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**Fortschritte der Chemie
organischer Naturstoffe**

**Progress in the
Chemistry of Organic
Natural Products**

**Founded by
L. Zechmeister**

**Edited by
W. Herz, G. W. Kirby,
R. E. Moore, W. Steglich,
and Ch. Tamm**

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Phenolic Constituents of Licorice (*Glycyrrhiza* Species)

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1. Introduction

The Leguminosae is an economically important family in the Dicotyledonae with many cultivated species, *e.g.*, beans and peas. The family also contains many well-known medicinal plants. It is composed of 17,000 or more species that constitute nearly one twelfth of the world's flowering plants (1). Traditionally the family has been divided into three subfamilies, Caesalpinioideae, Mimosoideae and Papilionoideae, which are sometimes recognized as separate families Caesalpinaceae, Mimosaceae and Papilionaceae. The International Code of Botanical Nomenclature permits alternative nomenclatures, the family names being replaced by Fabaceae, Fabales and Faboideae, and this usage will be common (2).

Licorice (liquorice, kanzoh in Japanese, gancao in Chinese) is the name applied to the roots and stolons of some *Glycyrrhiza* species (Fabaceae) and has been used by human beings for at least 4000 years. The earliest written reference to the use of licorice is contained in the Codex Hammurabi dating from 2100 B.C., and the subsequent history in the West has been described in the earlier reviews (3–6). In the Far East, references to the effectiveness of licorice are contained in the “Shen Nong Ben Cao Jing”, the first Chinese dispensatory whose original anonymous volumes probably appeared by the end of the third century (7, 8). In the Chinese book, 365 crude drugs are classified into three classes (upper: plants with lowest side-effects and nontoxic useful for health care; middle: plants that are nontoxic or possess only weak toxicity in whose use care must be exercised; lower: toxic and only for clinical use). Licorice is described as belonging to the upper class and is recommended for its life-enhancing properties, for improving health, for cures for injury or swelling and for its detoxification effect (9). One hundred ten prescriptions are recorded in the earlier Chinese medicinal book “Shang Han Lun” as of C.E. 1065 (Its original version “Shang Han Zu Bing Lun” probably appeared between the third and fifth century), where seventy prescriptions include licorice (8, 10).

Following extraction, the herb yields the licorice products of commerce which are used as flavoring for American type tobaccos, chewing gums, candies, *etc.* (11–13), sweetening agents (11, 14–16), and as a depigmentation agent in cosmetic (17–19) and pharmaceutical products, *e.g.*, anti-ulcer drugs (Aspalon[®], Caved-S[®], *etc.*) (20, 21). Clinical studies of licorice make it one of the most thoroughly studied herbs (6); these include its toxicity (22), antitumagenic activity (23), anti-ulcer effect (24), protective action for hepatotoxicity (25), antitumor promoting activity (26), anti-caries effect (27), antimicrobial effect (28),

etc. The crude drug is also the raw material for the drug glycyrrhizic acid (1) and its derivative carbenoxolone (5). But the most important industrial use of the herb is in the production of additives as flavor and sweetening agents (13, 29).

The genus *Glycyrrhiza* consists of about 30 species (30) and chemical researches have so far been carried out on 13 of them (31). *G. glabra* L. is distributed in Africa, Asia, Australia, Europe, the Middle East and North America. The species includes some varieties frequently called Spanish or Italian licorice (*G. glabra* L. var. *typica* Reg. et Herd.), Persian or Turkish licorice (var. *violacea* Boiss.), Russian licorice (var. *glandulifera* Reg. et Herd. or var. *glandulifera* Waldst. et Kit.) and European licorice (in China). *G. uralensis* Fischer grows in Asia and Russia (Far East) and is termed Ural, Mongolian or Chinese licorice, and *G. korshinskyi* Grigorj. is widely distributed in the former Soviet Union. *G. lepidota* Pursh is found in Central and North America and called wild licorice. *G. echinata* L. (sometimes called *G. macedonica* Boiss. et Orph.) occurs in Asia, Europe, the Middle East, Iran and European Russia. *G. aspera* Pallas. is a small plant, relatively unimportant in commerce, and is found in Asia, the Middle East, Europe and in Russian Asia (31). *G. triphylla* Fischer et Mey. grows in Afghanistan, Iran, Pakistan and Russian Asia, but differs from the other *Glycyrrhiza* species in morphology as well as chemistry. The species is now regarded as separate from *Glycyrrhiza* and may be transferred to the genus *Meristotropis* (30, 32).

