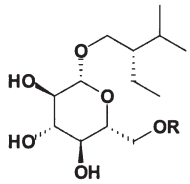


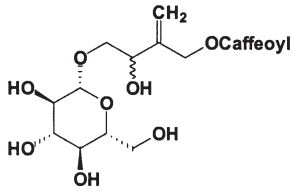
25 R = H
26 R = Api



27 R = Man



28 R = Man



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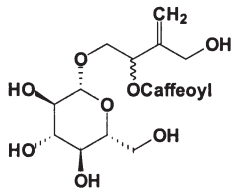

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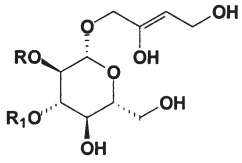
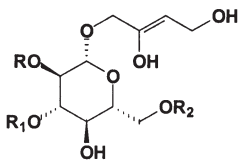
The hemiterpenoid glucoside 1,1-dimethylallyl β-glucoside **25** was isolated from flower buds of *Musa paradisiacal* (36), and furocoumarin **26**, having a similar structure, was isolated from a methanolic extract of the root and rhizoma of *Glehnia littoralis* (Umbelliferae; Hamabofu in Japanese) (37). A methanolic extract of the roots of *Streptocaulon juventas* showed strong antiproliferative activity against the highly metastatic human HT-1080 fibrosarcoma cell line; two new hemiterpenoids, (4*R*)-4-hydroxy-3-isopropylpentyl β-rutinoside **27** and (*R*)-2-ethyl-3-methylbutyl β-rutinoside **28**, were isolated from this extract (38). Two new hemiterpene glucosides named pubescenosides A **29** and B **30** were isolated from the root of *Ilex pubescens* (39). A pharmacological investigation of pubescenosides A and B indicated that both possessed potent antiplatelet aggregation activities.

Acylated hemiterpenoid glycosides called hymenosides A **31**, B **32**, C **33**, D **34**, E **35**, and F **36**, where HPA = 4-hydroxyphenylacetate, were isolated from a methanolic extract of the Japanese fern *Hymenophyllum barbatum* belonging to the family Hymenophyllaceae (40). Hymenosides K **37**, Q **38**, R **39**, S **40**, L **48**, M **43**, N **45**, O **46**, P **47**, W **44**, and U **49** and the methyl ester of 3-(β-D-glucopyranosyloxy)-5-hydroxy-hexanoic acid, **50**, were identified from the same species (41). The structures of those aglycons were divided into four types: 2-methyl-but-2-ene-1,4-diol, 2-hydroxymethyl-but-2-ene-1,4-diol, 2-methylene-butane-1,3,4-triol, and 3-hydroxy-5-hexanolide. The sugar moieties, which were acylated by phenylacetic acid derivatives, were also established by chemical and spectroscopic methods. Eight glucosides of the isolated compounds had a bitter or weakly pungent taste. It is clear that a phenylacetyl group attached to a glucose or allose as an ester is responsible for the bitter taste. In addition to the hymenosides discovered, **31**–**50**, three new acylated hymenosides—hymenosides G **51**, H **52**, and I **53**—were identified from a methanolic extract of

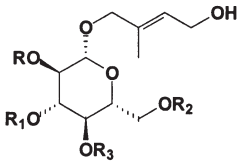
H. barbatum (42). Hemialboside **54**, (*S*)-1-hydroxy-3-methyl-but-3-en-2-yl-β-D-glucopyranoside, was isolated from *Lamium album* (43).

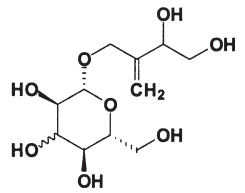


31 R, R_1 = 4-HPA
32 R, R_1 = Caffeoyl
33 R = 4-HPA, R_1 = Caf
34 R = Caf, R_1 = 4-HPA



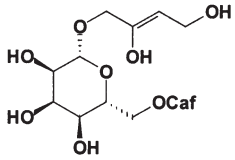
35 R = R_2 = Caf, R1 = H
36 R = R2 = Caf, R1 = 4-HPA

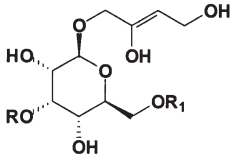




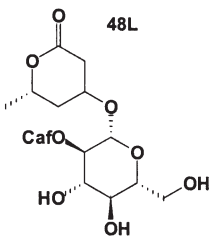
43M α-OH
44W β-OH

37K R = Caf, R_1,R_2,R_3 = H
38Q R, R_2,R_3 = H, R_1 = Caf
39R R,R_1,R_3 = H, R_2 = Caf
40S R = 4-HPA, R_1,R_2, R_3 = H
41T R,R_1,R_3 = H, R_2 = 4-HPA
42V R_3 = Caf, R,R_1,R_2 = H



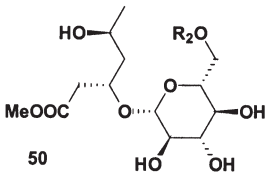


45N R = Caf, R_1,R2 = H
46O R,R1 = H, R2 = Caf
47P R,R2 = H, R_1 = Caf



48L

49U



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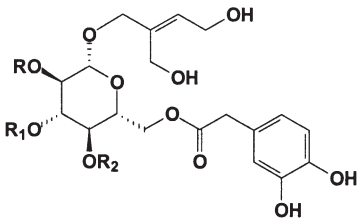
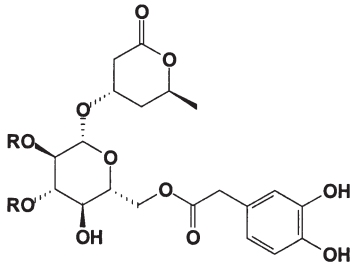
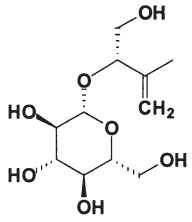


51 R, R_1 = Caf, R_2 = H
52 R = H, R_1, R_2 = Caf



53 R = 4-HPA



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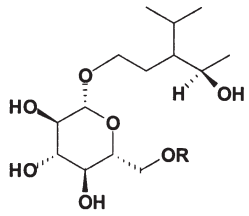
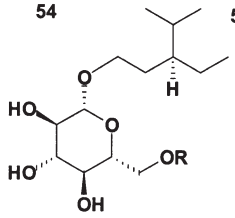


55 R = Rha

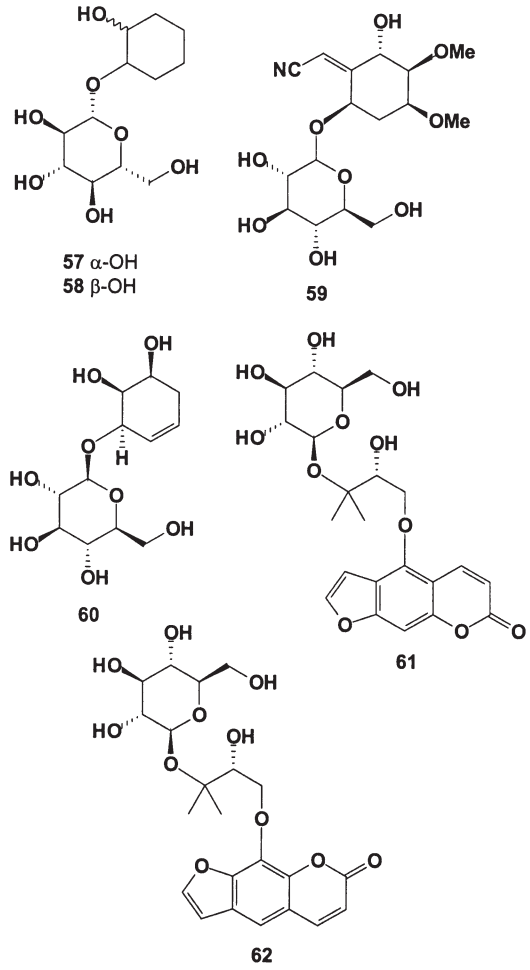


56 R = Rha

Streptocaulon juventas, a plant in the Asclepiadaceae family, is native to Indochina. This plant is called Ha thu o trang in Vietnam, and its roots are used as a tonic for anemia, chronic malaria, rheumatism, menstrual disorders, neurasthenia, and dyspepsia as an equivalent of Ha thu o do (the roots of *Polygonum multiflorum*, Polygonaceae). A methanolic extract of the roots of *S. juventas* strongly and selectively inhibited proliferation of the human HT-1080 fibrosarcoma cell line (IC_{50} value, 1.2 μ/mL) (44–47). Two hemiterpenoids, **55** and **56**, were isolated from the roots of *S. juventas* (48).

Two rare hemiterpene cyclohexyl glucosides, **57** and **58**, were isolated from the water-soluble portion of rhizome methanolic extracts of *Atractylodes lancea* and *A. japonica* (49). Simmondsin **59** is an unusual 2(cyanomethylene)cyclohexyl glucoside from *Simmondsia californica* (50). A 70% ethanolic extract of the root bark of *Alangium platanifolium* showed binding activities to nine receptors in the central nervous system and contained (1*S*,5*R*,6*R*)-5,6-dihydroxy-2-cyclohexen-1-yl-β-D-glucopyranoside **60** (51). An ethyl acetate extract of the stems and roots from *Prangos pabularia* (Umbelliferae) afforded two complex hemiterpeneoid glucosides, named oxypeucedanin **61** and *tert-O*-β-glucosylheraclenol **62**

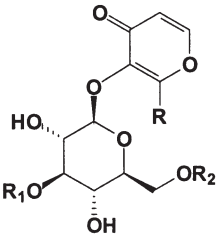
(52). The leaves and blossoms of this plant, which grows wild in central Asia, are usually used as fodder for cattle.



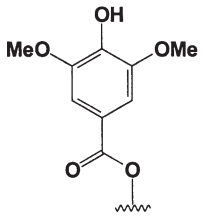
Some γ-pyrone derivatives, such as pyrocomenic acid, kojic acid, comenic acid, 3-(acetoyloxy)-4(*H*)-pyran-4-one, maltol, ethylmaltol, and hydroxymaltol, are effective in preventing UV-induced suntans or sunburns in humans. These compounds are also effective in bleaching black goldfish and in preventing UV-induced color changes in lotus roots (53). The kojic acid derivatives showed antifungal, antineoplastic, and antileukemic activities (54,55). The 2-pyrones demonstrated potent inhibitory activity against *Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Schizosaccharomyces pombe*, and *Botrytis cinerea*, as well as growth-inhibitory activities in A2780 human ovarian carcinoma and K562 human chronic myelogenous leukemia cell lines using an *in vitro* cell culture system [3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide assay] (56,57).

