An Update on Secondary Metabolites from *Glycyrrhiza* Species

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Abstract: Secondary metabolites have been obtained from the *Glycyrrhiza* species (Fabaceae) including *G. glabra, G. echinata, G. uralensis, G. triphylla and G. macedonica*. These compounds **1-25** belong to the classes, steroid, saponin, flavonoid, flavonoid glycoside, triterpenic acid, coumarin, phenolic derivative, chalcone and chalcone glycoside. This review will describe the isolated compounds **1-25**, obtained from *Glycyrrhiza* species with their biological activities up to 1966.

Keywords: *Glycyrrhiza glabra, Glycyrrhiza echinata, Glycyrrhiza uralensis, Glycyrrhiza triphylla, Glycyrrhiza macedonica*, Licorice.

INTRODUCTION

The role of natural products is always very important in the discovery and development of new pharmaceuticals. They may be as clinically useful drugs, as starting material to produce synthetic or semi-synthetic drugs, or as lead compounds from which a new synthetic drug can be designed [1]. Plants are extensively used medicinally all around the world and are an important aspect of various traditional medicine systems. The application of phytotherapy has increased, especially in developed countries during the past few decades [2]. Despite advancements in synthetic chemistry, about 80% of the world's populations still depend upon medicinal plants for the treatment of diseases [3,4].

The genus *Glycyrrhiza* belongs to the family Fabaceae. *Glycyrrhiza* consists of about 30 species belong to Asia, North and South America, Europe as well as Australia, including *G. uralensis*, *G. aspera*, *G. glabra*, *G. korshinskyi, G. inflata* and *G. eurycarpa*. *Glycyrrhiza glabra* includes three varieties: Persian and Turkish liquorices assigned to *G. glabra* var. *violacea*, Russian liquorice is *G. glabra* var. *gladulifera*, and Spanish and Italian liquorices are *G. glabra* var. *typical* [5]. *G. uralensis*, *G. inflata* and *G. glabra* are the only species mentioned in the Chinese Pharmacopoeia, their Chinese name is *gan-cao*, which means "sweet herb". It is also known as liquorice, kanzoh, sweet root and yasti-madhu [5,6]. It is a perennial herb, which is 3-5 feet in height, smooth rising from thick rhizome.

Glycyrrhiza plant is used as galactagogue, emmenagogue, laxative, contraceptive, anti-asthmatic drug and antiviral agent. It has been suggested for dyspepsia and gastric and duodenal ulcers as well as an anti-inflammatory agent during allergenic reactions in folk medicines [7]. *Glycyrrhiza* root powder has exhibited significant hepatoprotective action against ascorbate dependent oxidation endogenous polyenic lipids in rat liver [8]. The ethanolic extract of *Glycyrrhiza* showed anticonvulsant activity against pentylenetetrazol (PTZ) and lithium pilocarpine induced seizures in mice. It also exhibited anti-carcinogenic and anti-hepatotoxic activities [9,10].

Phytochemical Analysis of the Genus *Glycyrrhiza*

Phytochemical analysis of the aerial parts of the genus *Glycyrrhiza* revealed the presence of various secondary metabolites, **1**-**25** isolated from *Glycyrrhiza glabra, G. echinata, G. uralensis, G. triphylla, G. macedonica* and Liquorice up to 1966. These compounds belong to the classes, steroid **1**, saponins **2**, flavonoids **3**-**4**, flavonoid glycosides **5**-**6**, triterpenic acids **7**-**15**, coumarins **16**-**17**, phenolic derivatives **18**-**19**, chalcones **20**-**21** and chalcone glycosides **22**-**25**. Their structures are represented in Figure **1** and their detail is also mentioned in Table **1**.

Steroids

Zayed and co-workers in 1964 isolated β-sitosterol (**1**) from *G. glabra*, which was a very common compound present in plants [11]. It has potential to reduce blood cholesterol levels and benign prostatic hyperplasia (BPH) [12,13].