Many *Glycyrrhiza* species are found in China, but in the Northeast only *G. uralensis* and *G. pallidiflora* Maxim. (prickly fruit licorice, pseudo-licorice; inu kanzoh in Japanese) grow. On the other hand, in northwestern China *G. inflata* Batalin, *G. aspera*, *G. glabra*, *G. uralensis* and yellow licorice (*G. eurycarpa* P.C. Li = *G. uralensis* × *G. inflata*, a newly named species previously conflated with *G. korshinskyi*) are distributed (33–35). The pure species are rarely found in the region because of facile hybridization. *G. yunnanensis* P.C. Li (Malay licorice) is found in southwestern China and *G. squamulosa* Franch. grows in the central region (33, 36). Annually some 3,000–6,000 tons of licorice are imported into Japan (37) where one fifth is used clinically in traditional Sino-medicine (Kanpo-yaku in Japanese). Chinese licorice (*G. uralensis*) is used for this purpose owing to its pure sweetness without bitter taste. However the supply from China is decreasing.

As for the components of *Glycyrrhiza* species, the essential oil (11, 38–40), and the occurrence of alkaloids (41–45), polysaccharides (46–62), a polyamine (63), triterpenes (64–67), fatty acids (68) and amino acids (69) as well as triterpenoid saponins and flavonoids have

Table 1. *Review Articles of Licorice published between 1967–1995*

Author	Item	Reference numbers	(Period) ^a	Ref.
RUSSO	Sapogenin	23	(1937–1967)	(70)
OTSUKA	History, Chinese medicine	16	(–1969)	(9)
KUMAGAI	Pharmacology	31	(1946–1971)	(71)
WATANABE	Pharmacology	33	(1944–1971)	(72)
OURA <i>et al.</i>	Pharmacology	39	(1955–1972)	(73)
SHIBATA and SAITOH	Phenol, pharmacology	78	(1934–1972)	(74)
YAMAMOTO	Pharmacology, therapeutics	9	(1959–1972)	(75)
YANO	Pharmacology	41	(1950–1972)	(76)
BALTASSAT-MILLET <i>et al.</i>	Pharmacology	98	(1948–1975)	(77)
SHIBATA and SAITOH	Pharmacology, phenols	39	(1934–1978)	(78)
GIBSON	History, pharmacology	45	(1948–1979)	(4)
LIU	History, Xinjiang licorice	26	(1597–1979)	(79)
MAEDA	Sweetening	9	(1851–1979)	(11)
NISIMOTO and YASUDA	Production	10	(1970–1980)	(80)
SHIBATA	Sapogenin, phenol	26	(1935–1980)	(81)
LUTOMSKI	Saponin, therapeutics	101	—	(82)
JIANG <i>et al.</i>	Sweetening	18	(1967–1981)	(16)
SHIBATA	Phenol, sapogenin, pharmacology	15	(1959–1985)	(83)
CAI <i>et al.</i>	Saponin, sapogenin	71	(1935–1987)	(84)
LIU and LIU	Phenol	39	(1972–1988)	(85)
AYABE	Callus culture	52	(1975–1989)	(86)
BIELENBERG	Saponin, pharmacology	42	—	(87)
KIKUTI	Sweetening	14	(1979–1989)	(88)
FENWICK <i>et al.</i>	History, phenol, sapogenin, sweetening	120	(1943–1990)	(5)
LUTOMSKI <i>et al.</i>	Pharmacology	88	(1948–1990)	(6)
KITAGAWA	Saponin, phenol	6 ^b	(1974–1991)	(89)
YONEDA	Production	7	(1974–1991)	(29)
HIAI and NAGASAWA	Pharmacology	60	(1962–1992)	(90)
KITAGAWA and HORI	Saponin, phenol	29	(1975–1992)	(91)
BAKER	Pharmacology	46	(1948–1992)	(92)
YIN and GUO	Whole items (hand book)	308	(1946–1992)	(93)
HU and SHEN	Therapeutics	36	(1958–1993)	(94)
JIA and QIU	Phenol (aerial parts)	20	(1966–1993)	(95)
SAITO	Molecular genetics	3 ^b	(1990–1994)	(96)
FENG	Studies in China, phenol	9	(1981–1994)	(97)
ILDIS and CHCD	Structure (data base)	95	(1949–1994)	(31)

^a The period means published years of collective citation references in the review articles.

