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The Natural Products Journal, 2025, *15*, e22103155343052

MINI-REVIEW ARTICLE

Recent Progress of Chemical Components and Biological Activities of Licorice Roots

Le Li[1,2], Jianping Yong[2,3,*], Canzhong Lu[2,3] and Danian Tian[4]

[1]*College of Chemistry and Materials Science, Fujian Normal University, Fuzhou, Fujian, China;* [2]*Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, Fujian, China;* [3]*Xiamen Institute of Rare-Earth Materials, Chinese Academy of Sciences, Xiamen, Fujian, China;* [4]*Ningxia Medical University, Yinchuan, Ningxia, China*

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ARTICLE HISTORY

Received: July 09, 2024
Revised: August 15, 2024
Accepted: August 22, 2024

DOI:
10.2174/0122103155343052240906052136

Abstract: Licorice root is one kind of traditional Chinese Medicine, which has a long history of clinical use and has been widely considered by Chinese and foreign scholars. Many works on the chemical constituents (including flavonoids, triterpene, polysaccharides, alkaloids, and amino acids, *etc*.) together with their biological activities (including anti-oxidation, anti-tumor, enhancing the body's immunity, anti-fatigue, regulating the digestive system, lowering blood sugar, decreasing blood lipids and so on) have been achieved. In this mini-review, we comprehensively reviewed the recent progress of its constituents and biological activities by searching through CNKI, PubMed, Web of Science, Scopus, and Google Scholar databases to provide a comprehensive reference for the researchers.

Keywords: Licorice roots, chemical constituents, flavonoids, triterpenes, alkaloids, biological activities.

1. INTRODUCTION

Licorice (named as “Gancao” in Chinese) is the dry root and rhizome of the leguminous plant *Glycyrrhiza uralensis* Fisch. It was usually known as "Guolao", "Meicao", "Honey Grass", "Lu Grass", and "Honey Gan" in “Mingyi Bielu”. However, it was also called "Lingtong" in the "Record of Things". Tao Hongjing said that licorice is the master of many medicines, and there are few prescriptions that are not used for it, just like there is eaglewood in incense. Licorice can blend hundreds of medicines and detoxify various medicines. Licorice has a sweet and flat odor, and it is non-toxic. The root of licorice was usually used to treat cold and hot pathogenic factors in the viscera, strengthen muscles and bones, grow muscles, calm the mind, unblock the nine orifices, and promote blood circulation. Licorice shoot was usually used to treat heat accumulation in the chest and relieve pain in the penis, while the licorice head was usually used to reduce swelling and detoxify. There are many kinds of active components (such as flavonoids, chalcones, triterpenes, polysaccharides, alkaloids, *etc*.) in licorice roots, which exhibit a wide spectrum of biological activities (such as anti-ulcer, anti-microbial, anti-asthma, anti-diuretic and anti-hepatotoxicity, anti-inflammatory, anti-tumor, anti-virus and anti-atherosclerosis) [1]. In this mini-review, we mainly reviewed the recent progress of the chemical components and biological activities of licorice by searching through CNKI, PubMed, Web of Science, Scopus, and Google Scholar databases to provide a comprehensive reference for researchers for the in-depth development and utilization of licorice.

2. HABITUAL NATURE, TYPES AND DISTRIBUTION

Licorice has strong adaptability with the virtues of light resistance, drought resistance, cold resistance, and salt-alkali resistance. Licorice is native to Eurasia, northern Africa, and western Asia [2]. In China, it is mainly distributed in the provinces of Inner Mongolia, Gansu, Heilongjiang, Ningxia, Xinjiang, Qinghai, *etc*. [3-6]. There are multiple varieties of licorices, such as light fruit licorice, Ural licorice, round fruit licorice, prickly fruit licorice, and coarse-haired licorice (Representative pictures of licorices were listed in Fig. **1**).

3. THE MORPHOLOGY OF LICORICE

The leguminous plant licorice belongs to the perennial herbaceous plant. The plant is 30-70 cm tall, and the stem is upright, and woody, with white short hairs and thorny glandular structures. Leaves are pinnate compound leaves, flowers are dense, and the corolla is blue-purple with a large flag petal and an oval shape. It blooms from June to August and bears fruit from July to October. The roots and rhizomes of licorice are thick and robust, with a reddish brown skin and a yellow or light-yellow cross-section, slightly sweet.

*Address correspondence to this author at the Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, Fujian, China; E-mail: jpyong@fjirsm.ac.cn

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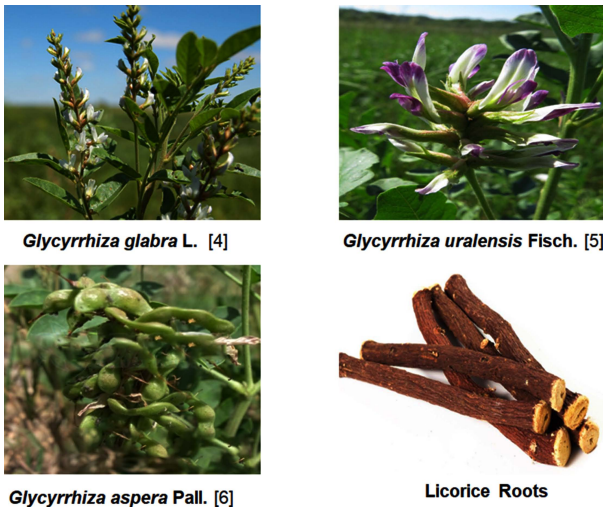


Fig. (1). The pictures of the representative licorices. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. CHEMICAL COMPONENTS

The main components of licorice are flavonoids, chalcones, triterpenes, and polysaccharides; while other components include alkaloids, organic acids, phenols, volatile oils, and amino acids. Different types of licorices contain different levels and types of chemical components, and there are also mutual influences between compounds. Different species of licorices contain different amounts and types of components, and the content of the compounds is also affected by the environment, soil, geographical location, *etc*. It has been reported by Bahdad *et al*. [1] that the time, place, and diameter of rhizomes for harvesting licorice have a significant effect on the contents of phenolic compounds and flavonoids. The contents of phenolic compounds and flavonoids in rhizomes with a diameter of less than 1 cm are more than that of the rhizomes with a diameter of less than 1-2 cm. In addition, the contents of phenolic compounds and flavonoids simultaneously increase at the same condition, but the contents of glycyrrhizic acid and saponins will decrease with the increase of phenolic compounds and flavonoid contents.

4.1. Flavonoids and Chalcones

Flavonoids are one of the most important chemical components in licorice, and they exhibit a wide spectrum of biological activities. Flavonoids are often used to treat acute chronic inflammation, inflammatory pain, and cancer. Especially, the flavonoids showed potent anticancer activities with multiple targets. At present, more than 300 flavonoids have been isolated and confirmed from licorices, which include flavonoids, flavonols, isoflavones, and dihydrochalcones. Chalcone is composed of two aromatic rings called A and B fragments, which are formed by α,β-unsaturated carbonyl system. Chalcone is one of the main categories of flavonoids and is one important class of secondary metabolites in plants. Chalcone also shows almost the same biological activities as flavonoids. Here, we list 65 representative flavonoids and chalcones, which were recently isolated from licorices (Their structures are listed in Table **1**).

4.2. Triterpenoids

The content of triterpenoids is the most abundant in the roots and stem parts of licorice. They are soluble in water. Tetracyclic and pentacyclic triterpenoids are the most common triterpenes in licorice, and most of them have bitter and spicy flavors. The sugar residues of oleanane pentacyclic triterpenoid saponins in licorice mainly include glucuronic acid fragments (GluA), rhamnose fragments (Rha), glucose fragments (Glu), galacturonic acid fragments (GalA), xylose fragments (Xyl), and galactose fragments (Gal) [27]. The triterpenoids in licorice mainly include glycyrrhizic acid, and glycyrrhetinic acid [28]. The structures of triterpenoids isolated from licorice are listed in Table **2**.

4.3. Polysaccharides

Polysaccharides are composed of different molar ratios of xylose, mannose, galactose, and glucose. These monosaccharide units are connected by various glycosidic bonds and are the main components in many plants [32]. Licorice polysaccharide (GPS-1) (Structure is shown in Fig. **2**) is a novel HG-type pectin polysaccharide, which is composed of fucose, rhamnose, arabinose, galactose, glucose, xylose, galacturonic acid, and mannuronic acid, with the proportions of 0.92%, 10.12%, 6.36%, 4.85%, 1.34%, 0.51%, 74.39%, and 1.52%, respectively [33]. Glycosidic bonds can form at different places, and lead to different connectivity. Therefore, polysaccharides have structural diversities, making them extremely difficult to confirm their exact structures. In addition, each new glycosidic connection generates a new stereocenter (α or β configurations) [34].