Saponins

Kobert and co-workers in 1915 isolated glycyrrhizin (**2**) from *Glycyrrhiza* species [14]. Glycyrrhizin (**2**) is also called glycyrrhizic acid (**2**). It is exceedingly sweet

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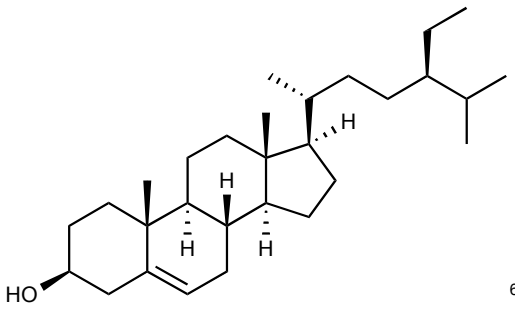
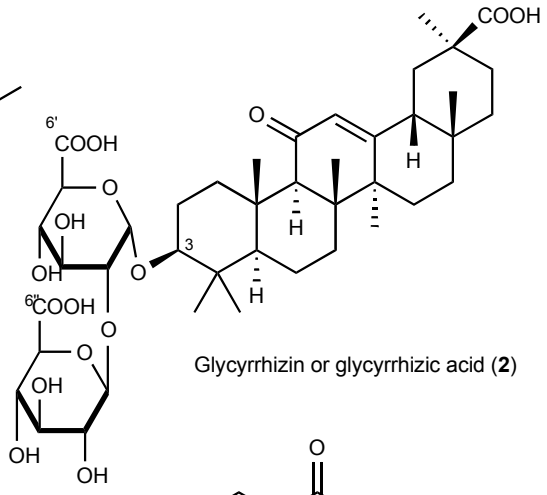
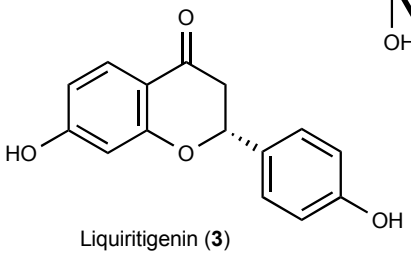


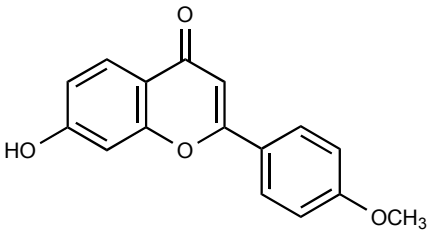
β-Sitosterol (**1**)



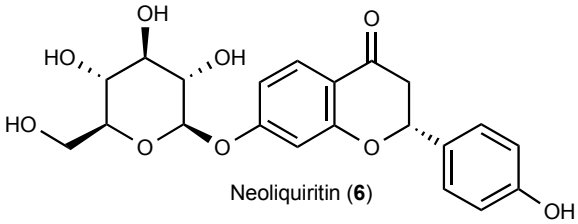
Glycyrrhizin or glycyrrhizic acid (**2**)



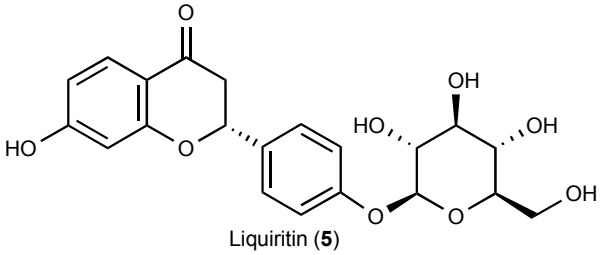
Liquiritigenin (**3**)



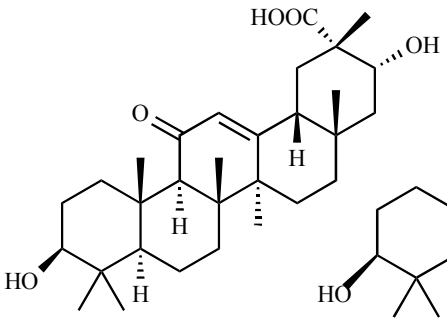
7-Hydroxy-4'-methoxyisoflavone (**4**)



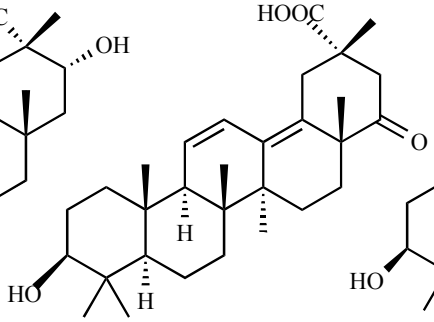
Neoliquiritin (**6**)