^b Numbers of references with respect to licorice. The article encloses the other topics.

been reported (31). The earlier reviews of licorice are listed in Table 1. The present article briefly reviews the chemistry and biological activity

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of saponins obtained from *Glycyrrhiza* species and is devoted mainly to the phenolic constituents with isoprenoid substituent(s) such as the 3-methyl-2-butenyl (prenyl) group. New methods used for structure determination of prenylated phenols (flavonoids) found during in our chemical study of the phenolic compounds are also described.

2. Triterpenoid Saponins

2.1. Glycyrrhizic Acid

Glycyrrhizic acid is the major triterpenoid saponin in licorice root and is used frequently as a tool for recognizing the herb. This saponin has also been called glycyrrhizin, glycyrrhizinic acid or glycyrrhetic acid glycoside and has been obtained from *G. glabra*, *G. uralensis*, *G. inflata*, *G. aspera*, *G. korshinskyi* and *G. eurycarpa* (36, 98–100). The presence of glycyrrhizic acid has been known for one hundred years (3) and many investigators have studied the structures of the aglycone (1) and the saponin for its biological activity (101–125). These studies established its chemistry as that of an oleanane type triterpene. The structure of glycyrrhizic acid had been assigned as 3-*O*-[β -D-glucuronopyranosyl-(1 \rightarrow 2)- α -D-glucuronopyranosyl]glycyrrhetic acid. In 1989, structure elucidation of the saponin was finished using modern NMR techniques and the structure was established as **2** (3-*O*-[β -D-glucuronopyranosyl-(1 \rightarrow 2)- β -D-glucuronopyranosyl]-glycyrrhetic acid) by KHALILOV *et al.* and the revised structure (**2**) was also confirmed by SHIBATA (126). This structure (**2**) had also been assigned to uralsaponin A obtained from *G. uralensis* and *G. eurycarpa* (127, 128). Thus the structure elucidation of uralsaponin A needs further experiments.*

Glycyrrhizic acid (**2**) and its potassium and ammonium salts have an intensely sweet taste. This taste is completely removed by hydrolysis of the saponin to its aglycone, glycyrrhetic acid (**1**).[†] The distribution of saponins in different organs of *G. glabra* has been reported by TABATA *et al.* (66); glycyrrhizic acid is found in the thickening root and the stolon, but not in the seed, leaf and stem. On the other hand, soyasaponins are detected in the seed, hypocotyl and rootlet.

* The saponin could not be detected in a recent HPLC study of *Glycyrrhiza* species collected in China (36, 225).

[†] The sapogenin is also called glycyrrhetic acid, glycyrrhetin or enoxolone (International Nonproperty Name (INN) with WHO).