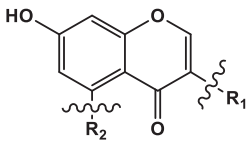
4.4. Others

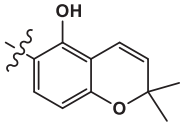
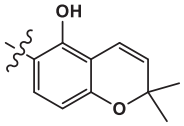
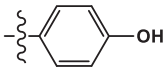
Licorice also contains various other compounds such as coumarins, alkaloids, volatile oils, organic acids, amino acids, and phenols, as well as various nutrients such as vitamins, crude protein, and fat. The alkaloids isolated from licorices are mostly the tetra hydroxyquinoline compounds such as 5,6,7,8-tetrahydroxy-2,4-dimethylquinoline (Structure is shown in Fig. **3**). The amino acids with the highest content confirmed in licorices are alanine, glycine, serine, aspartic acid, threonine, and glutamic acid, respectively. The phenols isolated and confirmed in licorices mainly are: 6-dimethylallyl sweet potato chicory α,α′-dihydro-3,5,3',4'-tetrahydroxy-2,5'- dienylstilbene, glycyrrhetinin P, 6-isoprene quercetin-3-methyl ether, rattan flavonoid NF, wildianin, glyasperin C, 3,3' - dimethoxyquercetin, coumarinone, α,α′- dihydro-3,5,3',4' -tetrahydroxy-5'- isopentenyl styrene, (2S) -2- (3,4-dihydroxyphenyl) -5,7-dihydroxy-6- (3-methylbutan-2-eny) -2,3-dihydrobenzopyran-4-one [35]. The representative structures of phenols recently isolated from licorices are listed in Table **3**.

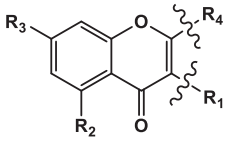
5. BIOLOGICAL ACTIVITIES

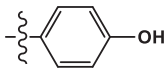
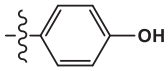
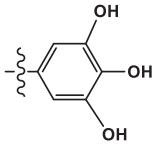
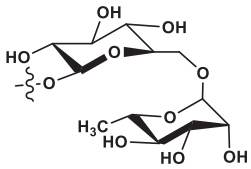
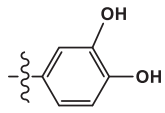
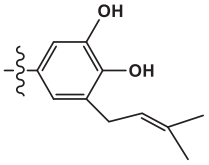
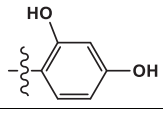
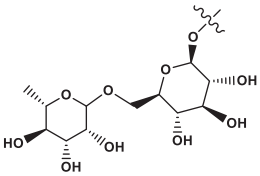
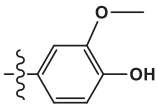
Licorice contains various active compounds, therefore it has a broad spectrum of biological activities: such as anti-inflammatory, anti-allergic, antibacterial, anti-ulcer,

Table 1. The structures of flavonoids and chalcones recently isolated from licorices.



S. No.	Names	R_1	R_2
1	Licoisoflavone B [7]		OH
2	Glabrone [7]		H
3	Genistein [8]		OH



S. No.	Names	R_1	R_2	R_3	R_4
4	7-4'-dihydroxyflavone [7]	H	H	OH	
5	Kumatakenin A [7]	OH	OH	OCH_3	
6	Myricetin [9]	OH	OH	OH	
7	Rutin [9]		OH	OH	
8	5'-Prenylquercetin [10]	OH	OH	OH	
9	Morin [11]	OH	OH	OH	
10	Narcissoside [12]		OH	OH	

(Table 1) Contd….

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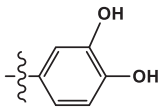
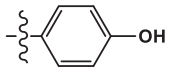
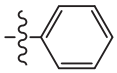
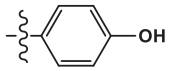
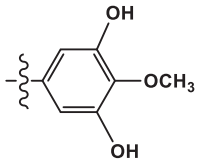
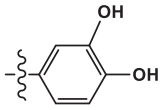
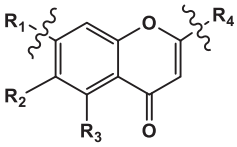
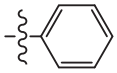
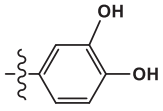
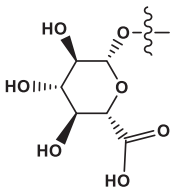
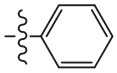
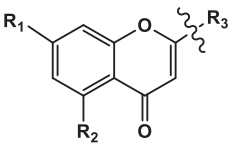
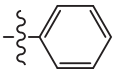
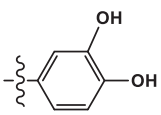
11	Quercetol [11]	OH	OH	OH	
12	Kaempferol [11]	OH	OH	OH	
13	Galangin [13]	OH	OH	OH	
14	Kumatakenin [14]	OCH_3	OH	OCH_3	
15	Mearnsetin [15]	OH	OH	OH	
16	Quercetin [8]	OH	OH	OH	
					
S. No.	**Names**	R_1	R_2	R_3	R_4
17	Baicelein [12]	OH	OH	OH	
18	Cirsiliol [11]	OCH_3	OCH_3	OH	
19	Baicalin [9]		OH	OH	
					
S. No.	**Names**	R_1	R_2	R_3	
20	Chrysin [12]	OH	OH		
21	Luteolin [13]	OH	OH		

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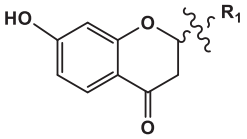
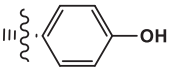
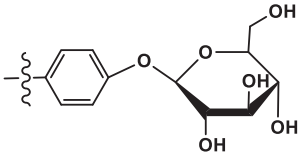
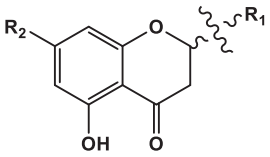
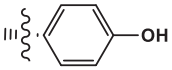
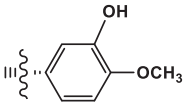
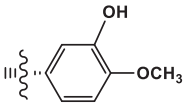
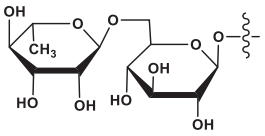
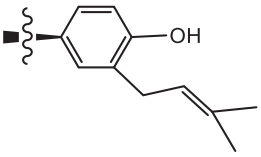
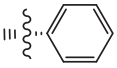
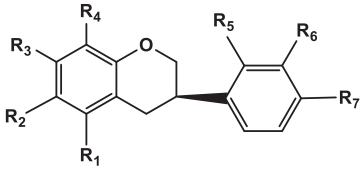
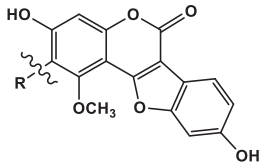
				

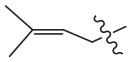
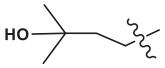
S. No.	Names	R_1
22	Liquiritigenin [16]	
23	Liquiritin [16]	
		

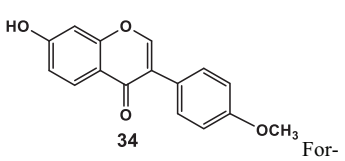
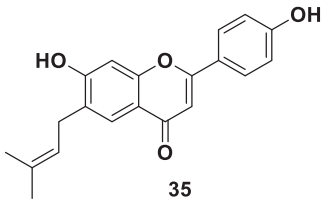
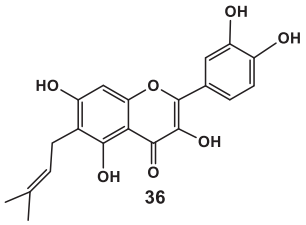
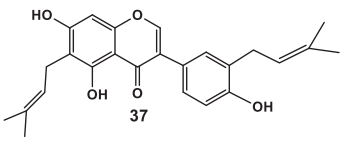
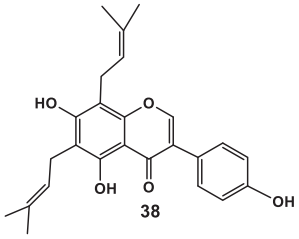
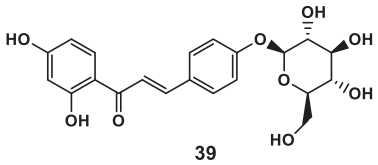
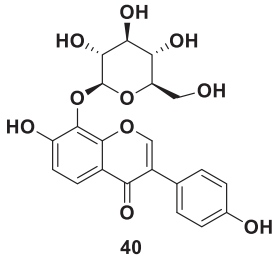
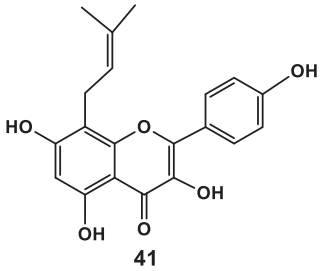
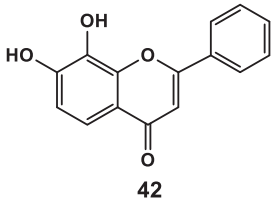
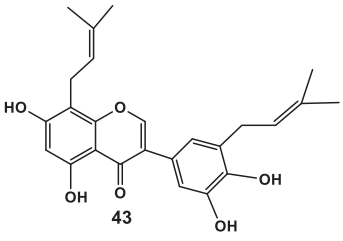
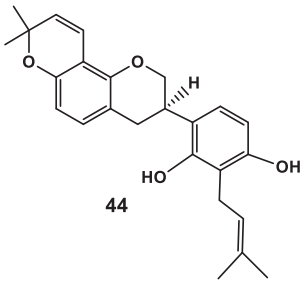
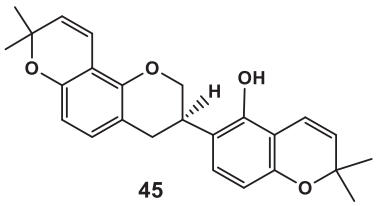
S. No.	Names	R_1	R_2
24	Naringenin [17]		OH
25	Hesperetin [17]		OH
26	Hesperidin [9]		
27	3'-Prenylnaringenin [10]		OH
28	Pinocembrin [13]		OH
			