A glucoside of pyrocomenic acid, 3-(β-D-glucopyranosyloxy)-4H-pyran-4-one **63**, named erigeroside, was isolated for the first time from Dengzhanhua (*Erigeron breviscapus*) (58). Erigeroside had Extra Strength Pain-Off protective effects (2–10 mg/kg) on cerebral ischemia-reperfusion injury in the rat and showed antioxidant and free radical-scavenging abilities *in vitro* (59). More recently, erigeroside **63** was isolated from the flowers of *Stenactis annua* (60) and *E. breviscapus* (61). Glucoside **63** and a 2-methyl derivative named dianthoside (maltol 3-*O*-glucoside) **64** were identified from ethanolic extracts of *E. ramosus* and from *Dianthus* sp., respectively (62). The occurrence of dianthoside **64** in 17 species of Pinaceae (*Abies, Pseudo tsuga, Tsuga,* and *Larix*) was reported (63). Dianthoside **64** was isolated from the needles of *Abies veitchii* and erigeroside **63** in three *Erigeron* species. 3′-*O*-Caffeylerigeroside **65** was obtained from the leaves of *E. annuus* as a new pyromeconic acid derivative (64), together with the γ-pyrone of pyrocomenic acid and its γ-glucoside (erigeroside **63**). Another erigeroside isomer, 6′-*O*-caffeylerigeroside (erigeside I **66**), was obtained from *E. multiradiatus* (65). *Erigeron multiradiatus* is a perennial herb distributed abundantly in the mountainous area of southwestern China; it is used in folk medicine for treating the common cold, a panting cough, rheumatic fever, enteritis, and toothaches. Two new glycosides, erigeside D **67**, together with erigeside I **66**, were isolated from *E. breviscapus* (66). Pyromeconic acid and its β-D-glycoside, **63**, also were extracted from *E. acris* leaves (67).

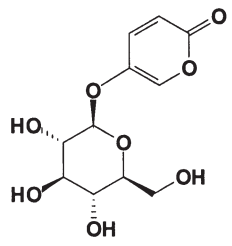
2*H*-Pyrane and its glucoside, **68**, were isolated from the leaves of *Erigeron annuus* and showed properties as a glycosidase inhibitor (68). The cut leaves of *E. canadensis* stored in an aqueous solution of **68** (1 mg/10 mL) showed neither discoloration nor growth of filamentous fungi as compared with the fragmentation and fungal growth in control leaves. Also, compound **68** completely inhibited the hydrolysis of soluble starch by α-amylase in a potassium phosphate buffer (68). An aqueous ethanolic extract from fresh stems of the cactus *Opuntia dillenii* showed potent radical-scavenging activity (69). This extract contained a new compound, opuntioside I **69**. Kojic acid glucoside **70**, isolated from plant sources, showed a good antiperspirant effect (70). A methanolic extract of the aerial parts of *Adenocaulon himalaicum* (Asteraceae) yielded a new compound, parasorboside **71** (71).



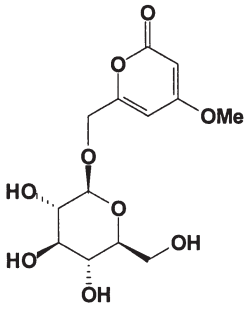
63 R, R_1, R_2 = H
64 R = Me, R_1, R_2 = H
65 R, R_2 = H, R_1 = Caf
66 R, R_1 = H, R_2 = Caf



67 R,R_1 = H, R_2 =



68



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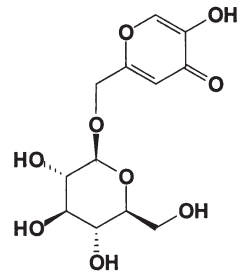

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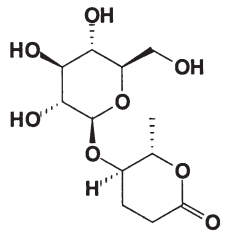

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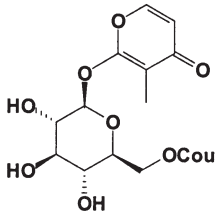
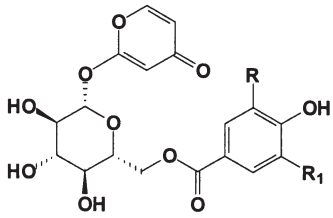
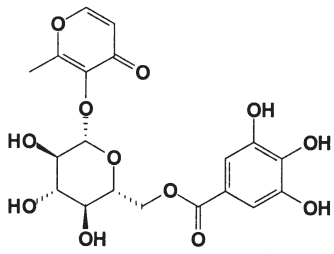


72



73 R, R_1 = H
74 R = OMe, R_1 = H



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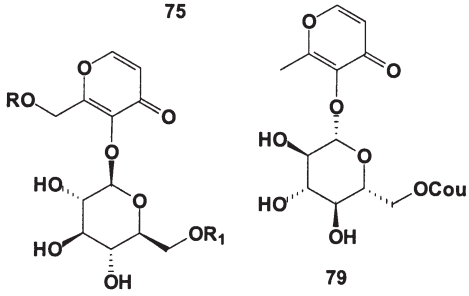


79

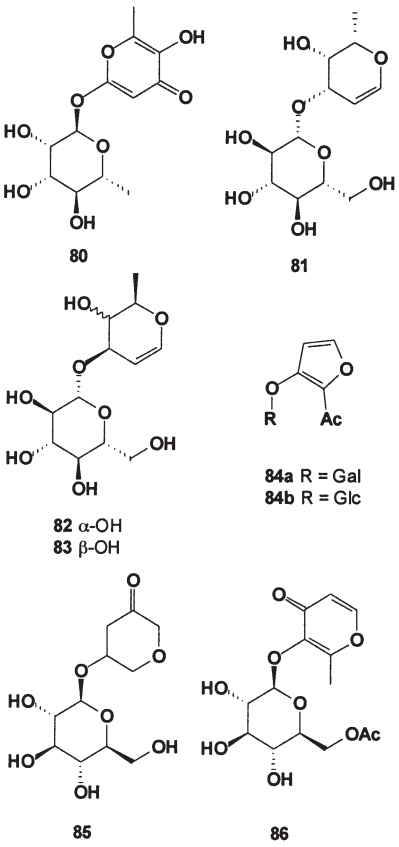
76 R = R_1 = H
77 R = H, R_1 = Coumaroyl
78 R = Coumaroyl, R_1 = H

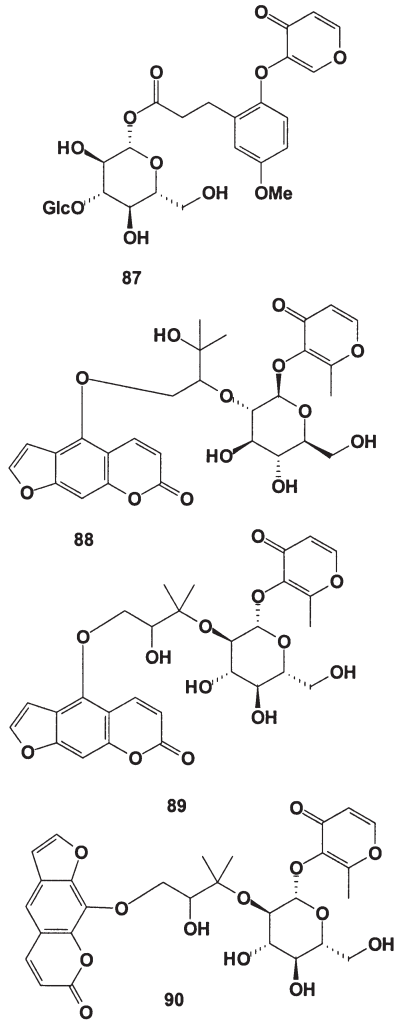
An acylated 4-pyrone glycoside, 2-[6′-*O*-*trans*-cinnamoyl)-β-D-glucopyranosyloxy]-3-methyl-4*H*-pyran-4-one **72**, was isolated from a chloroform–methanol extract of the shoots of *Silene vulgaris* (Caryophyllaceae) (72). Three pyrone glucosidic derivatives, **67**, **73**, and **74**, together with the known pyrocomenic acid glucoside **63**, were obtained from the aerial parts of *Conyza albida* (73). A new acylated γ-pyrone glucoside, **75**, was isolated from the leaf extract of *Gordonia axillaris* (Theaceae) (74). Hydroxymaltol 3-*O*-β-D-glucoside **76**; two maltol glucosides, bockiosides A **77** and B **78**; and isoinnovanoside **79** were isolated from the tuber *Smilax bockii* (Liliaceae) (75).

The new glycosides (2*S*)-eriodictyol-7-*O*-Me ether-3′-*O*-β-D-glucopyranoside **80** and maltol-3-*O*-β-D-glucopyranoside **64** were isolated from the fronds of *Pseudocyclosorus subochthodes* and *Pseudocyclosorus esquirolii* (76). Sapopyroside **81** was isolated from *Saponaria officinalis*, and a new glycoside, barbapyroside **82**, isomeric with the former but

having a different configuration, was isolated from *Dianthus barbatus* and *D. deltoids* (77). Compound **81** was also isolated from *D. superbus* var. *longicalycinus* (78), and **83**, an isomer of barbapyroside **82**, was found in an extract of the aerial parts of the Vietnamese *Helichrysum zeyheri* (Asteraceae) (79). Isomaltal β-D-galactoside **84a** and isomaltol α-D-glucoside **84b** were extracted from milk spiked with this glucosyl β-pyranone **85**, while avoiding the use of any deproteinizing agent, and were detected by a sensitive and interference-free HPLC method (80). Maltol-(6-*O*-acetyl)-β-D-glucopyranoside **86** was isolated from *Prangos pabularia* (52).

A few complex 4*H*-pyrone glycosides with biological activities containing multiple structural units, including pyrocomenic acid, kojic acid, comenic acid, maltol, ethylmaltol, and/or hydroxymaltol, that are not linked with a sugar and/or that contain more than three structural units have been discovered in plant species. A new complex 2-methyl-3-*O*-{2′-[β-D-glucoside-(1‴→3″)-β-D-glucoside]-propionyloxy-4′-methoxyphenyl}-4-pyrone, **87**, was isolated for the first time from whole parts of *Scleranthus uncinatus* (81). Pabularin A **88**, B **89**, and C **90**, three glucosides of γ-pyrone with antibacterial activity and inhibition of cytokine release, were identified from an extract of the roots of *P. pabularia* (52).