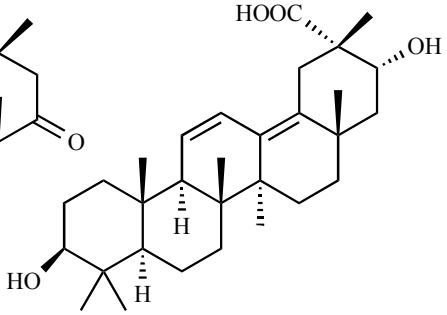
Liquiritin (**5**)



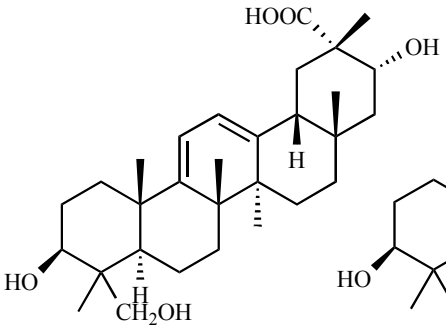
Glabric acid (**7**)



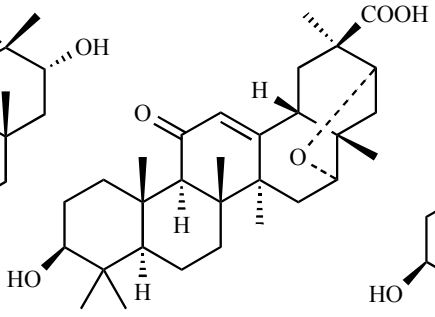
Meristotropic acid (**8**)



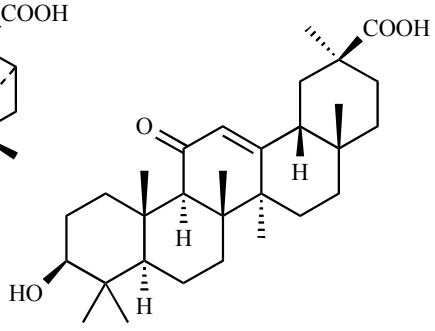
Macedonic acid (**9**)



Echinatic acid (**10**)



Liquoric acid (**11**)



Glycyrrhetic acid (**12**)

(Figure 1). Continued.