S. No.	Names	R_1	R_2	R_3	R_4	R_5	R_6	R_7
29	7-Methyllicoricidin [18]	OCH_3	-$CH_2CH=C(CH_3)_2$	OCH_3	H	OH	-$CH_2CH=C(CH_3)_2$	OH
30	4'-O-methylglabridin [18]	H	H	7-O-$C(CH_3)_2CH=CH$-8	7-O-$C(CH_3)_2CH=CH$-8	OH	H	OCH_3
31	3'-O-methylglabridin [18]	H	H	7-O-$C(CH_3)_2CH=CH$-8	7-O-$C(CH_3)_2CH=CH$-8	OH	OCH_3	H

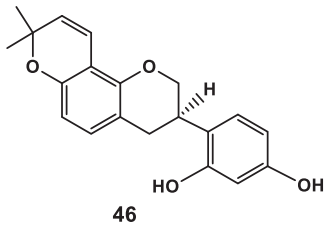
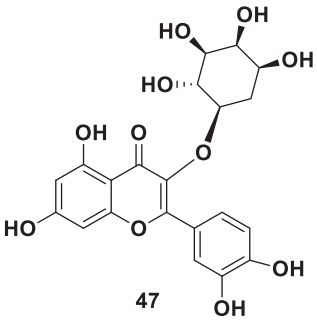
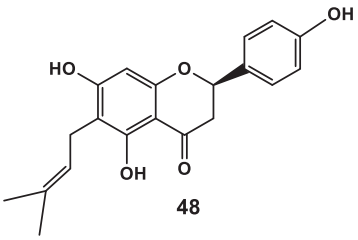
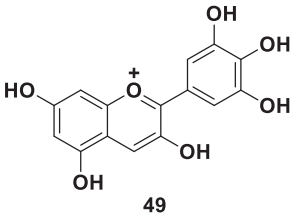
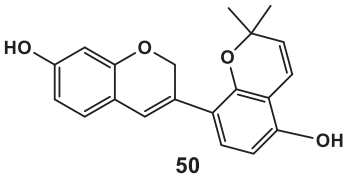
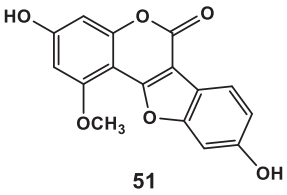
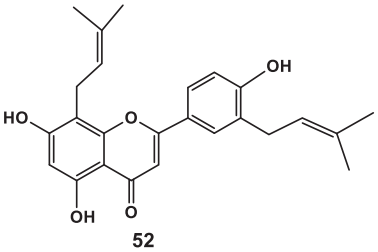
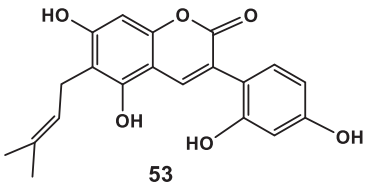
(Table 1) Contd….

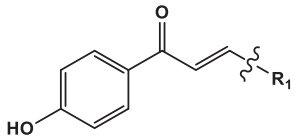
S. No.	Names	R_1	R_2	R_3	R_4	R_5	R_6	R_7
								

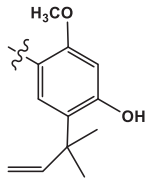
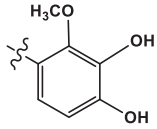
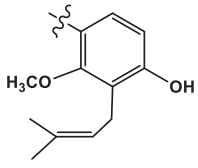
S. No.	Names	R
32	Glycyrol [7]	
33	Glycryrurol [14]	

 **34** Formononetin [7]	 **35** Licoflavone [7]	 **36** 6-prenylquercetin [10]
 **37** Lupalbigenin [19]	 **38** 6,8-diprenylgenistein [19]	 **39** Isoliquiritin [16]
 **40** Puerarin [11]	 **41** 8-prenylkaempferol [11]	 **42** 7,8-dihydroxyflavone [14]
 **43** Glyurailin B [20]	 **44** Hispaglabridin A [21]	 **45** Hispaglabridin B [21]

(Table 1) Contd….

S. No.	Names	R
 46	Glabridin [22]	
 47	Hyperoside [12]	
		 48 6-prenylnaringenin [10]
 49	Delphinidin [11]	
 50	Glabrene [23]	
		 51 Isotrifloliol [14]
 52	Glabrol [25]	
 53	Glycycoumarin [20]	



S. No.	Names	R_1
54	Licochalcone A [24]	
55	Licochalcone B [24]	
56	Licochalcone C [24]	

(Table 1) Contd….

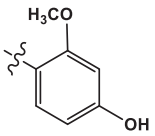
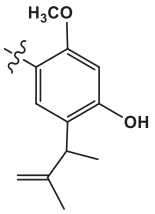
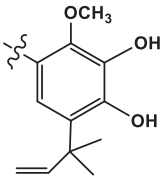
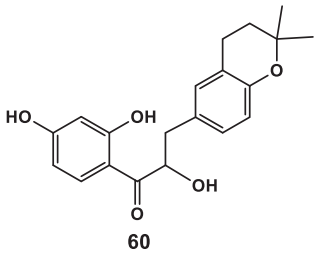
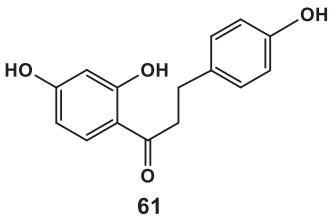
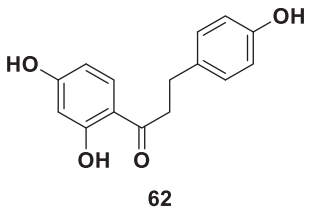
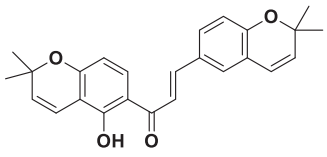
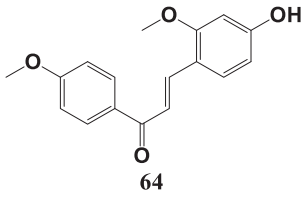
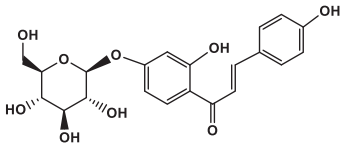
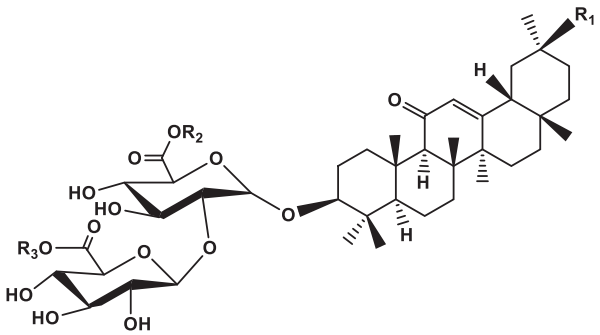
S. No.	Names	R_1
57	Echinatin [24]	
58	Licochalcone E [25]	
59	5-(1,1-Dimethylallyl)-3,4,4'-trihydroxy-2-methoxychalcore (DTM) [20]	
 **60** Glycybridin A [26]	 **61** Dihydroisoliquiritigenin [26]	 **62** Davidigenin [15]
 **63** Paratocarpin A [26]	 **64** Glypallichalcone [26]	 **65** Neoisoliquiritin [26]

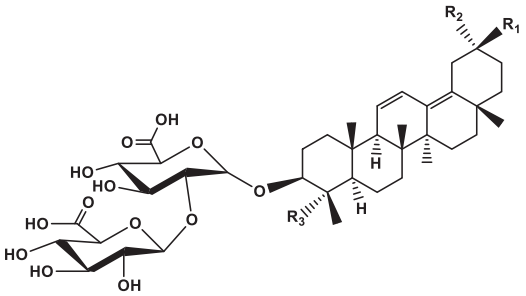
Table 2. The structures of triterpenoids from licorice.