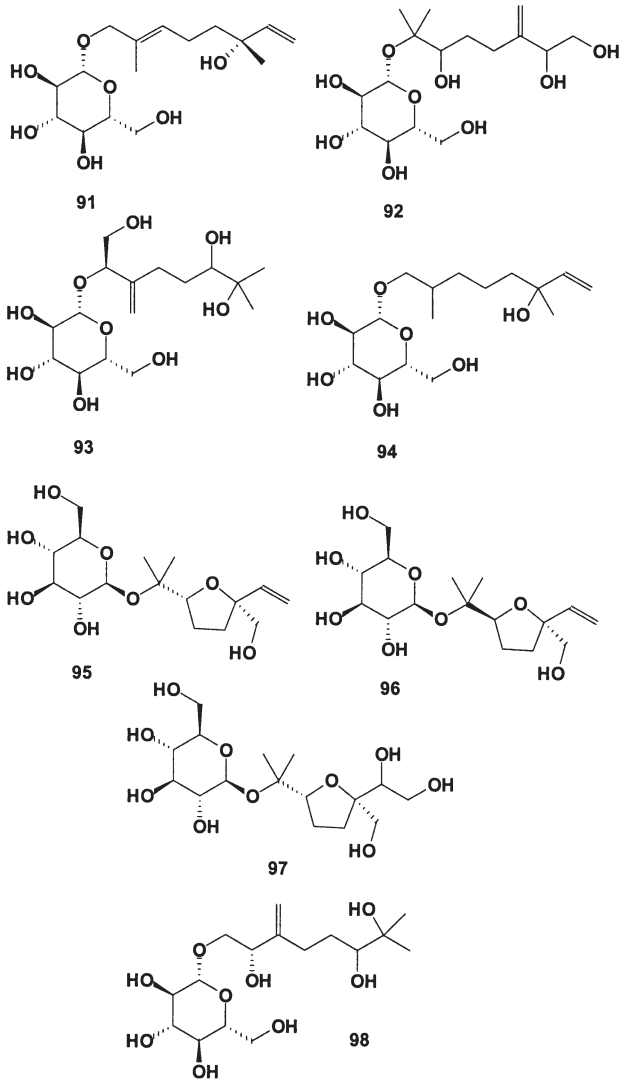


MONOTERPENOID GLYCOSIDES

Monoterpenoids have a head-to-tail formation of their 10-carbon precursor, geranyl pyrophosphate (14,15). Some of their oxygenated derivatives, such as alcohols, ketones, and carboxylic acids, are present in plant volatile oils, and were also identified from microorganisms and some marine sources (82). Monoterpenoids often have a strong smell. They are the source of such scents as spearmint (carvone), bergamot and lavender (both of which contain linalyl acetate), and sweet rose (nerol) (83,84). Acyclic monoterpenoids occur in insect pheromones as well (85,86). Acyclic, monocyclic, and bicyclic monoterpenoids vary in pharmacological use as expectorants, anticholesteremics, anthelmintics, antiseptics, and insecticides (82,84,87). Iridoids are also monoterpenoids based on a cyclopentan-[*C*]-pyran skeleton, which may consist of 10, 9, or (rarely) 8 carbon atoms, in which C_{11} is more frequently missing than C_{10}. This class of monoterpenoids can be subdivided into five groups according to their chemical structures: acyclic (or linear), monocyclic, monocyclic iridoids, bicyclic, and bicyclic iridoids. Glycosidic compounds belonging to all five groups are represented below.

Acyclic Monoterpenoid Glycosides

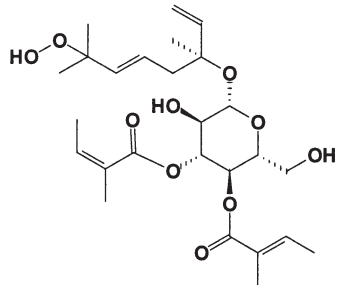
From the water-soluble fraction of a methanolic extract of the herbal medicine fennel (*Foeniculum vulgare*), betulalbuside A **91** and five new acyclic monoterpenoid glycosides, **92–97**, were identified, three of which (**95–97)** contain an oxide linkage (88). Ajowan (*Carum ajowan*, also spelled ajwain, the Hindi name for tiny), which belongs to the family Umbelliferae, is cultivated mainly in southern India and is known as a popular aromatic herb and spice. Its fruit has been used as much for medicine as in cooking, and is primarily used to control flatulence and indigestion. Ajowan contains thymol, which is a germicide and antiseptic, and is prescribed for diarrhea, colic, and other bowel problems to help expel wind and mucus. Sometimes used in the treatment of asthma, the seeds are smoked in a pipe to relieve shortness of breath (89). A methanolic extract of the fruit of *C. ajowan* (ajowan) was found to contain a new acyclic monoterpenoid and its glycoside, **98** (90).



Aster scaber (Asteraceae) has been used in traditional Korean and Chinese medicine to treat bruises, snakebites, headaches, and dizziness. The aerial part of *A. scaber* yielded two new monoterpene peroxide glycosides, (3*S*)-3-*O*-(3′,4′-diangeloyl-β-D-glucopyranosyloxy)-7-hydroperoxy-3,7-dimethylocta-1,5-

diene **99** and (3*S*)-3-*O*-(3′,4′-diangeloyl-β-D-glucopyranosyloxy)-6-hydroperoxy-3,7-dimethylocta-1,7-diene **100** (91).

Prunioside A **102**, a unique, highly oxidized monoterpene glycoside, was isolated from a methanolic extract of the roots of *Spiraea prunifolia* var. *simpliciflora* (92). The ester derivatives of prunioside A **102** showed suppressive effects on the generation of nitric oxide in murine macrophage-like RAW 264.7 cells stimulated by lipopolysaccharide and γ-interferon.



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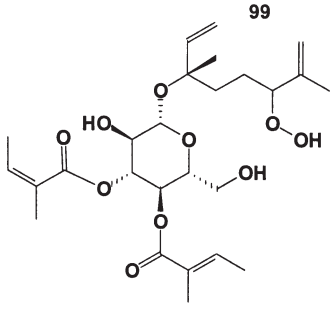

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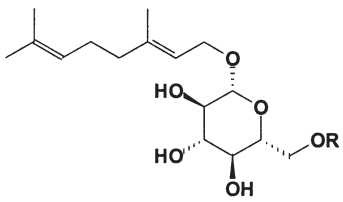
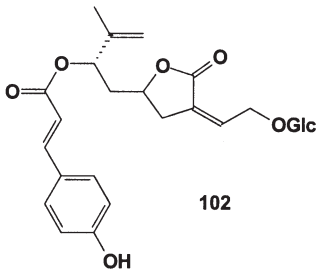
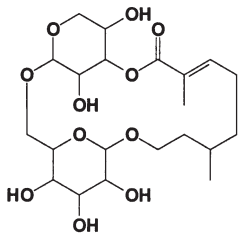


101 R = Rha



102

Unusual monoterpenoid glycosides were isolated from extracts of the stem bark of *Winchia calophylla* (93). The new compounds included two cyclodiglycosides, named wincaloside A **103** and wincaloside B **104**. A similar novel monoterpene glycoside, mileenside **105**, was isolated from *Swertia mileensis* (94). *Linaria capraria* (Scrophulariaceae), a species endemic to the Tuscany archipelago (Italy), was found to contain acyclic glucoside **106** (95) and glycoside **107**, and the known betulalbuside A **91** was found in the Turkish trees *Phlomis samia* and *P. carica* (96).



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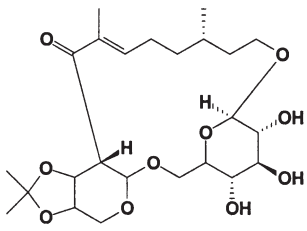

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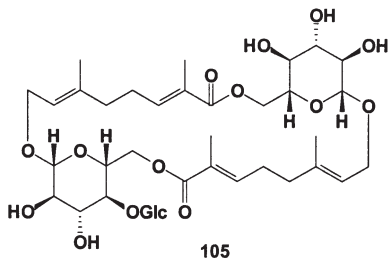

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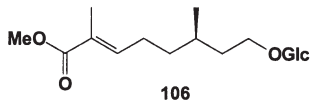

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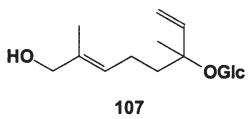
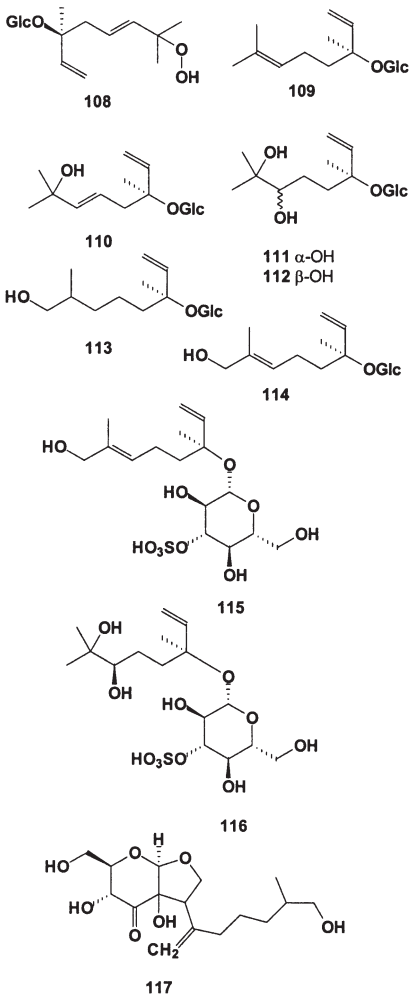


107

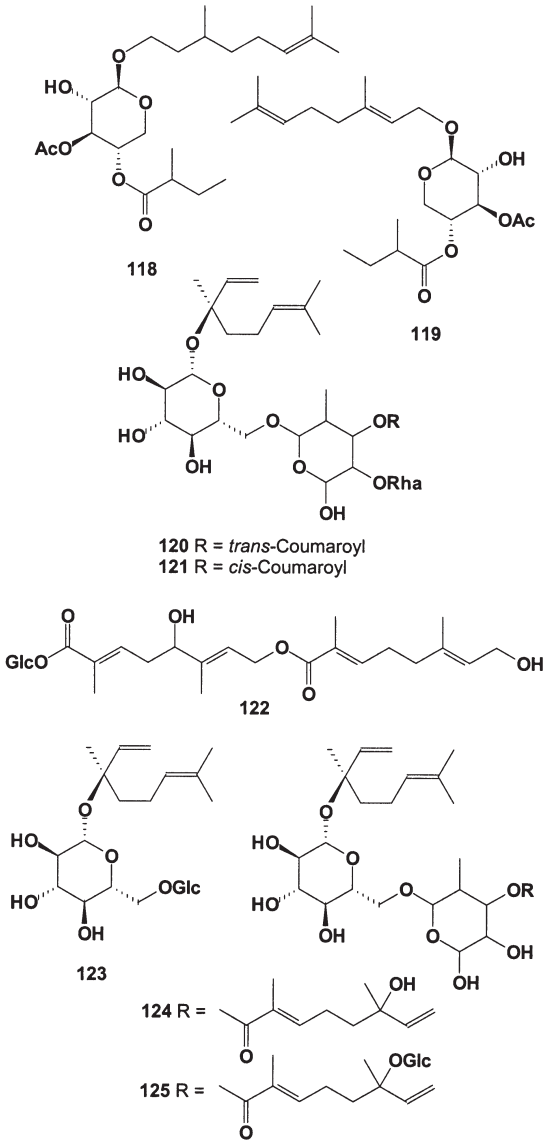
Three monoterpene glucosides, **108**–**110**, including one new hydroperoxide, **108**, were isolated from a methanolic extract of the Korean *Portulaca oleracea* (family Portulacaceae) (97). *Portulaca oleracea*, commonly known as purslane in the United States, is an herbaceous weed. It can be found growing wild and/or cultivated in much of the world. It existed in the New World before the arrival of Columbus and was found in Europe by the late 16th century. Purslane (also called wild portulaca, or pigweed) can be found growing in cold-climate areas (Canada) as well as warm areas (the Caribbean). It has been used in salads and as a medicinal plant for hundreds of years. Both aqueous and ethanolic extracts of *P. oleracea* showed gastroprotective action, validating its use in folk medicine for gastrointestinal diseases; both extracts showed a dose-dependent reduction in the severity of ulcers (98). From the water-soluble fraction of a methanolic extract of coriander (the fruit of *Coriandrum sativum*), which has been used as a spice and medicine since antiquity, four new monoterpenoid glycosides,