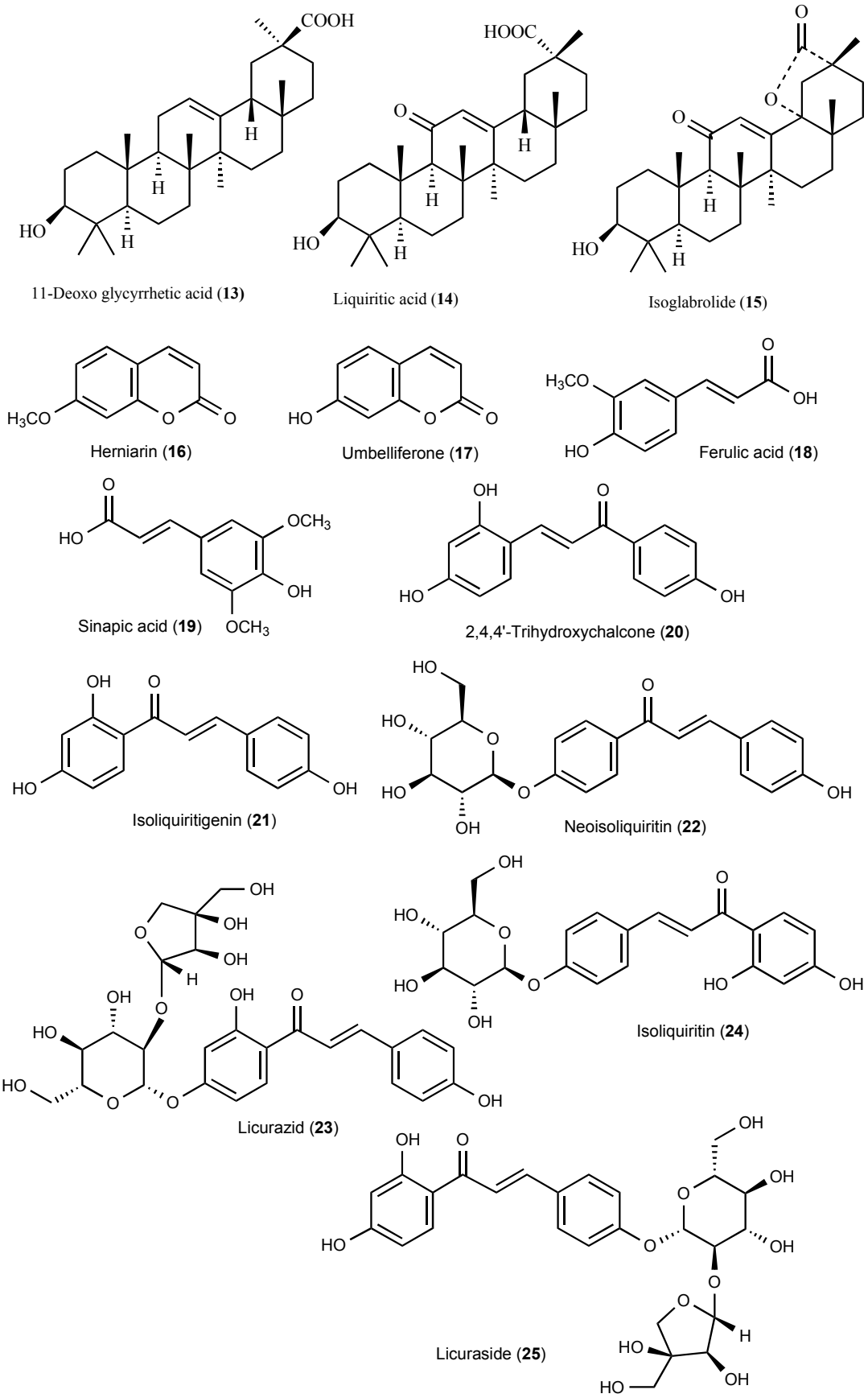


Figure 1: Structures of Secondary Metabolites obtained from *Glycyrrhiza* species.

Table 1: Secondary Metabolites from *Glycyrrhiza* Species

S. No.	Name of Compound	Class of Compound	*Glycyrrhiza* species	Reference
1	β-Sitosterol (**1**)	Steroid	*G. glabra*	11
2	Glycyrrhizin or glycyrrhizic acid (**2**)	Saponin	*G.* species, *G. glabra* and *G. echinata*	14,16
3	Liquiritigenin (**3**)	Flavonoid	Licorice, *G. uralensis*, *G. glabra* and *G. uralensis*	17-20
4	7-Hydroxy-4′-methoxyisoflavone (**4**)	Flavonoid	Licorice	21
5	Liquiritin (**5**)	Flavonoid glycoside	*G. glabra*, *G. uralensis*, Licorice, *G. glabra* and *G. uralensis*	19,20,22
6	Neoliquiritin (**6**)	Flavonoid glycoside	*G. uralensis*, *G. glabra* and *G. uralensis*	19,20
7	Glabric acid (**7**)	Triterpenic acid	Licorice	24
8	Meristotropic acid (**8**)	Triterpenic acid	*G. triphylla*	25
9	Macedonic acid (**9**)	Triterpenic acid	*G. macedonica*	26
10	Echinatic acid (**10**)	Triterpenic acid	*G. echinata*	27
11	Liquoric acid (**11**)	Triterpenic acid	*G. glabra*	28
12	Glycyrrhetic acid or Uralenic acid (**12**)	Triterpenic acid	*G. glabra* and *G. uralensis*	28,29
13	11-Deoxo glycyrrhetic acid (**13**)	Triterpenic acid	*G. glabra*	30
14	Liquiritic acid (**14**)	Triterpenic acid	*G. glabra*	30
15	Isoglabrolide (**15**)	Triterpenic acid	*G. glabra*	31
16	Herniarin (**16**)	Coumarin	Licorice	18
17	Umbelliferone (**17**)	Coumarin	Licorice	18
18	Ferulic acid (**18**)	Phenolic derivative	Licorice	18
19	Sinapic acid (**19**)	Phenolic derivative	Licorice	18
20	2,4,4′-Trihydroxychalcone (**20**)	Chalcone	*G. glabra*	17
21	Isoliquiritigenin (**21**)	Chalcone	*G. uralensis*, *G. glabra* and *G. uralensis*	19,20
22	Neoisoliquiritin (**22**)	Chalcone glycoside	*G. uralensis, G. glabra* and *G. uralensis*	19,20
23	Licurazid (**23**)	Chalcone glycoside	*G. uralensis, G. glabra* and *G. uralensis*	19,20
24	Isoliquiritin (**24**)	Chalcone glycoside	*G. glabra* and *G. uralensis*	20
25	Licuraside (**25**)	Chalcone glycoside	*G. glabra*	36

and the main sweet tasting compound from Liquorice root. It is also used to prevent liver carcinogenesis in patients with chronic hepatitis C [15]. Baytop in 1954 also isolated it from roots and juice of *G. glabra* and *G. echinata* [16].