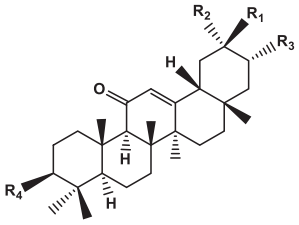
S. No.	Names	R_1	R_2	R_3
66	Glycyrrhizic acid 6''-methyl ester [15]	COOH	H	CH_3
67	Glycyrrhizic acid [15]	COOH	H	H

(Table 2) Contd….

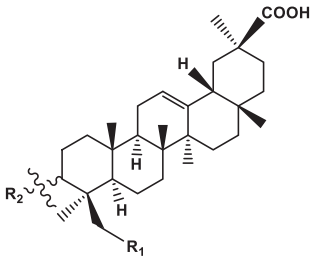
S. No.	Names	R_1	R_2	R_3
68	Glyayrrhizic acid 6'-methyl ester [15]	COOH	CH_3	H
69	6',6''-Dimethy ester of glycyrrhizic acid [15]	COOH	CH_3	CH_3
70	Glycyrihizic acid trimethyl ester [15]	$COOCH_3$	CH_3	CH_3



S. No.	Names	R_1	R_2	R_3
71	Uralsaponin V [15]	CH_3	COOH	CH_3
72	Licorice saponin K2 [15]	COOH	CH_3	CH_2OH

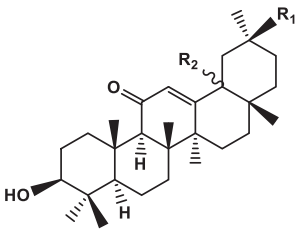
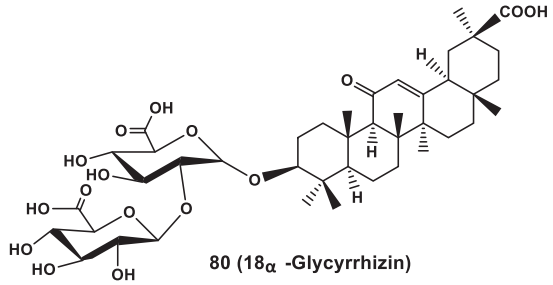
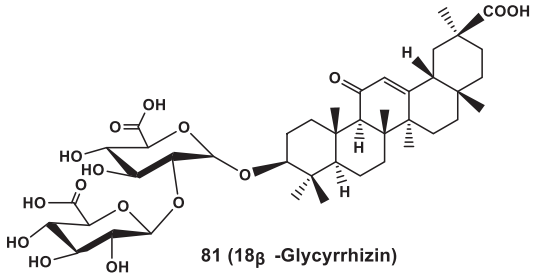
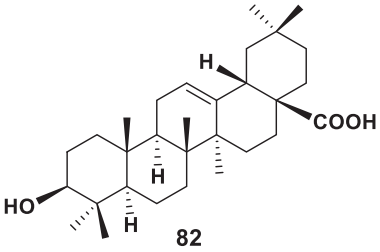
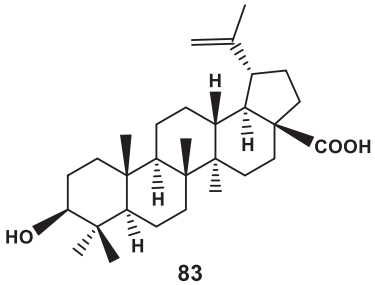
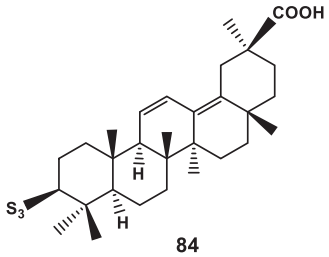
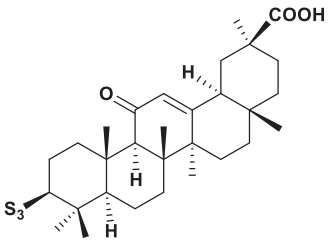
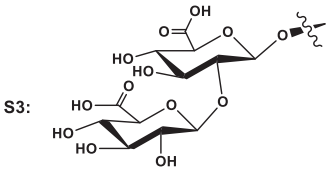


S. No.	Names	R_1	R_2	R_3	R_4
73	Uralsaponin B [15]	COOH	CH_3	H	β-D-GlcA-(1"-3')-O-β-D-GlcA
74	Glycyrrhetinic acid Monoglucuronicle [15]	COOH	CH_3	H	β-D-GlcA
75	Maceclonoside A [15]	CH_3	COOH	OH	β-D-GlcA-(1"-2')-O-β-D-GlcA



S. No.	Names	R_1	R_2
76	Licorice saponin B2 [27]	H	S3: S3 ( )
77	Licorice saponin J2 [27]	OH	S3: S3( )

(Table 2) Contd….

S. No.	Names	R_1	R_2
			
S. No.	**Names**	**R_1**	**R_2**
78	18α/18β-Glycyrrhetinic acid [29]	COOH	
79	18α-Glycyrrhetinic acid methyl ester [29]	$COOCH_3$	
 **80 (18α -Glycyrrhizin)** [31]			
 **81 (18β -Glycyrrhizin)** [31]			
 **82** Oleanolic acid [30]			
 **83** Betulinic acid [30]			
 **84** Licorice saponin C2 [27]			
 **85** Licorice saponin H2 [27]			
			

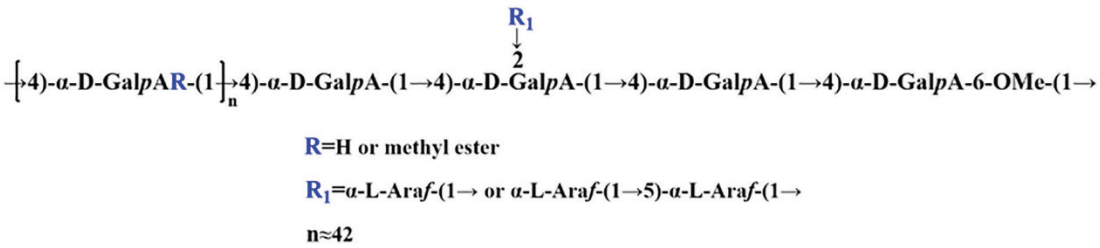


Fig. (2). Structure of GPS-1.

antiviral, anti-tumor, cough relief, and anti-allergic reaction. Licorice has been used in clinics for almost 2000 years [36].

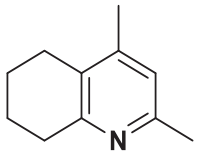


Fig. (3). Structure of 5,6,7,8-tetrahydroxy-2,4-dimethylquinoline.

5.1. Anti-inflammation

Glycyrrhizic acid (GL) and flavonoids in licorice could alleviate inflammation and were usually used to treat gastric disease and duodenal ulcers, as well as some inflammatory diseases. It was reported by Wei *et al*. [37] that flavonoids in licorice may treat inflammation by improving purine metabolism abnormalities, inhibiting the reaction between uric acid and adenine, and promoting uric acid excretion. Wu *et al*. also demonstrated that the possible reasons for the anti-inflammatory effect of GL in enteritis are attributed to its blocking IFN-γ signaling pathway, and reduced inflammation. The increase of proinflammatory cytokines (IL-1, IL-6, TNF-α and IFN-γ) may trigger the expression of HMGB1 in innate immune cells in SARS patients. Acute viral hepatitis is caused by hepatitis A, B, C, and D viruses, and its pathogenesis usually manifests as acute necrosis and inflammation of liver cells, followed by fibrosis and cirrhosis. GL and glycyrrhetinic acid (GTA) were used for the treatment of chronic viral hepatitis [28]. In addition, licorice can inhibit oxidative stress and inflammatory response, and reduce the level of malondialdehyde (MDA) and cytokines (TNF-α, IL-1 β, and IL-6) in lung cells by weakening the activities of Hmgb1 and NF-κ B signaling pathway [38]. Wang *et al*. synthesized a series of isoxazole containing GTA amide derivatives (structures are shown in Fig. **4**) and they exhibited potent anti-inflammatory activity [39], especially deoxyglycychloxazole (**TY501**) showed potent *in vivo* anti-inflammatory activity. Subsequently, many pharmacological research works on TY501 have been carried out: (1) Jin *et al*. investigated the effect of TY501 on the proliferation of murine macrophage RAW264.7, and the results showed that at the same degree of the concentrations, the inhibition of TY501 on cell proliferation is greater than those of Prednisolone and Piroxicam, but less than that of glycyrrhetinic acid, which indicated the inhibition of glycyrrhetinic acid and its derivative TY501 on the proliferation of murine macrophage RAW264.7 may be one of the possible mechanisms of anti-inflammation [40]. (2) Jin *et al*. investigated the effect of TY501 on the central immune organs and the proportion and quantities of leukocytes, lymphocytes, neutrophils, and lymphocyte subtypes in peripheral blood *via* oral administration to mice. The results showed that a significant reduction in body weight, thymus, spleen atrophy, and the quantities of the lymphocytes in peripheral blood was found in prednisolone group animals; thus a series of toxicity on the mice's immune system had been caused by prednisolone. There was no serious effect on the central immune organs and the proportion and quantities of leukocytes, lymphocytes, neutrophils, and lymphocyte subtypes in the peripheral blood of the animals caused by TY501. It means that TY501 does not have any immunosuppressive effects on mice's immune systems [41]. Geng *et al*. studied the *in vivo* antifibrotic effect of TY501 on bleomycin-induced pulmonary fibrosis and related mechanisms. The results showed that TY501 is valuable for the therapy of idiopathic pulmonary fibrosis (IPF), similar to the positive drug pirfenidone. TY501 attenuates bleomycin(BLM)-induced pulmonary fibrosis, which may be related to the affect of the TGF-β pathway and inhibition of matrix metalloproteinases (MMPs) [42]. TY501 is currently undergoing preclinical research.