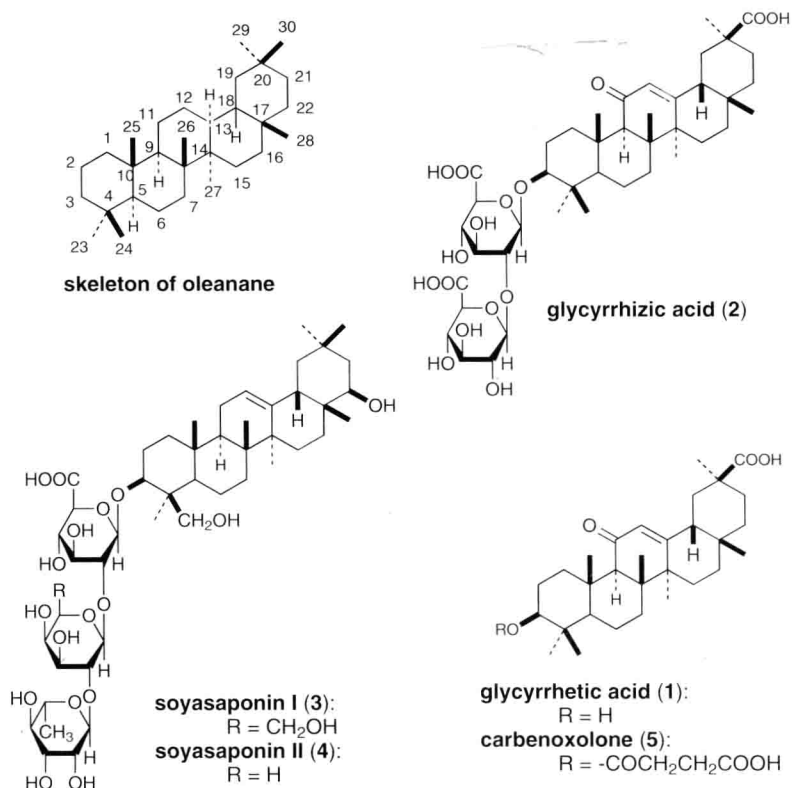


Fig. 1

Many investigators have studied the plant tissue culture of *Glycyrrhiza*, but the production of glycyrrhizic acid in this manner is only reported in the patent literature (129–137). The production of soyasaponins I (3) and II (4) in cell suspension cultures of *G. glabra* has been reported by TABATA *et al.*, and the contents are greatly influenced by plant growth hormones (138). The production of saponins by hairy root cultures transformed by Ri plasmids of *Agrobacterium* has been reported by SANKAWA *et al.* (139). One of the liquid culture lines of the hairy roots of *G. uralensis* produced glycyrrhizic acid in a yield of 4.7%.

Glycyrrhizic acid and structurally related saponins possess a sweet taste and flavor-potentiating characteristics and have been employed

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industrially for this reason (15, 140). The sweet taste of glycyrrhizic acid (170 times as sweet as sucrose) is not felt immediately. Thus the reagent is usually used along with other sweetening agents such as sucrose, glucose, stevioside, *etc.* The saponin is also used to mask the salty aftertaste of soy sauce and salty foods (141). Some glycyrrhetic acid glycosides have been synthesized by MIZUTANI *et al.*, who examined their sweetness (15, 142, 143). Among them, glycyrrhetic acid monoglucuronide is sweeter than glycyrrhizic acid (about 5.5 times) and its flavor-potentiating action is more effective for a milky, chocolate and coffee flavor.

Glycyrrhizic acid (ammonium or potassium salt) and its derivative carbenoxolone (INN, 3-carboxy-1-oxopreoxylglycyrrhetic acid, **5**) are used in the treatment of peptic ulcers and other gastro-intestinal disorders and as an antiinflammatory agent (21, 144, 145). These agents are metabolized by the same metabolic pathway, but differ in the time course (90). In treatment of chronic hepatitis and as a precaution against transfusion hepatitis, glycyrrhizic acid is also used by injection in large amounts (146, 147). Japanese researchers have reported the inhibitory effect of glycyrrhizic acid on the infectivity and cytopathic activity of human immunodeficiency virus (HIV) (148). Clinical studies of the saponin conducted in Japan have shown promising results for HIV carriers (149–157). Intravenous injection of high doses of glycyrrhizic acid brings about improvement in liver function that is damaged in many HIV positive hemophiliacs. This therapy also prevents the side effects of azidothymidine (AZT). The researchers expect that the treatment protects asymptomatic HIV carriers from AIDS (150, 151, 156).

2.2. Structures of Minor Sapogenins

About fifty other sapogenins have been isolated from *Glycyrrhiza* species. Their structures are shown in Figs. 2–6.

2.2.1. *Glycyrrhiza glabra*

ELGAMAL *et al.* have isolated a minor sapogenin, liquoric acid (**6**), from *G. glabra*, and proposed a structure having an intramolecular ether linkage (158). Thirteen minor sapogenins, glabrolide (**7**), 11-deoxoglabrolide (**8**), liquiritic acid (**9**), isoglabrolide (**10**), 11-deoxoglycyrrhetic acid (**11**), 3 β -hydroxy-11,13(18)-oleanadien-30-oic acid (glypallidifloric