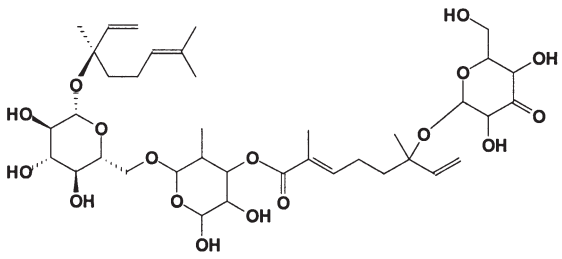
111–**114**, a hemiterpenoid, **6**, and two rare new monoterpenoid glucoside sulfates, **115** and **116**, were identified (99). An unusual monoterpene glycoside named dissectol A **117** was isolated from the ethanolic extract of *Incarvillea dissectifoliola* (100,101). Antimicrobial bioassays showed that **117** had modest inhibitory activity against *Mycobacterium tuberculosis* when compared with rifampicin in an agar diffusion assay.



Polemonium viscosum (blue whirl) yielded several new diterpenes with labdane and pimarane skeletons and two new monoterpene glycosides, **118** and **119** (102). Two monoterpene glycosides, (3*S*)-*O*-α-L-rhamnopyranosyl-(1→3)-[4-*O*-(*E*)-coumaroyl]-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-linalool **120** and (3*S*)-*O*-α-L-rhamnopyranosyl-(1→3)-[4-*O*-(*Z*)-coumaroyl]-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-linalool **121**, were isolated from a methanolic extract of the leaves of *Eriobotrya deflexa* (103). Digipenstroside **122**, a novel dimeric open-chain monoterpene glucoside, was isolated from the leaves of *Penstemon digitalis* (104).

Five new acyclic monoterpene glycosides were isolated from the leaves of *Viburnum orientale* (Caprifoliaceae) (105): monoterpene diglycoside anatolioside **123**, and four derivatives of **123** containing additional monoterpene and sugar units connected by ester and glycoside bonds, i.e., anatoliosides A **124**, B **125**, C **126**, and D **127**. A new open-chain monoterpene glycoside, anatolioside E **128**, was isolated from the leaves of *V. orientale* in addition to the known acyclic monoterpene glycosides betulalbuside A **91**, betulalbuside B **129**, and glucoside **114** (106). The two stereoisomeric monoterpenoid glycosides, betulalbusides A **91** and B **129**, were also isolated from the leaves of *Betula alba* (Betulaceae) and from the fruits of *Chaenomeles japonica* (Rosaceae) (107).





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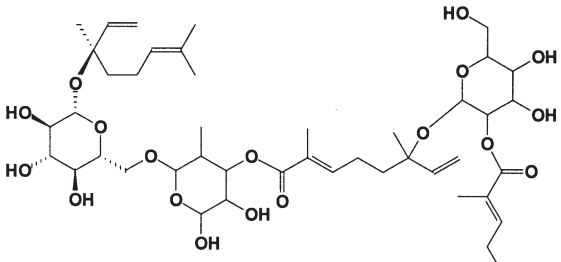

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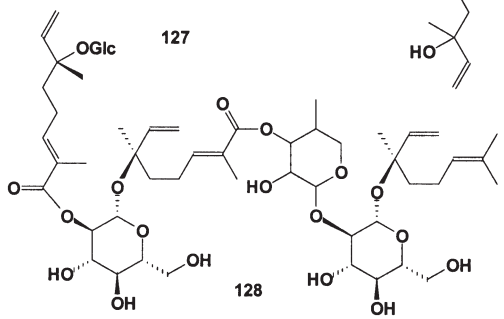

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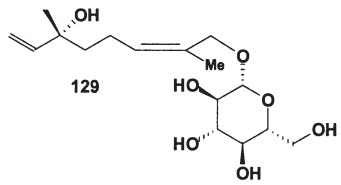

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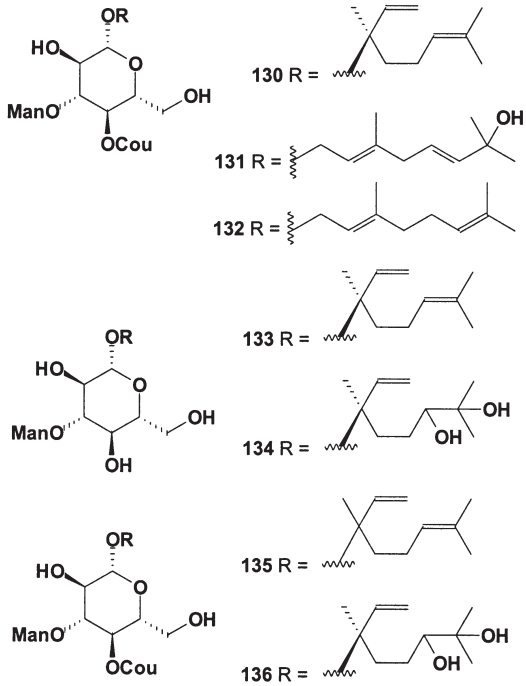
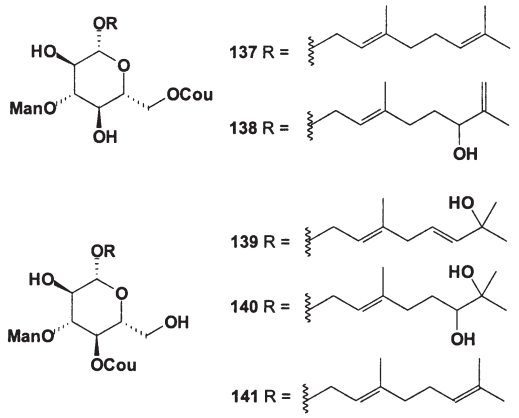
Lipedoside B III **130** (also known as lipedoside B IIIb) and two new monoterpene glycosides, kudingosides A **131** (also known as ligurobustoside C) and B **132** (also known as ligurobustoside I), were isolated from the bitter tea Ku-Ding-Cha (*Ligustrum pedunculare*) (108). Kudingosides A and B inhibited acyl-CoA:cholesterol acyltransferase, with IC_{50} values of 2.70×10^{-3} M and 2.88×10^{-3} M, respectively. Five monoterpene glycosides, lipedosides B-I **133**, B-II **135**, B-III **130**, B-VI **134**, and B-V **136**, were isolated together with three known constituents, anatolioside **123** (the diglycoside of linalool), linalool (not the glycoside), and osmanthuside B (the phenylethanoid glycoside), from *L. pedunculare* (109). The monoterpene glycosides **123**, **130**, and **133**–**136** were also present in the bitter tea (*L. pedunculare*) (110). The crude glycoside fraction was found to strongly protect human LDL from oxidation. The results obtained demonstrated that the bitter tea as a beverage contained effective antioxidants that may have benefits similar to those of green tea in terms of antioxidant activity. The monoterpenoid glycosides named ligurobustosides A **142**, B **141**, C **131**, E **137**, F **138**, I **139**, J **143**, and K **140**, as well as compound **132**, were isolated from the leaves of *Ligustrum robustum* (111).





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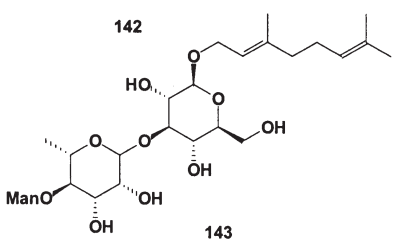
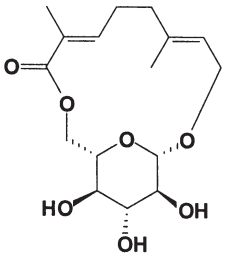


143

A new monoterpene glycoside, 2,6-dimethyl-2*E*,6*E*-octadienoic acid 1,6′-lactone 8-β-D-glucopyranoside **144**, was isolated from *Swertia punicea* (112). A dimeric monoterpenoid glycoside having a structure similar to mileenside **105**, named diclirip ariside A **145**, was isolated from an aqueous ethanolic extract of the whole plant *Dicliptera riparia* (113).

Acidic fractions obtained from the roots of *Paeonia peregrina* and *Paeonia tenuifolia* inhibited the growth of *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* (114). The roots of *P. peregrina* afforded two new acylated "cage-like" monoterpene glucosides, named paeonidaninols A **146** and B **147** (115). Paeoniae Radix (*Paeonia lactiflora*), a Chinese herbal extract, inhibited hepatoma cell growth by inducing apoptosis in a p53-independent pathway (116). A similarly active monoterpene glycoside, 6-*O*-β-D-glucopyranosyl-lactinolide **148**, was isolated from the Japanese Paeoniae Radix (*P. filciflora*); **148** was found to inhibit the release of histamine from rat peritoneal exudate cells induced by an antigen–antibody reaction (117).