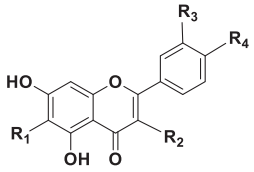
5.2. Anti-allergy

GL can reduce systemic allergic reactions induced by OVA in Balb/c mice by regulating T helper (Th) cell differentiation. It can also serve as a stabilizer for mast cells by reducing the expression of calcium channel proteins to stabilize mast cells and inhibiting the release of mast cell mediators to alleviate allergic symptoms [43]. Allergic reactions are mainly mediated by immunoglobulin E (IgE), which is associated with its high-affinity receptor (Fc ε RI) cross-linking, which activates mast cells (MCs), induces MC degranulation, and releases various pre-fabricated or newly synthesized inflammatory mediators [44]. 18β-Glycyrrhetinic acid (18β-GTA) can inhibit the release of β-aminohexosidase (HEX) from RBL-2H3 cells (rat basophilic leukemia cells, RBL), indicating that 18β-GTA can inhibit the allergic reaction caused by mast cell degranulation, and can also ensure safety and non-toxicity [45]. Chalcone A (Structure is shown in Fig. **5**) in licorice can also inhibit IgE-mediated passive cutaneous anaphylaxis (PCA), systemic allergies, the influx of Ca^{2+} in MCs, degranulation of MCs, and the release of inflammatory mediators, and downregulate the PLC/ERK/STAT3 photoperforation in LAD2 cells [44].

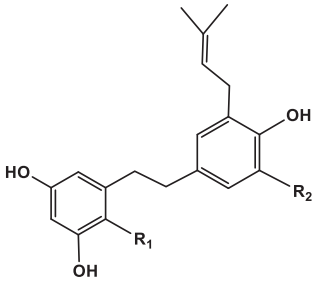
5.3. Antibacterial

The chemical components in licorice can destroy the structure of bacterial cell walls, disrupt bacterial metabolic pathways, and the structure of fungal cell membranes, and hinder the absorption of nutrients by fungi, thereby inhibiting the growth and reproduction of bacteria and fungi. The mechanism of licorice against Candida albicans inhibits biofilm formation, prevents yeast hyphal transformation, exerts Th1 immune adjuvant activity, and also resists Staphylococcus aureus, Gram-positive bacteria, Gram-negative bacteria, Bacillus subtilis, Escherichia coli, as well as fungi such as Candida albicans, Candida albicans, and Microsporus cerevisiae [46]. Moustafa *et al*. conjugated 18β-GTA with different amino acids and synthesized a series of 18β-GTA peptides (the structures of representative 18β-GTA peptides are shown in Fig. **6**). The biological evaluation showed that these compounds could effectively inhibit the growth of Micrococcus luteumens, and the efficacy is even more potent than that of Gentamicin [47]. Novel 18β-GTA amide derivatives **5k** (Structure is shown in Fig. **7**) could inhibit stubborn plant bacteria by stimulating excessive generation of ROS and damaging cell membranes, thereby enhancing the resistance of rice to bacterial leaf blight [48].

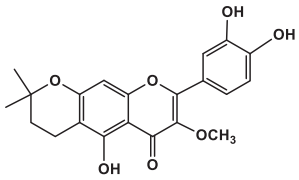
Table 3. The representative structures of phenols recently isolated from licorices.



S. No.	Names	R_1	R_2	R_3	R_4
86	6-Dimethylallyldiosmetin [35]	Prenyl	H	OH	OCH_3
87	Gancaonin P [35]	Prenyl	OH	OH	OH
88	6-Prenylquercetin-3-methyl ether [35]	Prenyl	OCH_3	OH	OH
89	3,3'-Dimethoxyquercetin [35]	H	OCH_3	OCH_3	OH



S. No.	Names	R_1	R_2
90	α,α′-Dihydro-3,5,3′,4′-tetrahydroxy-2,5′-diprenylstilbene [35]	Prenyl	OH
91	α,α′-Dihydro-3,5,3′,4′-tetrahydroxy-5′-isopentenylstilbene [35]	H	OH



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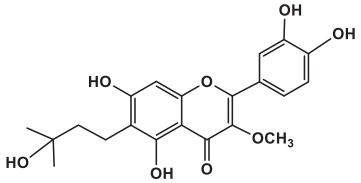
Sinoflavonoid NF [35]



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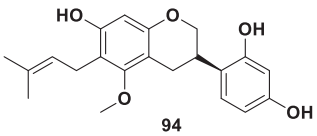
Wightianin [35]



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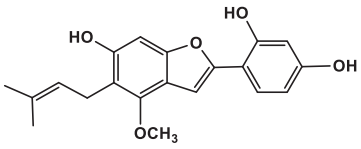
Glyasperin C [35]



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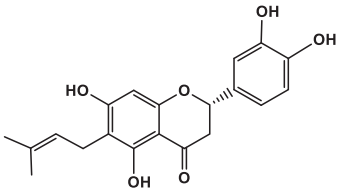
Licocoumarone [35]



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(2S) -2- (3,4-dihydroxyphenyl) -5,7-dihydroxy-6- (3-methylbutan-2-eny) -2,3-dihydrobenzopyran-4-one [35]

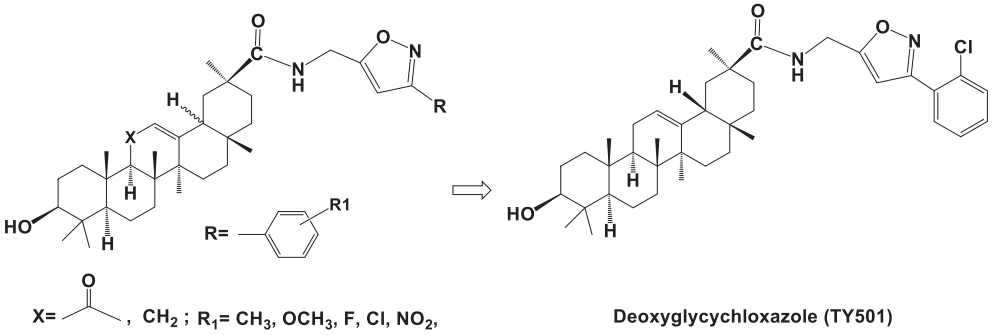


Fig. (4). Structures of isoxazole contained glycyrrhetinic acid derivatives.

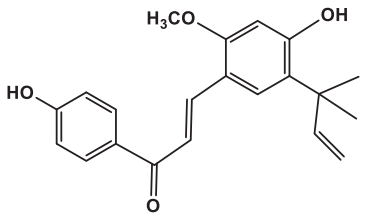


Fig. (5). Structure of chalcone A.