acid, **12**), glycyrrhetol (glycyrrhetol)* (**13**), 21 α -hydroxyisoglabrolide (**14**), 24-hydroxyglycyrrhetic acid (**15**), 24-hydroxy-11-deoxoglycyrrhetic acid (**16**), 18 α -hydroxyglycyrrhetic acid (**17**), liquiridilic acid (glyunnansapogenin B₁, **18**) and 24-hydroxyliquiritic acid (**19**), have been isolated from this species by CANONICA and RUSSO *et al.* (159–166). Glabric acid has been isolated by BEATON and SPRING (167), and the structure (**20**) was elucidated by mass spectroscopic methods by ELGAMAL and FAYEZ (168). The isolation of 3,24-dihydroxy-11, 13(18)-oleanadien-30-oic acid (**21**) as a methyl ester has been reported by BOGATKINA *et al.* (169).[†] Uralenic acid has been isolated from *G. uralensis* and *G. glabra* by KIR'YALOV *et al.* (170, 171), and the compound was identified as 18 α -glycyrrhetic acid (**22**) by BELOUS *et al.* (172). The compound had been derived by isomerization of 18 β -glycyrrhetic acid (**1**) under basic conditions (124). ELGAMAL and EL-TAWIL have isolated 28-hydroxyglycyrrhetic acid (**23**) from the same species (173).

The lactones **7**, **8**, **10** and **14** might be artifacts formed during the isolation procedures and the parent compounds of **10** and **14** have not yet been isolated. The parent compounds of **7** and **8** have been isolated as described in the following subsections.

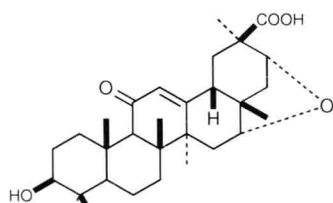
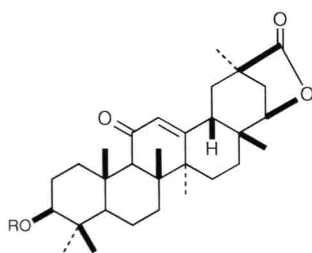
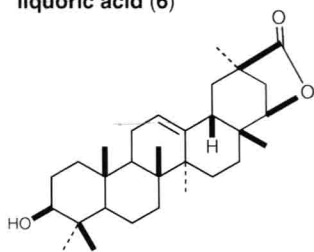
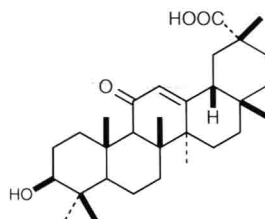
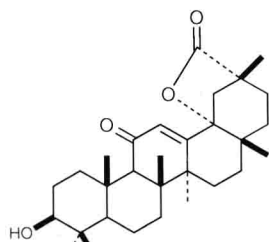
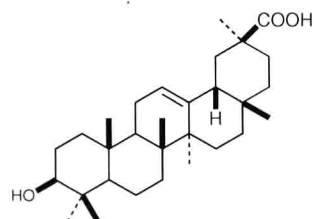
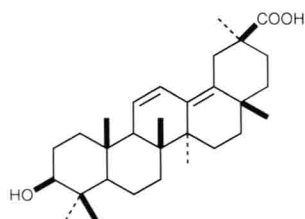
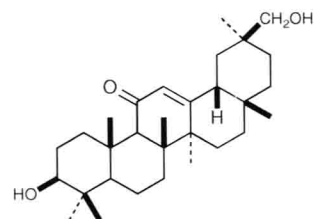
2.2.2. *Glycyrrhiza uralensis*