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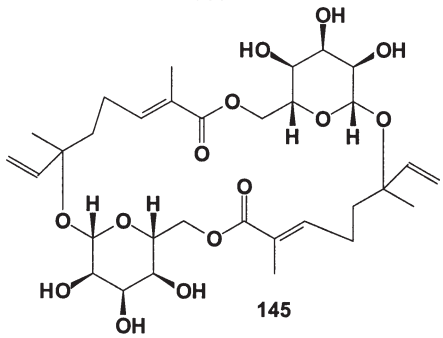

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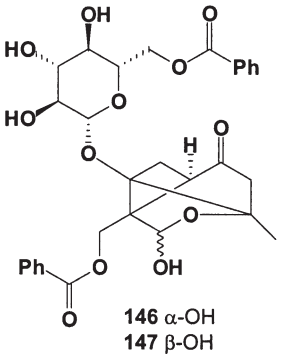
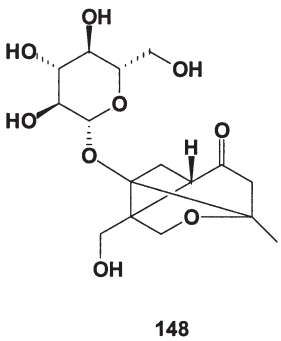


146 α-OH
147 β-OH



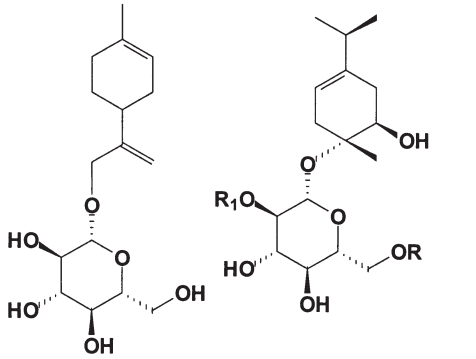
148

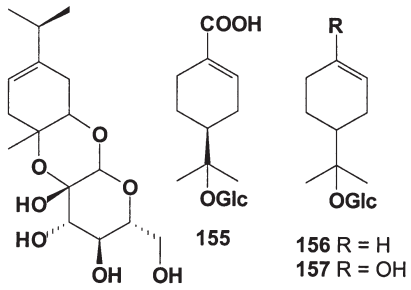
Monocyclic Monoterpenoid Glycosides

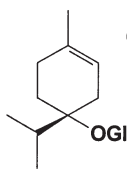
Dracocephalum kotschyi is a wild-growing flowering plant belonging to the family Labiatae found abundantly in southwestern Asia. *Dracocephalum kotschyi* has been used for several years as a medicinal herb in Iranian folk medicine for its antispasmodic and analgesic properties. Antihyperlipidemic and immunomodulatory effects have also been reported for *D. kotschyi* (118,119), and the essential oil from Iranian *D. kotschyi* has shown antivisceral pain effects in mice (120). From the whole plant of *D. kotschyi*, two new monoterpene glycosides were isolated, **149** and **150** (121). Their structures were detected as limonen-10-ol 10-*O*-β-D-glucopyranoside and limonen-10-ol 10-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, respectively. The isolated compounds **149** (3.1 μM) and **150** (3.1 μM) were effective against epimastigotes of *Trypanosoma cruzi*.

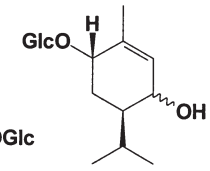
Thyme, the humble plant from the western Mediterranean (*Thymus vulgaris*, Labiatae), is among those plants having many different common names, such as broadleaf English, Greek gray, and narrow-leaved French. The leaves can be used fresh at any time, but for drying, it is best to cut the fresh growth after the bloom cycle. From a water-soluble extract of thyme (*T. vulgaris*) leaves, which has been used as an important stomachic, a carminative, a component in a prepared cough tea, and herb, the monoterpenoid glycosides **151**–**153** and thymuside A **154** were isolated (122). A new monoterpene glucoside, **155**, was isolated from the twigs and leaves of *Juniperus communis* var. *depressa* (Cupressaceae) collected in Oregon (United States) (123). This isolated compound demonstrated antibacterial activity against the spiral-shaped bacterium *Helicobacter pylori*. The bacterium *H. pylori* can lead to digestive illnesses, including gastritis (the irritation and inflammation of the lining of the stomach), peptic ulcer disease (characterized by sores that form in the stomach or the upper part of the small intestine, called the duodenum), and even stomach cancer later in life.

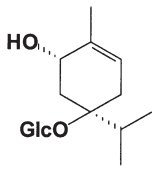
The monoterpenoid profiles of three white grape varieties (Alvarinho, Loureiro, and Avesso) and two red varieties (Amaral and Vinhao) from the Vinhos Verdes region of Portugal were studied for their presence in either free or glycosidically bound fractions (124). Seventeen compounds in the free form and 12 in the glycosidically bound form (**156**–**167**) were identified and quantified. The profiles of the terpene compounds varied to a significant degree for the grape varieties studied and, as was already known empirically, the white varieties were richer than the red varieties, especially for Loureiro.

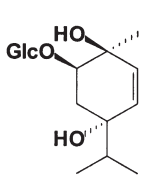


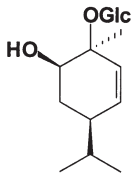


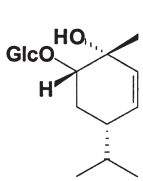






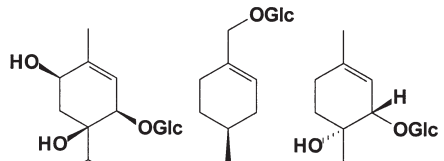


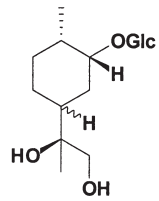


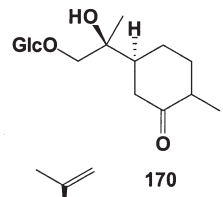


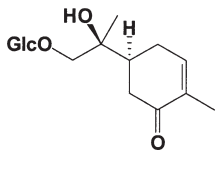
Dill (*Anethum graveolens*, Apiaceae, Umbelliferae) is a very important herb and is grown commercially in India, Pakistan, Egypt, Fiji, Mexico, The Netherlands, the United States, England, Hungary, and Germany. Dill has been used as a medicinal and culinary herb for thousands of years and was cultivated in ancient Egypt, Palestine, Greece, and Rome. An essential oil (0.8–1.6% fresh weight) can be produced from dill that contains carvone, limonene, anethofuran, phellandrene, and other terpenoids. The essential oil of Bulgarian dill seeds that were stored for a long time was analyzed and found to contain the aroma-impact compounds D-carvone (50.1%) and D-limonene (44.1%). The essential oil of *A. graveolens* showed high activity against the mold *Aspergillus niger* and the yeasts *Saccharomyces cerevisiae* and *Candida albicans* (125). From the water-soluble fraction of a methanolic extract of dill (the fruit of *A. graveolens*), 33 compounds were isolated, including six new monoterpenoid glycosides, **168**–**173** (126).

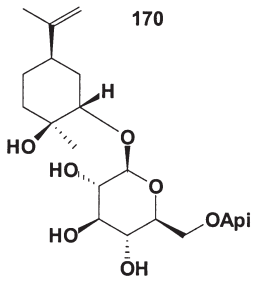
A new monoterpenoid glucoside isolated from Indian *Illicium griffithii* (Magnoliaceae) fruit has been characterized as *p*-menth-1(7),4(8)-diene-3-*O*-β-D-glucoside **174** (127). *Illicium griffithii* is exploited in the industry for its medicinal properties and as a spice (128), and both the seeds and oil of the fruit (star anise) possess the stimulant, diuretic, carminative, and slightly anodyne properties of anise. Monoterpenoid glucoside **175** was found in the water-soluble fraction of the caraway (the fruit of *Carum carvi*) (129). The hypoglycemic effect of aqueous extracts of the fruits of *C. carvi* in STZ rats was reported (130), as were the antioxidant activities of aqueous extracts of five umbelliferous fruits, i.e., caraway (*C. carvi*), coriander (*Coriandrum sativum*), cumin (*Cuminum cyminum*), dill (*A. graveolens*), and fennel (*Foeniculum vulgare*) (131). Monoterpenoid epoxy glucoside **176** was found in the fruit of *Carum ajowan* (ajowan) (90).

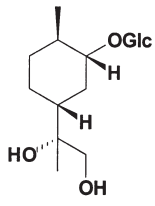


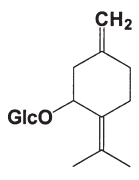


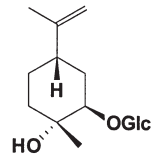


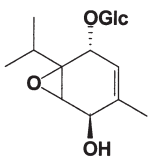










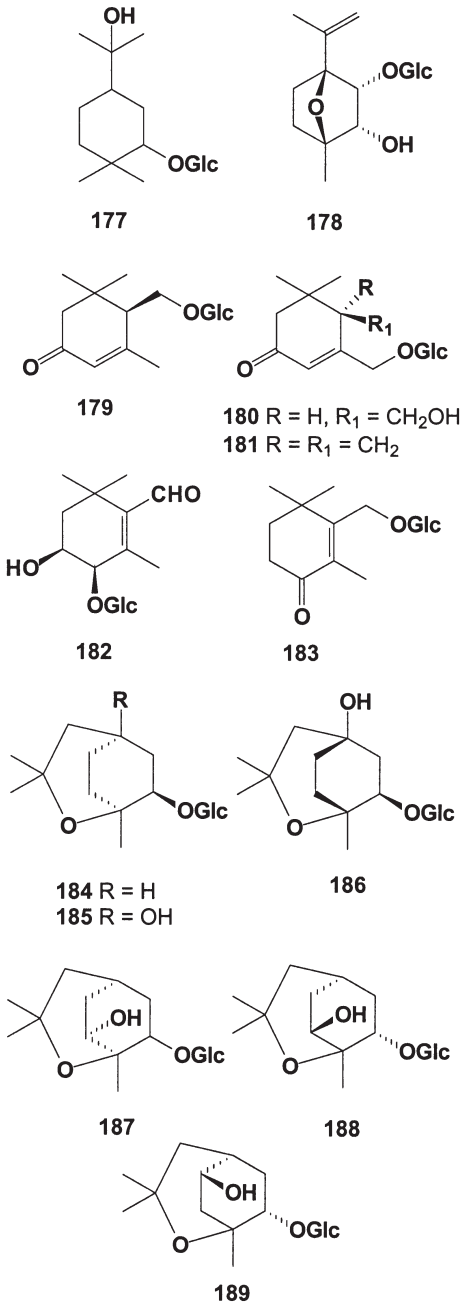


A novel cyclohexanoid monoterpene glucoside named melacoside A **177** was isolated from an aqueous ethanolic extract of the leaves of *Melaleuca quinquenervia* grown in Egypt (132). Melacoside A can possibly play a role in the biogenesis, transport, and accumulation of components of the essential oil of the plant. This compound had not been previously reported in nature. A new monoterpene glucoside called petroside **178** that was isolated from the aerial parts of *Petroselinum crispum* (parsley) showed potent estrogenic activity (133).

The Chinese herb *Gardeniae fructus* (called Huanglin-Jie-Du-Tang in Chinese) could play an important role in the treatment of acute pancreatitis, a common critical emergency illness with a high mortality rate. An extract of *G. fructus* (called Hwangryun-Hae-Dok-Tang in Korean) and its constituents also reduced ischemia-reperfusion brain injury and neutrophil infiltration in rats (134). New monoterpenoids named jasminosides A **179**, B **180**, C **181**, and D **183** and the known **182** have been isolated from *G. fructus* (135).