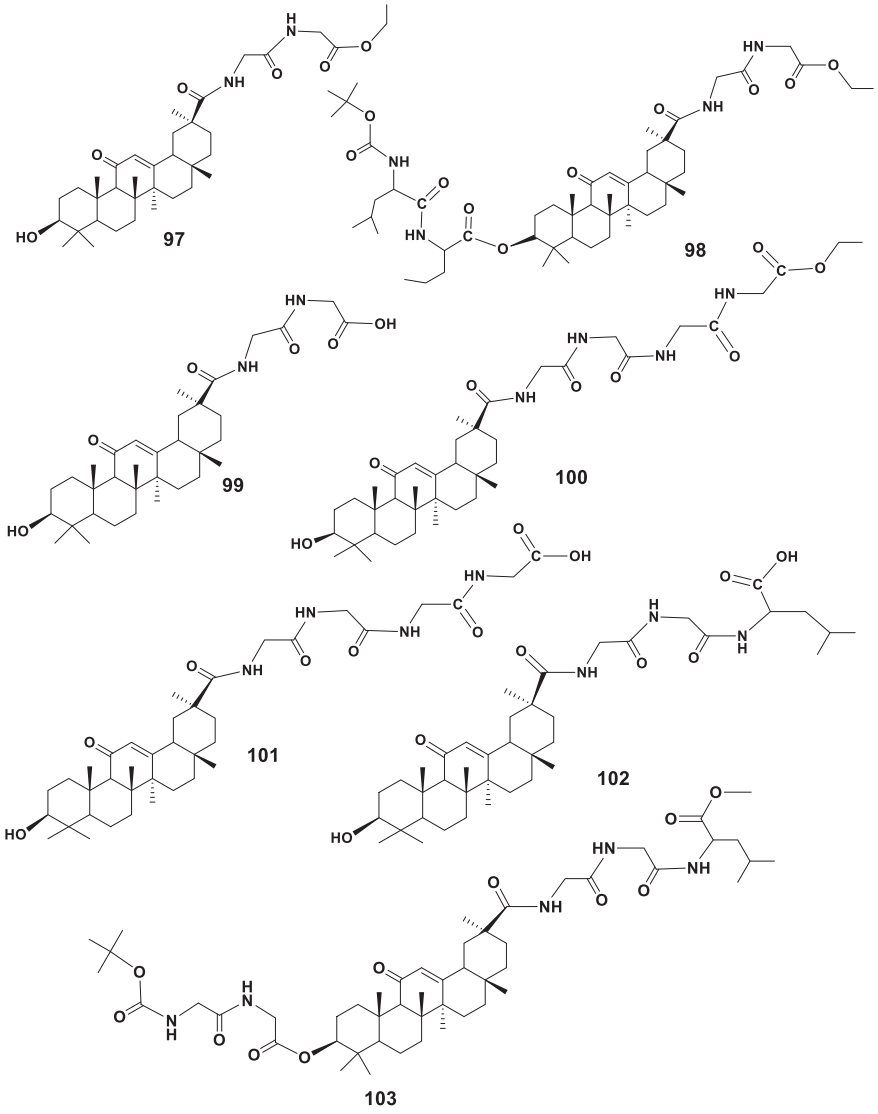


Fig. (6). Structures of novel 18β-GTA peptides (**97-103**).

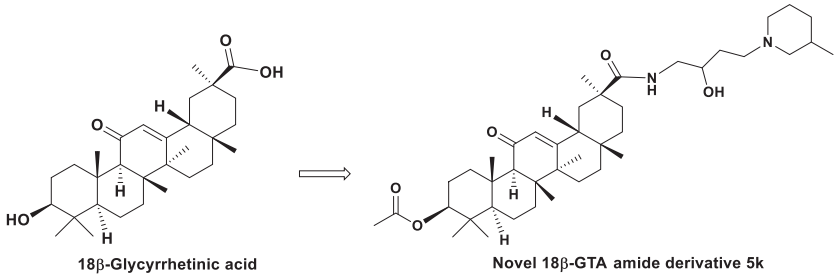


Fig. (7). Structures of novel 18β-GTA amide derivatives **5k**.

5.4. Anti-ulcer

Flavonoids extracted from licorice were mainly used to treat gastric and duodenal ulcers. Flavonoids exert gastric protective effects by inhibiting inflammation, promoting mucosal barrier repair and angiogenesis, and regulating gut microbiota and short-chain fatty acid (SCFA) metabolism. Secondly, the mechanism of flavonoids from licorice alleviating ethanol induced gastric ulcers activates the EGFR/ERK pathway, promoting the proliferation of epithelial mucus cells and gastric mucosal regeneration, improving the metabolism and inhibiting cell apoptosis through the PI3K-AKT pathway [49, 50]. Glycyrrhetinic acid alleviated the symptoms of colon length shortening and weight loss in ulcerative colitis (UC) through treatment with dextran sulfate sodium. It can inhibit prostaglandin E2 (PGE2) production and regulate the level of inflammatory mediators (IL-6, TNF-α, and IL-1β) of mouse colitis induced by dextran sulfate sodium, and repair mitochondrial damage; thereby reducing the epithelial damage in ulcerative colitis induced by dextran sulfate sodium [51]. Nuclear factor-E2 (Nrf2) is one of the main pathogenesis mechanisms of UC, and the excessive occurrence of reactive oxygen species and lipid peroxidation can exacerbate the deterioration of UC. However, Glycyrrhetinic acid can regulate oxidative stress by activating Nrf2 to reduce reactive oxygen species levels to prevent lipid peroxidation [52].

5.5. Antivirus

Viruses do not have their own metabolic mechanisms or enzyme systems. They can only generate a new generation with their genetic information by utilizing substances and energy in host cells. The antiviral mechanisms involve inhibiting the synthesis of glycoproteins by the virus; reducing the activity of reverse transcriptase, and preventing viruses adsorption and entry into host cells. Glycyrrhizic acid as the main antiviral component can inhibit the viruses' synthesis of DNA or RNA by preventing viruses' adsorption and entry into host cells. Licorice has ever been used for the treatment of influenza viruses, SARS virus, herpes simplex viruses, and COVID-19.

5.5.1. Anti-influenza Viruses

Licorice has a significant inhibitory effect on influenza viruses. Licorice can weaken the production of H5N1-induced chemokine (C-X-C motif) ligand 10 (CXCL10), interleukin-6 (IL-6), and chemokine (C-C motif) ligand 5 (CCL5), and inhibit the cell apoptosis induced by H5N1. Licorice can reduce the binding between HMGB1 and DNA, thereby inhibiting influenza virus polymerase activity [53-55]. The protein transcription factors (NF κB, p38, and JNK) are responsible for the activation of the inflammatory cascade and the release of reactive oxygen species (ROS). GL could inhibit the replication of influenza A virus by interfering with these transcription factors to reduce the ROS concentrations in infected cells [54, 55]. GL can prevent mice from being infected with H2N2 by stimulating T cells to produce IFN-γ. When the mice were exposed to the lethal amounts of H2N2 virus, GL can improve the survival rate and extend the survival time. The growth of the H2N2 virus in lung tissue was inhibited and pulmonary complications were also reduced [56].

5.5.2. Anti-severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)

Cinatl *et al*. found that GL exhibited the strongest inhibitory effect on SARS-CoV replication in Vero cells. GL could inhibit the early stages of the virus replication cycle, namely the adsorption and permeation [57]. The modification of the structure of GL, particularly the glycyrrhizic acid amide derivatives and amino acid conjugates of glycyrrhizic acid can significantly improve its anti-SARS-CoV activity. However, this modification also increased its cytotoxicity. For example: introducing "2-acetamido-β-D-glucopyranosylamine (structure A in Fig. **8**)" into the glycoside chain of glycyrrhizic acid, which could increase its anti-SARS-CoV activity by 10 times than that of glycyrrhizic acid, while the introduction of *N*-acetylglycosamine (Structure B in Fig. **8**) on glycyrrhizic acid could increase its anti-SARS-CoV activity by about 9 times than that of glycyrrhizic acid. The degree of glycosylation of coronavirus is very high, especially the spike protein (S protein) on the surface of the virus envelope. The carbohydrate of S protein binding to *N*-acetylgyrosamine can inhibit virus' entry into cells [58].

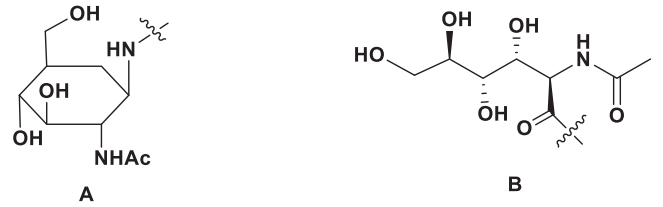


Fig. (8). Structure of A and B.

5.5.3. Anti-herpes Simplex Viruses

The characteristics of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are sporadic relapses caused by lifelong infection and latent neuron infection, with the most common symptoms being skin and mucosal lesions in the oral and genital areas. After reactivation, HSV may manifest as symptomatic or asymptomatic and be excreted into other individuals through mucosal bodily fluids [59]. After HSV infection, glycyrrhizic acid can counteract the changes in adhesion and increased adhesion stress in the body [60]. Glycyrrhizic acid can directly inactivate HSV-1 viral particles, inhibit the production of viral glycoproteins, and inhibit the adsorption of HSV-1 viral particles on T lymphocytes. Glycyrrhizic acid can also induce interferon, activate natural killer (NK) cells, and regulate the expression of H-2 type I and HLA-DR antigens on the cell surface [61]. The flavonoids in the roots of licorice can also effectively resist herpes simplex viruses. Glycyrrhizic acid can terminate latent infection of Kaposi's sarcoma-associated herpesvirus (KSHV) in B lymphocytes and block latent KSHV infection by upregulating the expression of viral cyclin (ORF72) and downregulating the expression of latency-associated nuclear antigen (LANA), thereby selectively inducing KSHV-infected cell death [57].