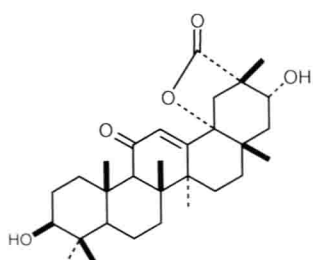
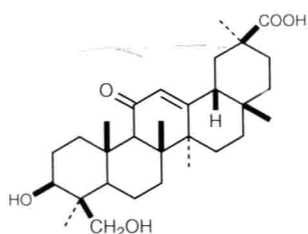
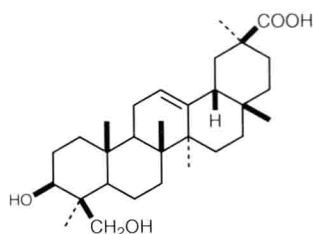
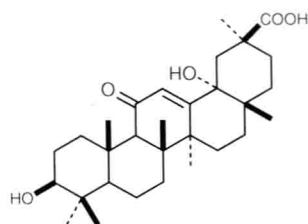
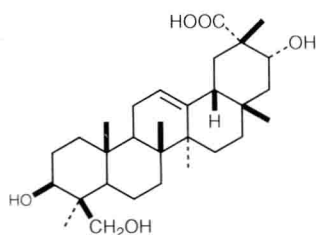
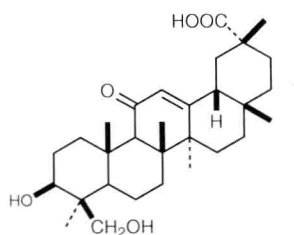
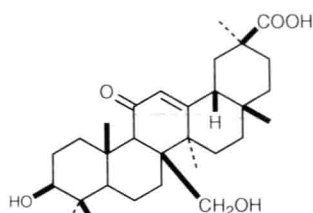
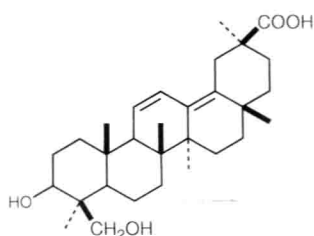
ZHANG and her co-workers have reported the isolation of 24-hydroxyglabrolide (**24**), uralenolide (**25**) and glyuranolide (isolated as a methyl ester) (**26**) from *G. uralensis* (174–177). A formyl ester (**27**, Fig. 2) of glabrolide (**7**) and 22 β -acetoxyglycyrrhetic acid (**28**),[#] the latter considered as the parent compound of glabrolide (**7**), have been isolated by SHEN *et al.* (178). The sapogenins **7**, **12–15**, **17** and **22** have been also isolated from this species (174, 175, 179).

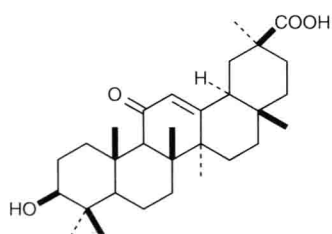
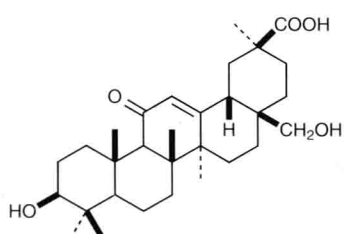
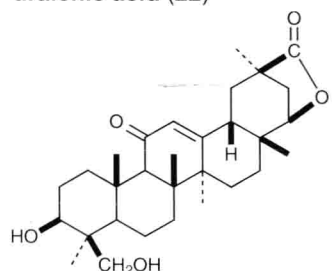
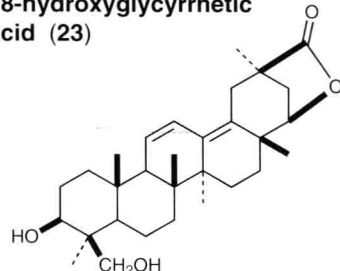
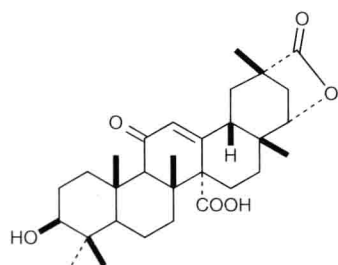
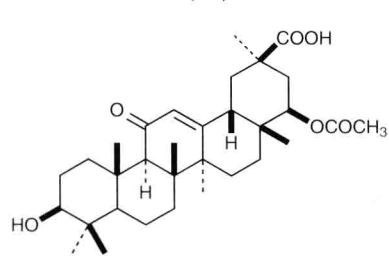
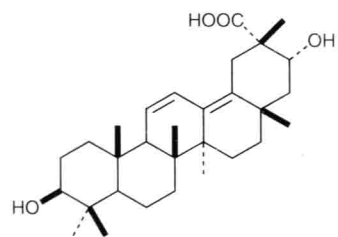
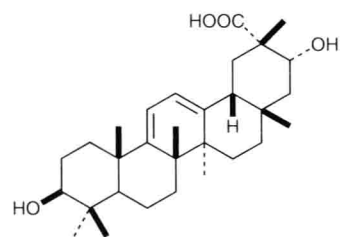
* The trivial name "glycyrrhetol" was used in the English abstract of the original paper, and "glycyrrhetol" has been used in Chemical Abstracts (163).