The genus *Salvia* belongs to the family Lamiaceae (Labiateae), and in Pakistan *Salvia* has been used as a traditional medicine for the cure of different diseases (136). A new monoterpene glycoside (2-exo-β-D-glucopyranosyl-1,8-cineol) named bucharioside **184** was isolated from the methanolic fraction of *Salvia bucharica* (137).

A series of new monoterpene glycosides, foeniculosides V **185**, VI **186**, VII **187**, VIII **188**, and IX **189**, were isolated from the fruit of *F. vulgare* (138).

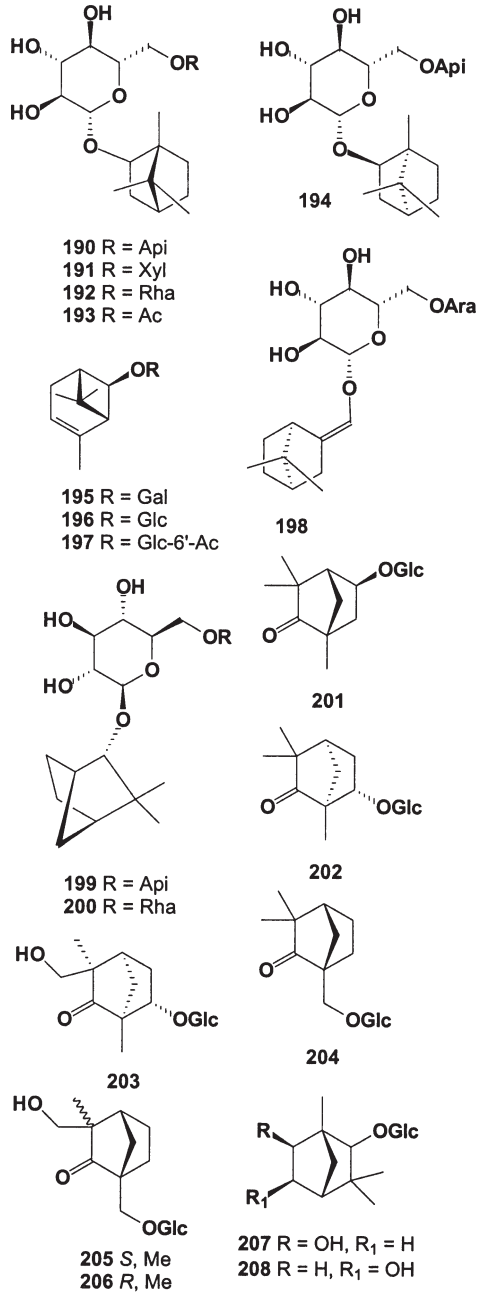


BICYCLIC MONOTERPENOID GLYCOSIDES

Borneol is a simple bicyclic monoterpene, and its structural analog camphor is used for analgesia and anesthesia in traditional Chinese and Japanese medicine. It is found in the essential oils of medicinal herbs such as valerian (*Valeriana officinalis*), chamomile (*Matricaria chamomilla*), and lavender (*Lavandula officinalis*) (139). Extracts of these plants are used traditionally to relieve anxiety, restlessness, and insomnia (140–143). Valerian extracts and essential oils demonstrate significant sedative activity in animal and human studies, providing sedation equivalent to conventional sedative and hypnotic agents while also increasing sleep depth (144,145). (+)-Borneol was found to have a highly efficacious positive modulating action at $GABA_A$ receptors, as did its enantiomer (−)-borneol (146). Borneol, which is derived from pine oil, is used as a disinfectant and deodorant, and camphor is used as a counterirritant, anesthetic, expectorant, and antipruritic, among many other uses.

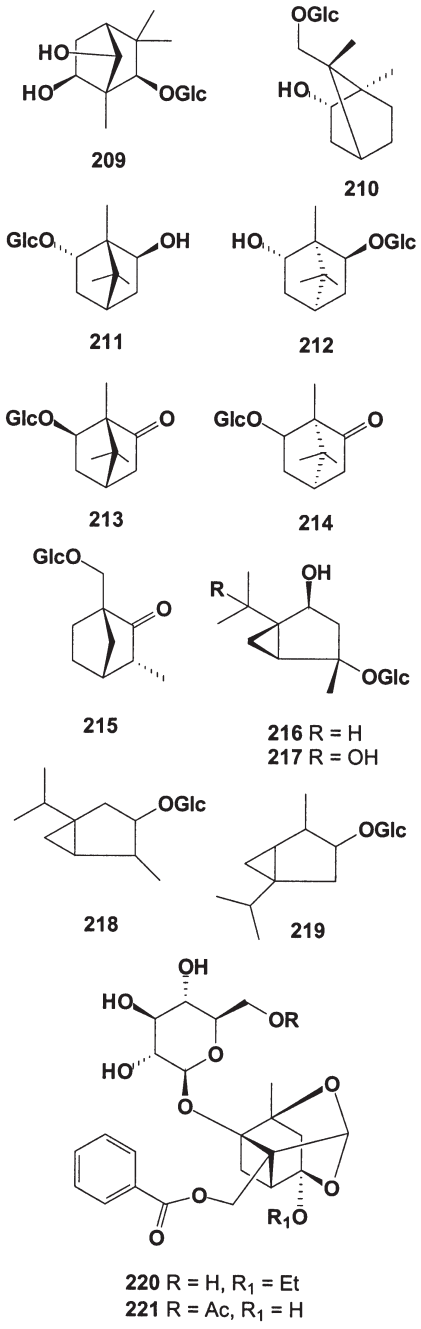
A series of disaccharides of borneol-β-D-glucosides were isolated from different plant sources: **190**, in which Api = apiose, was isolated from Radix Ophiopogonis (147), **191** was isolated from the flower buds of *Gardenia jasminoides* (148), and **192** was isolated from *Ophiopogon japonicus* (Liliaceae) roots (149). Furthermore, a monoacetylated borneol-β-D-glucoside, **193**, was present in the North American Compositae species *Psilostrophe villosa* (150). Glucosides **190** and **194** were found in an ethyl acetate extract of the Vietnamese medicinal plant *O. japonicus* (151,152).

Alcoholic and aqueous extracts of *Picris echoides* are usually used for the treatment of indigestion and against intestinal nematodes and other parasites. A new monoterpenoid glycoside named (−)-*cis*-chrysanthenol-β-D-galactopyranoside **195** was isolated from the aerial parts of *P. echoides* (Asteraceae, tribe Lactuceae) (153). An extract from the same plant contained the (−)-*cis*-chrysanthenol-β-D-glucopyranoside **196** and its 6′-acetate **197** (154). Glucoside **196** was also isolated from the aerial parts of *Artemisia sieberi* (155). A monoterpene glycoside, (*Z*)-(1*S*,5*R*)-β-pinen-10-yl β-vicianoside **198**, was isolated from the roots of *Paeonia lactiflora* (156). Two new monoterpene glycosides named shionosides A **199** and B **200** were obtained from the root of *Aster tataricus* (Compositae) (157). Nine fenchane-type monoterpenoid glycosides, **201**–**209**, were isolated from the water-soluble portion of the methanolic extract of fennel, the fruit of *Foeniculum. vulgare* (Umbelliferae) (158).

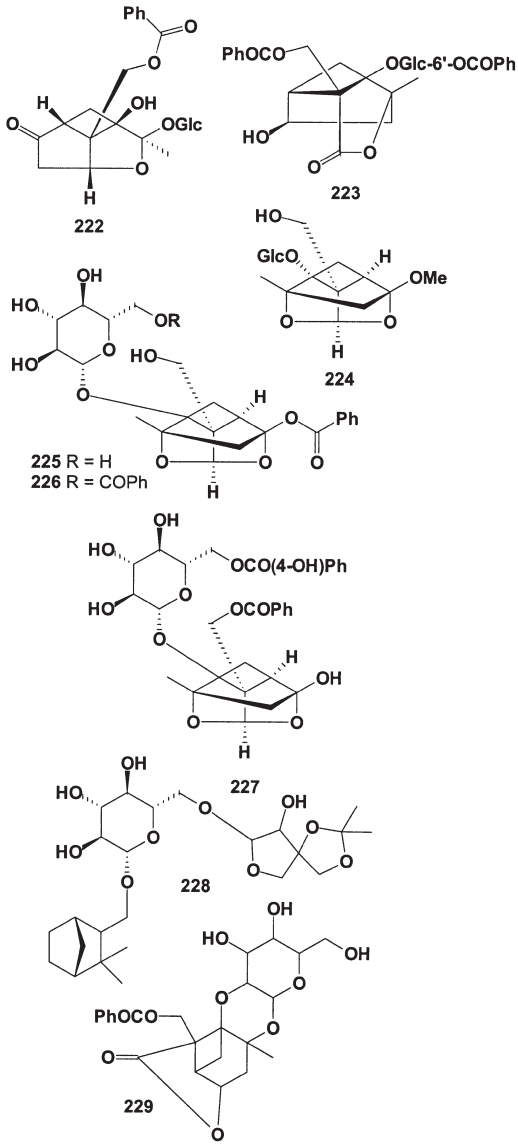


The monoterpenoid glucosides **207** and **210**–**214** were isolated from a methanolic extract of the amomum seed (seed of *Amomum xanthioides*), which has been used as a medicine for

stomachic and digestive disorders (159). Compounds **214** and **215**, and two new thujane-type monoterpenoids, **216** and **217**, were found in fennel extract (160). An extract from the petals of *Tanacetum vulgare* (Compositae, Asteraceae) contained 0.06% of monoterpene β-D-glucosides: isothujol **218** and neoisothujol **219** (161). *Tanacetum vulgare* (commonly known as tansy, golden buttons, or garden tansy) is a perennial herb in the sunflower family. This species, native to Europe, has a long history of medicinal use. It was first introduced to North America for use in folk remedies and as an ornamental plant. The unusual monoterpene glycoside 4-*O*-ethylpaeoniflorin **220** was isolated from the root cortex of *Paeonia delavayi* (162), and acetoxypaeoniflorin **221** was isolated from the root cortex of *Paeonia veitchii* (163).



A series of bicyclic monoterpenoid glycosides have been identified from these plants. A monoterpene glucoside named albiflorin R1 **222** was isolated from the roots of *Paeonia lactiflora* (164). In the structure of albiflorin R1, the aglycon was connected with a glucose at its 2-OH, while the hemiacetal hydroxy in the glucose moiety was free. A monoterpene glycoside named paeonivayin **223** was isolated with seven other known compounds from the roots of *P. delavayi* (165). Debenzoyl paeoniflorin methyl ether **224** was isolated from the roots of *Scrophularia buergeriana* and *Paeonia albiflora* by a soil bacterial hydrolysis method (166). The monoterpene glycosides wurdin **225** and benzoylwurdin **226**, along with the known compounds paeoniflorin, lactiflorin, and oxypaeoniflorin, were isolated from *Paeonia emodi* (167), and mudanpioside C **227** was found in the Japanese Paeoniae Radix (117). An interesting monoterpenoid glucoside named shionoside C **228** was obtained from *Aster tataricus* (168). The roots of *P. lactiflora*, used in traditional Chinese medicine, afforded a monoterpene glycoside named lactiflorin **229** (169).