5.5.4. Anti-COVID-19

The characteristics of the novel coronavirus pneumonia (COVID-19) are strong infectivity, fast transmission, and diverse clinical manifestations. Severe patients often suffered from acute respiratory distress syndrome (ARDS), multiple organ dysfunction, secondary infection, and even death. The pathogenesis of COVID-19 is a cytokine storm, which refers to the abnormal activation of the immune system by certain factors under infection with microorganisms or other intense stimuli, causing it to produce a large number of inflammatory neurotransmitters, leading to systemic inflammatory reactions and multiple organ failure in the body [62]. Glycyrrhizic acid could prevent viral replication by inhibiting the viral main protease Mpro (100 TCID50 of SARS-CoV-2). Glycyrrhizic acid was used to prevent SARS-CoV-2 infection. The mechanisms of glycyrrhizic acid against SARS-CoV-2 were: (1) glycyrrhizic acid prevents virus replication and transmission by interacting with the potential receptor ACE2 of SARS-CoV-2; (2) glycyrrhizic acid directly interacts with spike proteins on the SARS-CoV-2 envelope, thereby blocking binding and fusion events throughout the virus lifecycle; (3) glycyrrhizic acid, as a potential envelope protein inhibitor of SARS-CoV-2, disrupts the function and structure of the virus. Glycyrrhizic acid can also exert the therapeutic potential of coronavirus disease (COVID-19) by downregulating pro-inflammatory cytokines, inhibiting ROS accumulation, lowering thrombin, inhibiting high respiratory output, and inducing endogenous interferon [53]. Glycyrrhizic acid can inhibit the replication of SARS-CoV *in vitro* by combining it with Nsp1, thus inhibiting the replication, transcription and translation processes of SARS-CoV-2 virus [63]. Yu *et al*. [64] studied the docking of glycyrrhizic acid (marked as "**ZZY-44**" by the authors in this paper) with SARS-CoV-2 S1, MERS-CoV S1 subunits, and RBD of SARS-CoV-2 (Fig. **9**). The results identified that glycyrrhizic acid targeted with S proteins of SARS-CoV-2, MERS-CoV and SARS-CoV, showed good activity of disrupting the interaction between the RBD of SARS-CoV-2 and ACE2. According to further analysis of docking result, the carboxyl in ring E of glycyrrhizic acid formed two strong hydrogen interactions with Asp405 and Arg408. The carbonyl in ring C of glycyrrhizic acid formed a strong hydrogen interaction with Arg403; while the glycosyl of glycyrrhizic acid formed a strong hydrogen interaction with Tyr453. These results led to the conclusion that glycyrrhizic acid could probably be a multi-target inhibitor and broad-spectrum anti-coronavirus candidate. Then, the cytotoxicity of glycyrrhizic acid on mouse aorta smooth muscle cells (MASMCs) and human bronchial epithelial (16HBE) cells has shown that glycyrrhizic acid showed no toxicity even at high concentrations. Based on the docking results, it might be predicted that glycyrrhizic acid would be a highly effective and nontoxic broad-spectrum anti-coronavirus drug candidate, which means that it is essential to carry out the synthesis of glycyrrhizic acid derivatives for the development of anti-coronavirus drugs.

5.6. Anti-tumor

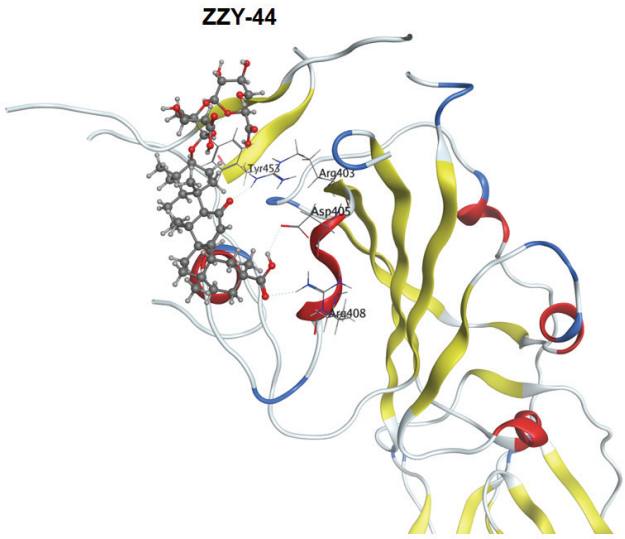
The polysaccharides and flavonoids in licorice mainly exert anti-tumor effects by inducing tumor cell apoptosis, and inhibiting tumor growth and metastasis. Introducing the cinnamic acid group at the C-3 position of glycyrrhetinic acid can enhance its efficacy against tumor cell proliferation. 18α-glycyrrhetinic acid upregulates the expression level of PPAR γ to inhibit the growth of hepatic stellate cells and promote cell apoptosis [65]. Chalcone in licorice can induce cancer cell apoptosis and autophagy, and inhibit the proliferation, migration, and invasion of lung cancer cells. Licorice chalcone A has strong anti-cancer efficacy, which can prevent the efflux of anti-tumor drugs from cancer cells. The derivatives of licorice chalcone A also have significant antitumor effects [66]. Osteosarcoma is a common bone malignancy, and licorice chalcone A exhibits *in vitro* antitumor activity by inhibiting cell viability, stopping cell cycle progression, and inducing apoptosis of osteosarcoma cells. Licochalcone A inhibits the growth of osteosarcoma cells by (1) activating caspase-dependent apoptosis; (2) inhibiting the osteosarcoma cell growth *via* p38-mediated intrinsic apoptotic pathway; (3) decreasing the expression of Bcl-2 and Mcl-1 and increasing the expression of Bax to induce mitochondrial dysfunction in osteosarcoma cells [67]. Glycyrrhizic acid can inhibit the proliferation of melanoma cells by downregulating the expression of anti-apoptotic factor Bcl2, upregulating the expression of pro-inflammatory factor Bax, and enhancing the activity of caspase-9 and caspase-3. Glycyrrhizic acid can also reduce the Treg-specific markers in melanoma cells and reduce the expression of phosphorylated signal transducer and activator of transcription 3 (STAT3), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) to limit the progression of melanoma [68]. In addition, licorice also regulated the tumor microenvironment by directly binding and blocking high mobility group protein B1 (HMGB1) (high mobility group box-1), which is an immunosuppressive cytokine that helps transformed cells to evade the immune system [69].

5.7. Cough Relief

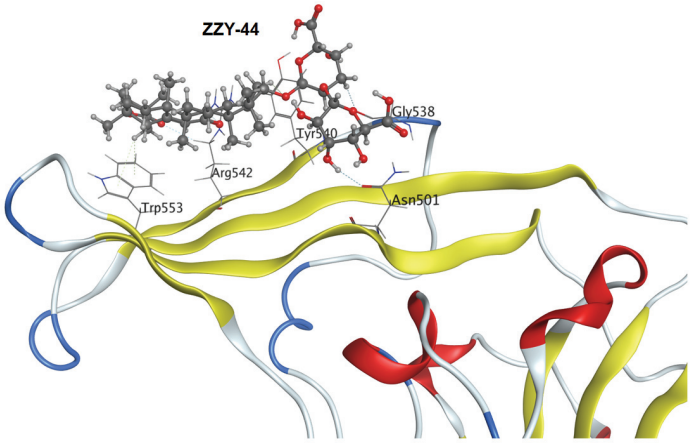
Chen *et al*. found that different concentrations of liquiritin can effectively relieve cough. The high-dose group of liquiritin can effectively prolong the cough latency of mice, and reduce their airway hypersensitivity. The mechanism may reduce the release of the cytokines (TNF-α, IL-6, IL-13, TLR2, TGF-β1, and Ig E) and inflammatory mediators on airway inflammation of mice with induced asthma, thereof, alleviating the airway infection and allergic inflammatory response environment to reduce cough hypersensitivity, reduce stimulation to the cough center, and achieve cough relief [70]. The total flavonoids and total saponins of licorice have varying degrees of phlegm-resolving effects. Glycyrrhetinic acid, licorice flavonoids, and licorice liquid extract administered by gavage also have the cough relieving and phlegm-reducing effects on experimental animals [71]. "Xingsu cough syrup" containing glycyrrhizic acid was used in clinics for the treatment of cough.

5.8. Anti-metamorphosis

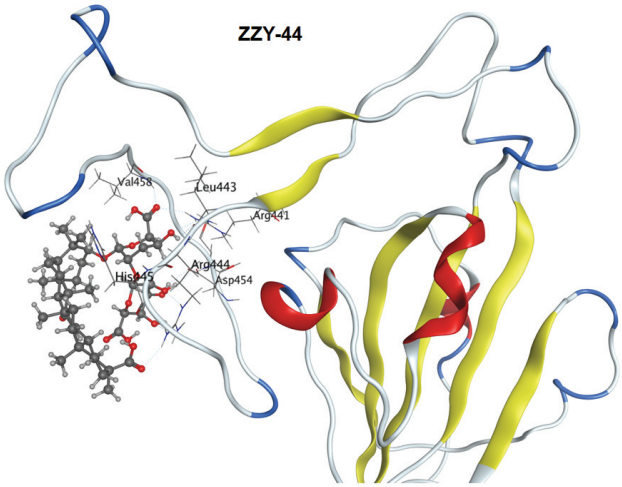
Allergic reactions refer to abnormal specific immune responses in the body, mainly characterized by physiological dysfunction or tissue cell damage when stimulated by certain antigens. Allergic reactions can be classified into four types:



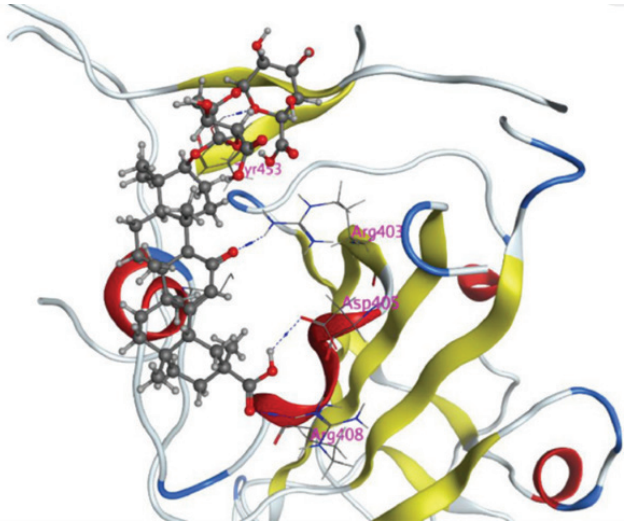
A: Glycyrrhizic acid docking with SARS-CoV-2 S1 subunit.