Flavonoids

Litvinenko and co-workers in 1963 isolated liquiritigenin (**3**) from the ethanolic extract of the roots of *G. glabra* [17]. It is an estrogenic compound. Reiners in 1964 isolated **3** from methanolic extract of Licorice root [18]. It was also isolated by Litvinenko in 1963 from *G. uralensis* [19] while Litvinenko and Obolentseva in 1964 again isolated it from *G. glabra and G. uralensis* [20]. Reiners in 1966 isolated 7-hydroxy-4'-methoxyisoflavone (**4**) from the roots of Licorice [21].

Flavonoid Glycosides

Shinoda and Ueeda in 1934 isolated a glucoside, liquiritin (**5**) from the extraction of the powder root of *G. glabra* L. with methanol [22]. Litvinenko in 1963 isolated liquiritin (**5**) and neoliquiritin (**6**) from *G. uralensis* [19]. Litvinenko and Obolentseva in 1964

again isolated liquiritin (**5**) and neoliquiritin (**6**) from *G. glabra and G. uralensis* [20]. Liquiritin (**5**) has significant antidepressant-like effects [23].

Triterpenic Acids

Beaton and Spring in 1957 isolated glabric acid (**7**) from Licorice root [24]. Kir'yalov and Naugol' naya in 1963 isolated meristotropic acid (**8**) from *G. triphylla* [25]. They also isolated macedonic acid (**9**) from the roots of *G. macedonica* and echinatic acid (**10**) from *G. echinata* [26,27]. Elgamal and co-workers in 1965 isolated liquoric acid (**11**) and glycyrrhetic acid (**12**) from the roots of *G. glabra* [28]. Kir'yalov and Naugol' naya in 1964 again isolated glycyrrhetic acid (**12**) from the alcoholic extract of the roots of *G. uralensis*, which is also known as uralenic acid (**12**) [29]. Canonica and co-workers in 1966 isolated 11-deoxo glycyrrhetic acid (**13**), liquiritic acid (**14**) and isoglabrolide (**15**) from *G. glabra* [30,31].

Coumarins

Reiners in 1964 isolated two coumarins, herniarin (1**6**) and umbelliferone (1**7**) from the methanolic extract of Licorice root [18]. Herniarin (1**6**) may be used as a reference material in the analysis of coumarin compounds whereas umbelliferone (**17**) has antioxidant properties.

Phenolic Derivatives

Reiners in 1964 obtained two phenolic derivatives, ferulic acid (1**8**) and sinapic acid (**19**) from the methanolic extract of Licorice roots [18]. Ferulic acid (1**8**) is an antioxidant; its small amount can inhibit melanin production in the process of skin whitening [32].

Chalcones

Litvinenko and co-workers in 1963 obtained 2,4,4'-trihydroxychalcone (**20**) from the ethanolic extract of the roots of *G. glabra* [17]. Litvinenko in 1963 also isolated isoliquiritigenin (**21**) from *G. uralensis* [19] whereas Litvinenko and Obolentseva in 1964 isolated again from *G. glabra and G. uralensis* [20]. It is potent GABA-A benzodiapine receptor positive allosteric modulator [33].

Chalcone Glycosides

Litvinenko in 1963 isolated neoisoliquiritin (**22**) and licurazid (**23**) from *G. uralensis* [19]. Litvinenko and Obolentseva in 1964 reported neoisoliquiritin (**22**) and licurazid (**23**) again with isoliquiritin (**24**) from *G. glabra and G. uralensis* [20]. Licurazid (**23**) has antitumor potential [34] whereas isoliquiritin (**24**) has antioxidant, anti-inflammatory and anti-depression activities [35]. Litvinenko and Kovalev in 1966 also isolated licuraside (**25**) from *G. glabra* [36].

CONCLUSION

The genus *Glycyrrhiza* has been considerable attention since the last decade. Therefore this review describes secondary metabolites, **1**-**25** obtained from various species of the genus *Glycyrrhiza* up to 1966. Regarding this survey, it is assumed that much more phytochemical and pharmacological investigation with biological activities of whole plants and their isolated secondary metabolites has ever been carried out on *Glycyrrhiza* species.

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