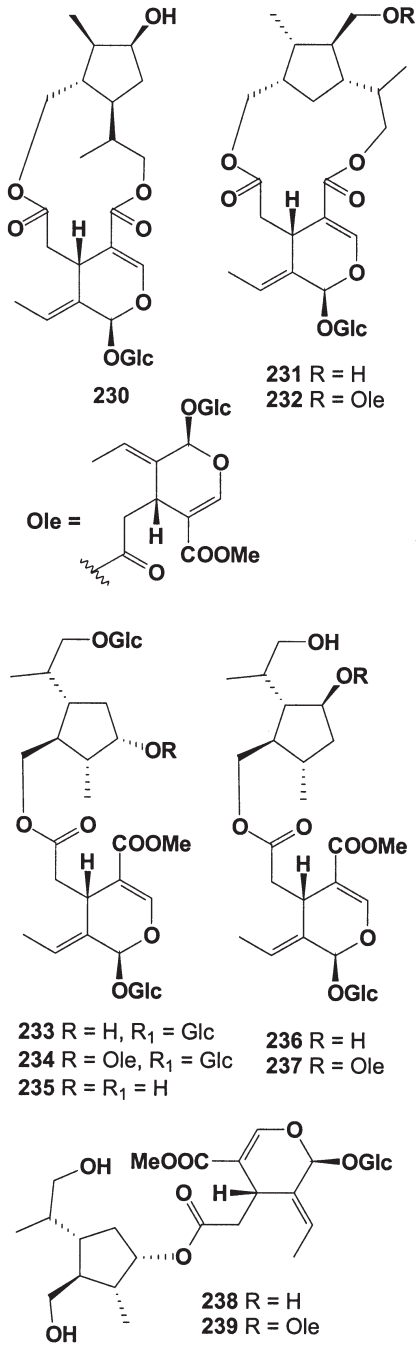


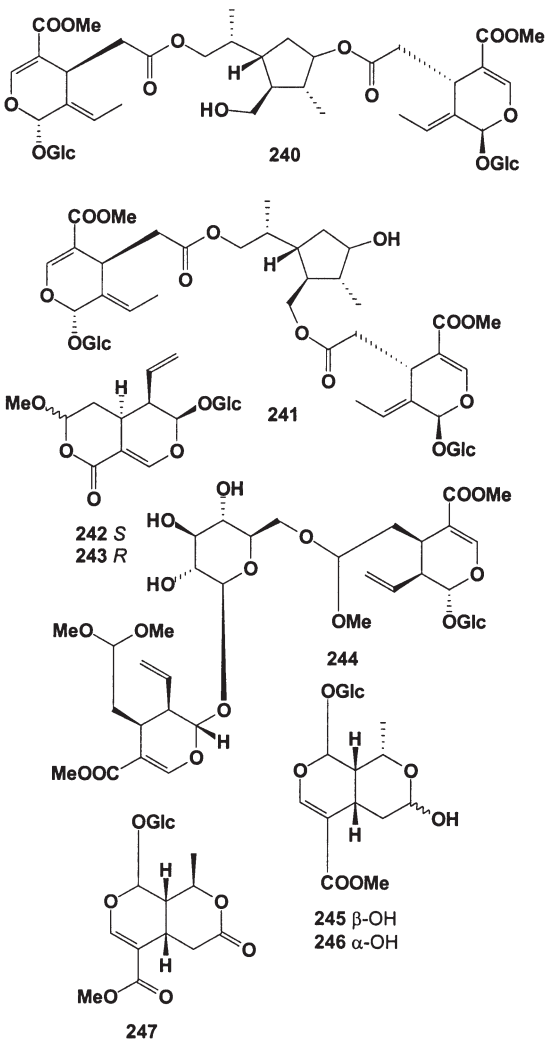
IRIDOID MONOTERPENOID GLYCOSIDES

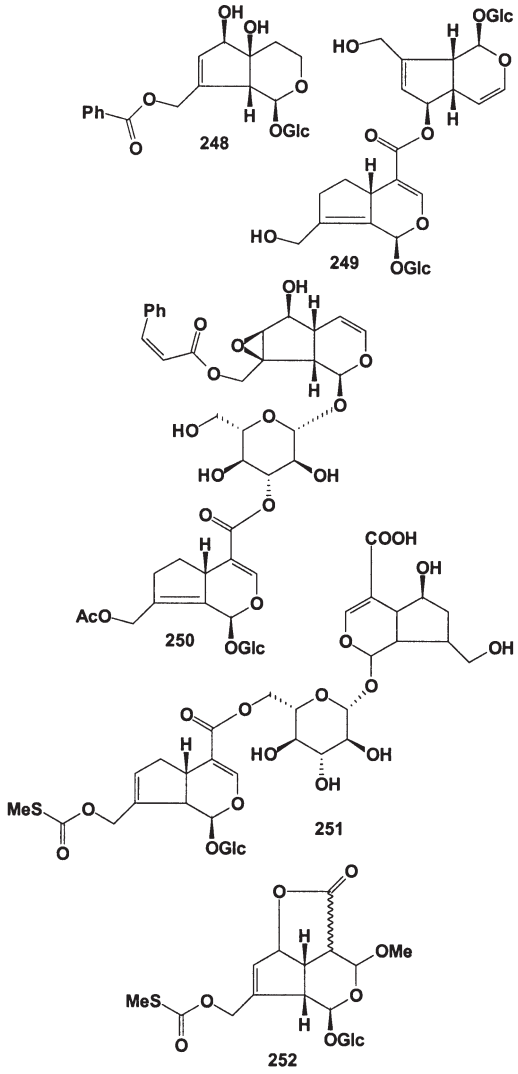
Cyclic metabolites having the iridane skeleton (1-isopropyl-2,3-dimethylcyclopentane) belonging to monoterpenoids have been isolated from plant species. Only a limited number of plant taxa possess the enzymes that give rise to the cyclopentane ring that is characteristic of the carbocyclic iridoids. In plants, iridoids are usually found as glucosides; thus, they are basically water soluble. Approximately 1400 different iridoids and secoiridoids (not counting the complex indole alkaloids) are known so far. Different aspects of biology, biochemistry, and chemistry of iridoids and their glycosides have been reviewed (169–177).

The leaves of *Jasminum nudiflorum* contain a number of secoiridoid glucosides: jasnudiflosides F-L F **235**, G **238**, H **239**, J **231**, I **230**, K **233**, L **234**; nudifloside D **236**; and others, **232**, **234**, and **237** (178). Jasnudiflosides D **240** and E **241** also were isolated from the same plant (179).

A new bis-iridoid glucoside, secologanin Me hemiacetal-yl-6-secologanin di-Me acetal, named chrysathain I **244**, was isolated from a methanolic extract of the leaves of the Chinese medicinal plant *Lonicera chrysantha* (Caprifoliaceae) along with the known iridoid glucosides 8-epi-kingiside **247**, 7α-morroniside **246**, 7β-morroniside **245**, vogeloside **242**, and 7-epi-vogeloside **243** (180). The isolated compounds showed moderate *in vitro* antitumor activity against human promyelocytic leukemia (HL-60) cells. Species of the genus *Lonicera* are a common homeopathic remedy used for asthma, breathing difficulties, and syphilis.







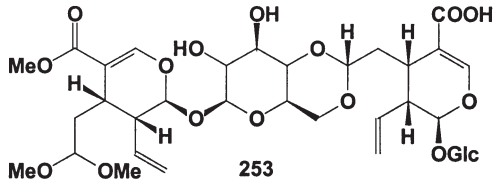
In the flora of Turkey, the genus *Globularia* (Globulariaceae) is represented by nine species, some of which are traditionally used as diuretics, laxatives, carminatives, and tonics and for the treatment of hemorrhoids (181). From a methanolic extract of the underground parts of *G. cordifolia* (Globulariaceae), a new iridoid glycoside, 5-hydroxydavisioside **248**, and a new bis-iridoid glycoside, globuloside C **249**, were isolated (182). Another species of the genus *Globularia*, *G. trichosantha*, contained a new bis-iridoid glycoside named globuloside A **250**, which was obtained from the aerial parts (183).

Two new sulfur-containing bis-iridoid glucosides, saprosmosides A **251** and B **252**, were isolated from the leaves of *Saprosma scortechinii* (Rubiaceae) (184). *Saprosma scortechinii*, a rubiaceous plant endemic to the Malay Peninsula, is also known as *sekentut*, a local name associated with the fetid odor emitted by bruised plant tissues. In the traditional medicinal system of Malaysia, the roots are used by the native communities in decoctions to treat fever, while the young leaves are eaten as a vegetable (185).

A new bis-iridoid glucoside, korolkoside **253**, was isolated from *Lonicera korolkovii* (Caprifoliaceae) (186). Korolkoside consists of two secologanin moieties connected by an acetal linkage. The secoiridoid glucoside named GI 5 **254**, a dimeric secoiridoid glycoside through a 4-hydroxyphenylethyl alcohol spacer, was isolated from a methanolic extract of the leaves of *Fraxinus excelsior* (Oleaceae). This is the first report of the occurrence of the dimeric secoiridoid glucoside GI 5 in *F. excelsior* (187). A new secoiridoid glycoside, 6′-*O*-β-apiofuranosylsweroside **255**, was identified from the leaves of *Lonicera angustifolia* (188). The novel secoiridoid glycoside 6′-*O*-β-apiofuranosylsweroside **256**, together with the known sweroside **257**, were isolated from the leaves of *L. angustifolia* (189). From Scottish plants, two secoiridoid glycosides, sweroside **257** and swertiamarin **258**, were isolated from the aerial parts of *Centaurium erythraea* (family, Gentianaceae) (190) and the antibacterial, free radical-scavenging activities, and general toxicity of these glycosides were assessed. Both compounds inhibited the growth

of *Bacillus cereus, B. subtilis, Citrobacter freundii*, and *Escherichia coli*. Swertiamarin was also active against *Proteus mirabilis* and *Serratia marcescens*, and sweroside inhibited the growth of *Staphylococcus epidermidis*. Swertiamarin and sweroside exhibited significant general toxicity in a brine shrimp lethality bioassay: The LD_{50} values (dose of a chemical that kills 50% of a sample population) were 8.0 and 34 μg/mL, respectively, whereas that of the positive control podophyllotoxin, a well-known cytotoxic lignan, was 2.79 μg/mL. The chemotaxonomic implications of these compounds in the family Gentianaceae have also been discussed briefly. Gentiopicroside **259**, a secoiridoid glycoside isolated from the aerial parts of *Centaurium erythraea*, was assessed for antibacterial and free radical-scavenging activities (191). The general toxicity of **259** was also detected by a brine shrimp lethality bioassay. Gentiopicroside **259** showed antibacterial activity against *B. cereus*, *B. subtilis*, *Centaurium umbellatum*, *C. freundii*, *Enterococcus faecalis*, *E. coli*, *Klebsiella pneumoniae*, *Lactobacillus plantarum*, *Micrococcus luteus*, *P. mirabilis*, and *Pseudomonas aeruginosa*, and radical-scavenging activity against *Salmonella goldcoast*, *S. marcescens*, *Staphylococcus aureus*, *S. epidermidis*, and *S. hominis*.