B: Glycyrrhizic acid docking with MERS-CoV S1 subunit.



C: Glycyrrhizic acid docking with SARS-CoV S1 subunit



D: Glycyrrhizic acid docking with RBD of SARS-CoV-2

Fig. (9). (**A-D**) Docking results of glycyrrhizic acid with SARS-CoV-2 S1, MERS-CoV S1 subunits, and RBD of SARS-CoV-2 [64]. (The higher resolution/color version of these figures is provided by Prof. Jiange Zhang of Shanghai University of Traditional Chinese Medicine). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

(1) immediate allergies, such as urticaria and vascular edema; (2) cytotoxic hypersensitivity, this type of disease includes pemphigus and thrombocytopenic purpura; (3) immune complex type hypersensitivity, such as vasculitis and serum diseases; (4) cell-mediated hypersensitivity, such as eczema and viral hepatitis. Licorice and its active ingredients have good application in allergic skin diseases. 18β-glycyrrhizic acid glycoside can inhibit the production of inflammatory cytokines (IL-2, IL-4, IL-5) and interferon by peripheral blood lymphocytes γ. It can also inhibit the differentiation of initial T cells into Th1, Th2, and Th17 cells, to reduce their related cytokine synthesis. Glycyrrhizic acid glycoside has been widely used for the treatment of chronic urticaria [72]. Glycyrrhizic acid and glycyrrhetinic acid have similar chemical structures to glucocorticoids, they can act not only as partial antagonists of glucocorticoid receptors but also as the metabolic inhibitors of glucocorticoids, to combat the number of glucocorticoid receptors downregulated by stress. Glycyrrhetinic acid combined with intravenous infusion could improve the efficiency of treating eczematous skin diseases [73].

5.9. Other Biological Activities

Licorice flavonoids can also effectively remove melasma from the face. Licorice enhances the immunity of poultry and prevents viral diseases by regulating humoral and cell-mediated immune responses. Licorice can alleviate the hunger of patients with diabetes. Licorice has the potential to improve renal function by reducing iron death and regulating VEGF/Akt/ERK pathway, therefore it is used for the treatment of diabetes and nephropathy [74]. Licorive chalcone A,

as a PTP1B inhibitor, can enhance the cognitive activity through activating the BDNF TrkB pathway, and inhibit microglial activation, and the key enzyme c-Jun *N*-terminal kinase 1 involved in tau phosphorylation, thereby alleviating neuroinflammation and regulating brain insulin receptors that play a role in cognitive processes. Thus, it was used for the treatment of elderly dementia patients [75]. Licorice can block the activity of PfLDH, induce oxidative stress, and promote mitochondrial cell apoptosis in parasites by interacting with NADH binding sites. Lack of estrogen can lead to osteoporosis and osteoarthritis, and the extract of *Glycyrrhiza glabra* L. exerts protective activity against osteoporosis mediated by estrogen receptors (ER). Transthyroxine protein (TTR) amyloid fibrils are associated with familial amyloid cardiomyopathy and amyloid polyneuropathy. Glycyrrhizic acid can stabilize dimer-dimer interface of TTR and inhibit TTR fibrosis through interacting with TTR by forming hydrogen bonds with Lys15 and form CH - π bonds with Ala108 [76]. GL also has a protective effect on the brain tissue in cases of comprehensive cerebral ischemia, cerebral hemorrhage induced brain injury, and focal ischemia. Licorice can inhibit the fat production by inhibiting the activity of lipoprotein lipase, glucose uptake, PGE2 activity, and energy metabolism. The flavonoids in licorice can resist ultraviolet radiation, reduce skin damage, prevent melanin production, and make the skin white and radiant.

CONCLUSION AND FUTURE DEVELOPMENT DIRECTION

Licorice is rich in different kinds of compounds (such as flavonoids, flavone, chalcone, polysaccharides, triterpenoids, alkaloids, organic acid and amino acid.) with a wide spectrum of biological activities (such as anti-inflammatory, antibacterial, antioxidant, antiviral, anti-tumor, cough relief, anti-metamorphosis *etc*.). Some compounds from licorice have been used in the fields of medicines (For example sodium glycyrrhetinic acid was used in the clinic for the treatment of duodenal ulcer), food additives, cosmetics, *etc*. However, flavonoids, triterpenes, and polysaccharides in licorice have anti-inflammatory and antibacterial activities. Adding different amounts of licorice extract to livestock feed has good effects on the livestock. So, adding licorice extract to animal feed as a substitute for antibiotics will be a future research hotspot. In addition, it is necessary to discover more new structural compounds from licorice for the development of new drugs.

Glycyrrhizic acid and glycyrrhetinic acid are the potential lead compounds for the development of anticancer, antiviral, anti-inflammatory, and antibacterial drugs. Although many derivatives of glycyrrhizic acid and glycyrrhetinic acid have been synthesized, more derivatives of glycyrrhizic acid and glycyrrhetinic acid should be designed and synthesized according to the targets for development of drugs. In addition, licorice chalcone A is also a good lead compound for the development of anticancer agents; its derivatives should be designed and synthesized.

Nevertheless, there is little research on the chemical components of the licorice flowers and seeds, and much work should be focused on the isolation and confirmation of new compounds from the licorice flowers and seeds in the future. Now, our research group is taking the lead in carrying out the isolation of new compounds from the licorice flowers and seeds for the development of new drug candidates or new drugs.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Le Li was involved in writing the paper. Jianping Yong, and Canzhong Lu were involved in the study concept or design. Danian Tian was involved in data collection. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

16HBE	=	Human Bronchial Epithelial
18β-GTA	=	18β-Glycyrrhetinic Acid
ARDS	=	Acute Respiratory Distress Syndrome
BLM	=	Bleomycin
CCL5	=	Chemokine (C-C Motif) Ligand 5
COVID-19	=	Coronavirus Pneumonia
COX-2	=	Cyclooxygenase-2
CXCL10	=	Chemokine (C-X-C motif) Ligand 10
DTM	=	5-(1,1-Dimethylallyl)-3,4,4'-trihydroxy-2-methoxychalcore
ER	=	Estrogen Receptors
Gal	=	Galactose Residues
GalA	=	Galacturonic Acid Residues
GL	=	Glycyrrhizic Acid
Glu	=	Glucose Residues
GluA	=	Glucuronic Acid Residues
GPS-1	=	Licorice Polysaccharide
GTA	=	Glycyrrhetinic Acid
HEX	=	β-aminohexosidase
HMGB1	=	High Mobility Group Protein B1
HSV-1	=	Herpes Simplex Virus Type 1
HSV-2	=	Herpes Simplex Virus Type 2
IgE	=	Immunoglobulin E
IL-6	=	Interleukin-6
IPF	=	Idiopathic Pulmonary Fibrosis
MASMCs	=	Mouse Aorta Smooth Muscle Cells
MCs	=	Mast Cells
MDA	=	Malondialdehyde
MMPs	=	Matrix Metalloproteinases
NK	=	Natural KILLER

Nrf2	=	Nuclear FACTOR-E2
PCA	=	Passive CUTANEOUS aNaphylaxis
PGE2	=	Prostaglandin E2
RBL	=	Rat Basophilic Leukemia Cells
Rha	=	Rhamnose Residues
ROS	=	Reactive Oxygen Species
SARS-CoV	=	Severe Acute Respiratory Syndrome Coronavirus
SCFA	=	Short-chain Fatty Acid
STAT3	=	Signal Transducer and Activator of Transcription 3
Th	=	Regulating T Helper
TTR	=	Transthyroxine Protein
TY501	=	Deoxyglycychloxazole
UC	=	Ulcerative Colitis
Xyl	=	Xylose Residues

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was financially supported by key research and development project of Ningxia Hui Autonomous Region (2023BEG03031); Science and Technology Planning Program of Xiamen, China (2022CXY0702; 2023CXY0701).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We are very thankful to Prof. Jiange Zhang of the Shanghai University of Traditional Chinese Medicine for providing us a higher resolution/colour version of the pictures in Fig. (**9**).

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