[†] A glycoside of 3 β ,24-dihydroxy-11,13(18)-oleanadien-30-oic acid (licorice-sapogenin K2, **67**) has been isolated from *G. uralensis* (205).

[#] The trivial name "22 β -acetoxyglabric acid" was used for the compound (22 β -acetoxy-3 β -hydroxy-11-oxo-12-oleanan-30-oic acid) in the English abstract of the article (178).

**liquoric acid (6)****glabrolide (7) : R = H**
(27) : R = -COOH**11-deoxoglabrolide (8)****liquiritic acid (9)****isoglabrolide (10)****11-deoxoglycyrrhetic acid (11)****3β-hydroxy-11,13(18)-
oleanadien-30-oic acid (12)**
(glypallidifloric acid)**glycyrrretol (13)**
(glycyrrhetol)**Fig. 2**

**21 α -hydroxyisoglabrolide (14)****24-hydroxyglycyrrhetic acid (15)****24-hydroxy-11-deoxyglycyrrhetic acid (16)****18 α -hydroxyglycyrrhetic acid (17)****liquiridolic acid (18)
(glyyunnansapogenin B₁)****24-hydroxyliquiritic acid (19)****glabric acid (20)****3,24-dihydroxy-11,13(18)-
oleanadien-30-oic acid (21)****Fig. 3**

**uralenic acid (22)****28-hydroxyglycyrrhetic acid (23)****24-hydroxyglylabrolide (24)****uralenolide (25)****glyuranolide (26)****22β-acetoxglycyrrhetic acid (28)****macedonic acid (29)****isomacedonic acid (30)****Fig. 4**

2.2.3. *Glycyrrhiza echinata* (*G. macedonica*)

This species does not produce glycyrrhizic acid (180). The isolation of two triterpene acids named macedonic acid and isomacedonic acid whose structures were assigned as 3,19-dihydroxy-11,13(18)-oleanadien-28-oic acid and 3,19-dihydroxy-9(11),12-oleanadien-28-oic acid, respectively, was reported by KIR'YALOV *et al.* (181–184). However, these structures have been revised to **29** and **30**, respectively, using chemical and spectroscopic methods, by ZORINA *et al.* (185, 186). Similarly structures of two other acids, echinatic acid and isoechinatic acid, also isolated by KIR'YALOV *et al.* and assigned as 3,15,22-trihydroxy-9(11), 12-oleanadien-28-oic acid and 3,15,22 (or 3,16,21)-trihydroxy-11,13 (18)-oleanadien-28-oic acid, respectively, (182, 187–189) were subsequently revised to **31** and **32** (glyyunnansapogenin E), respectively (190). More recently the isolation of 3 β ,21 α -dihydroxy-11,13(18)-oleanadien-28-oic acid (**33**) from the same species has been reported by MIRHOM *et al.* (191).

2.2.4. *Glycyrrhiza yunnanensis*

Glycyrrhetic acid has not been detected in this species (36), but six sapogenins, glyyunnansapogenins A–C (**34**–**36**) and F–H (**37**–**39**), were isolated by ZENG *et al.* (192–195). The isolation of glyyunnansapogenin B₂ (**40**) and 24-hydroxyglabrolide (**24**) has been reported by HU *et al.* (67). The known sapogenins oleanolic acid (**41**), **18** (glyyunnansapogenin B₁), **29**, **32** (glyyunnansapogenin E) and yunganogenin C (**42**) have also been isolated from this species (67, 193).

2.2.5. Other Species

Pallidifloric acid (**43**, as a methyl ester) has been isolated from *G. pallidiflora* by LIU *et al.* (196) as have the known sapogenins, **29**, **12** (glypallidifloric acid) and soyasapogenol B (**44**) (196–199). A known sapogenin glabrolide (**7**) was isolated from *G. aspera* (200) and 24-hydroxyglycyrrhetic acid (**15**) was obtained from *G. korshinskyi* (201). A new sapogenin squasapogenol (**45**) has been isolated together with two known sapogenins (**29** and **44**) from *G. squamulosa* by LIANG and ZHANG (202).

Several sapogenins (**46**–**55**) have been obtained as hydrolysis products of saponins from *G. uralensis* and *G. yunnanensis*. These are described in the next section.

References, pp. 110–140