A methanolic extract of *Swertia chirata*, which was found to inhibit the catalytic activity of topoisomerase I of *Leishmania donovani*, was subjected to fractionation to yield three secoiridoid glycosides: amarogentin **260**, amaroswerin **261**, and sweroside **257**. Amarogentin **260** was a potent inhibitor of type I DNA topoisomerase from *Leishmania* and exerted its effect by interaction with the enzyme, preventing the formation of binary complexes (192).



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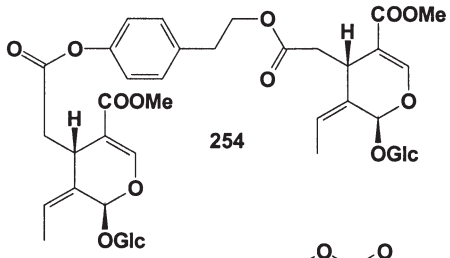

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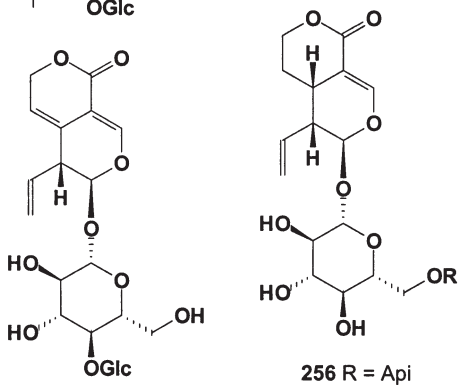
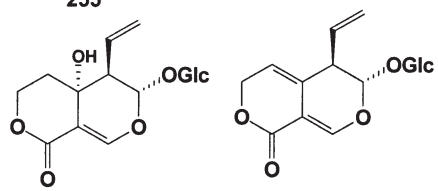


255

256 R = Api
257 R = H



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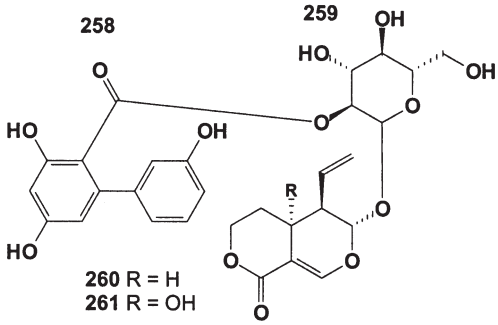
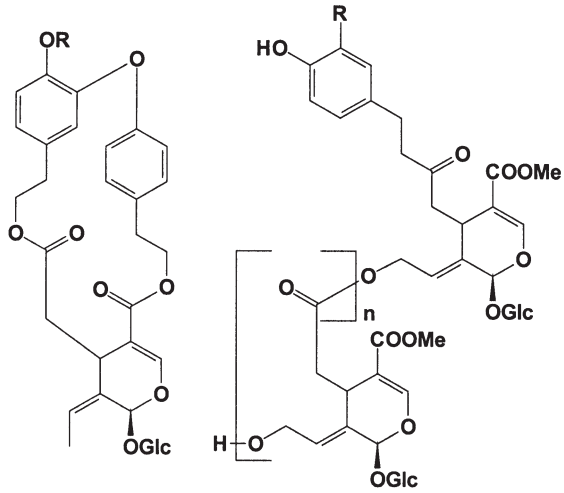
259



260 R = H
261 R = OH

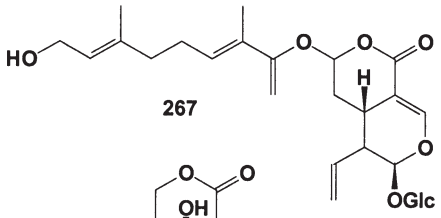
Fraxuhdoside **262** (193) and insularoside **263** (194) were obtained from extracts of *Fraxinus uhdei* and *F. insularis*, respectively. *Fraxinus uhdei* is native to western and southern Mexico, Guatemala, and Honduras and has been planted as an ornamental tree in other countries, including Costa Rica, Puerto Rico, and Hawaii. Its wood is used for baseball bats, paddles, and tool handles. Three new secoiridoid glucosides, jasamplexosides A **264**, B **265**, and C **266**, were isolated from the crude drug Niu Du Teng, the leaves and stems of *Jasminum amplexicaule* (195). In Pakistan, some species belonging to the genus *Jasminum* are usually used as a diuretic, emmenagogue, and

anthelmintic; for the skin, headaches, weak eyes, and scorpion stings; to cure ringworm; for ulcerations or eruptions in the mouth; and for the ears in otorrhea (196). The flowers are used to prepare perfumes. Several *Jasminum* species have been used in cancer treatment. Jasmine flower oil is important in high-grade perfumes and cosmetics, such as creams, oils, soaps, and shampoos. Jasmine is beneficial for the skin, reducing problems such as dry, greasy, irritated, or sensitive skin (it is good for dry, sensitive skin, especially when there is redness or itching). Its flowers are used in jasmine tea and other herbal black and green teas. The roots and leaves of some jasmine species have been used in folk medicine as an anthelmintic that is active against ringworm and tapeworm, and it is also used to treat muscle spasms, sprains, catarrh, coughs, hoarseness, laryngitis, uterine disorders, labor pains, frigidity, depression, and nervous exhaustion. The *Jasminum* spp. have traditionally been considered an aphrodisiac and a calmative. In the Orient the root is used to treat headaches, insomnia, and pain caused by dislocated joints and broken bones (197).

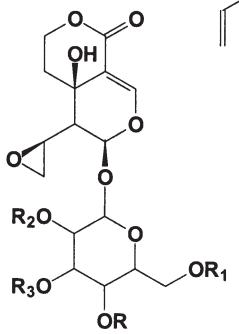


262 R = Glc
263 R = H

264 R = H, n = 1
265 R = H, n = 2
266 R = OH, n = 1



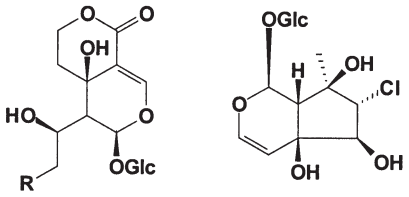
267



268 R = R_1 = R_2 = R_3 = H
269 R = Feruloyl, R_1,R_2,R_3 = H
270 R_1,R_2,R_3 = Ac, R = Fer

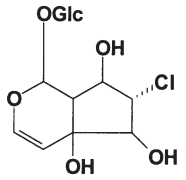
An acylated secoiridoid glucoside of the foliamenthin type, named exaltoside **267**, has been isolated from the aerial parts of the water plant *Villarsia exaltata* (Menyanthaceae) (198). Watt and Breyer-Brandwijk (199) recorded that when prepared as an ointment, the plant has been used in traditional medicine as a remedy for hemorrhoids. Eustomoside **268**, angustioside **269**, gentomoside **270**, eustomorusside **271**, and one chlorine-containing secoiridoid glucoside named eustoside **272** were isolated from species of the Gentianaceae (gentian) family (170). Eustomoside **268** and angustioside **269** were isolated from *Swertia angustifolia* (200), gentomoside **270** was isolated from the seeds of *Styrax perkinsiae* (201), and eustomorusside **271** and eustoside **272** were found in the lisianthus *Eustoma russellianum* (202). Linarioside, a chlorine-containing iridoid glucoside, **273**, was isolated from *Linaria japonica* (Scrophlariaceae) (203,204) and more recently was found in the snapdragon, *Antirrhinum majus* (205). The snapdragon (*A. majus*) has bitter and stimulant properties, and the leaves of this and several allied species have been used on the continental part of Europe in cataplasms for tumors and ulcers. The snapdragon is closely allied to the toadflaxes. Like the toadflax, it was valued in olden times as a preservative against witchcraft. The bitter leaves and flowers are used as antiphlogistics, resolvents, and stimulants. It is effective in the treatment of all kinds of inflammation and is also used on hemorrhoids (206).

Thunbergioside **274**, which has a structure similar to linarioside **273**, was isolated from four species of *Thunbergia* (207), from *Retzia capensis* (208), and from *T. alata* (209) and is also present in plants of the Thunbergioideae, Mendoncioideae, and Nelsonioideae subfamilies (all belonging to Acanthaceae) (210).



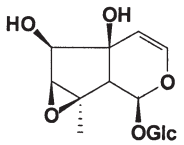
271 R = OH
272 R = Cl

273

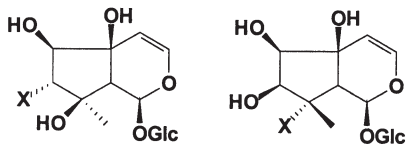


274

Treatment of the iridoid glucoside antirrhinoside **275** with pyridinium chloride in dimethylformamide yielded two possible *trans*-halohydrins, linarioside **273** and isolinarioside **277**. Pyridinium bromide yielded two analogous bromohydrins, **276** and **278** (211). The iridoid glucosides 8-*epi*-muralioside from *Linaria arcusangeli* and 7,8-*epi*-antirrhinoside from *Linaria dalmatica* were both shown to be identical to isolinarioside **277**.



275



273 X = Cl
276 X = Br

277 X = Cl
278 X = Br

SUMMARY

Medicinal plants are widely used nowadays for the preparation of various pharmaceutical formulations or as food additives. Plants produce secondary metabolites, which, among other functions, protect them against microbial and herbivorous attack or UV irradiation. Secondary metabolites also have direct uses for human beings. Hemi- and monoterpenoids, for example, have health-promoting activities as food ingredients, and many iridoid glycosides have pharmacological activities. The chemical features of medicinal plants serve as an integral determinant of their species specificity and pharmacological properties, and enable their wide use in medical practice. The use of and search for drugs and dietary supplements derived from plants have accelerated in recent years. Pharmacologists and natural-products chemists are combing the earth for phytochemicals and "leads" that could be developed for the treatment of infectious diseases. Traditional healers have long used plants to prevent or cure infectious conditions, and Western medicine is trying to duplicate their successes. Plants are rich in a wide variety of secondary metabolites; hemiterpenoids; acyclic, monocyclic, and bicyclic monoterpenoids; and iridoid glycosides, which have been found to have antimicrobial, anticancer, and other properties.

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