Acupuncture and Herbal Medicine

Licorice: comprehensive review of its chemical composition, pharmacodynamics, and medicinal value

Lingling Dang[1], Yajing Jin[1], Ye Yuan[1], Rui Shao[2,*], Yu Wang[1,*]

[1]School of Integrative Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China; [2]State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

Abstract

Licorice, a perennial herb of Leguminosa, is one of the oldest and most widely used herbal medicines worldwide. Its distinct sweet flavor and rich medicinal value make it an integral component of traditional Chinese medicine (TCM) formulations, which continue to be widely employed. The main chemical constituents of licorice include triterpenoid saponins, flavonoids, and polysaccharides. Experimental and clinical studies have demonstrated that various extracts and pure compounds derived from licorice exhibit a wide range of pharmacological properties including anti-inflammatory, antioxidant, antimicrobial, antiviral, antitumor, immune-regulatory, and neuroprotective activities. The bioactive constituents of licorice offer therapeutic benefits for cardiovascular and cerebrovascular diseases, diabetes mellitus, and liver disorders. This comprehensive review discusses the primary chemical constituents of licorice and their pharmacological activities, describes *in vivo* and *in vitro* models employed for studying licorice, and its potential targets and mechanisms of action. Furthermore, we discuss the toxicological profile, side effects, dosage recommendations, and clinical applications of licorice. This review aims to establish a foundation for further research on the safe and effective utilization of licorice while facilitating an in-depth exploration of its properties and fostering the development of novel therapeutic agents.

Keywords: Active ingredients, Clinical application, Licorice, Pharmacological activity

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Introduction

Licorice, a perennial herb in the Leguminosae family, originates from the dried roots and rhizomes of *Glycyrrhiza uralensis Fisch*., *Glycyrrhiza glabra L*., and *Glycyrrhiza inflata Bat*., and is the same source for medicine and food[1]. The main licorice production areas in China are located in Shanxi, Gansu, Inner Mongolia, Ningxia, and Xinjiang. The first three regions have long been regarded as authentic licorice production areas in China since ancient times[2]. Licorice is also widely distributed in Central Asian and European countries such as Spain, Persia, India, Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, and Russia[3,4].

Since ancient times, licorice has been prized globally for its rich medicinal value and unique, sweet taste. The use of licorice as a tonic has been rooted in traditional Chinese medicine (TCM) for millennia, making it an essential and frequently prescribed clinical herb. Remarkably, approximately 60% of Chinese medicine prescriptions incorporate this indispensable ingredient[5]. Licorice was first published in the "Divine Farmer's Classic of Materia Medica," which classified it as a superior herb. Its roots and rhizomes have the effects of tonifying *qi*, detoxifying, relieving pain, strengthening the spleen and stomach, relieving tussis, and promoting expectoration; they are widely used in TCM and are an indispensable part of TCM formulations[2,6]. With the advancement of modern science and technology, hundreds of compounds have been isolated from licorice, including triterpenoid saponins, flavonoids, polysaccharides, coumarins, amino acids, and alkaloids, which have been shown to exert a wide range of pharmacological effects, including anti-inflammatory, antioxidant, antiviral, antitumor, hepatoprotective, and neuroprotective effects[7–9]. The increasing potential applications of licorice in modern pharmaceutical and other industries necessitate a deeper understanding of its active ingredients and mechanisms.

This review comprehensively examines the primary chemical constituents and pharmacological properties of licorice, explores its clinical relevance and potential

*Corresponding author. Rui Shao, E-mail: rizycarrot@tjutcm.edu.cn; Yu Wang, E-mail: wangyu@tjutcm.edu.cn.

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significance, evaluates regulatory oversight and safety considerations, addresses existing challenges, highlights future research directions, and explores the potential of licorice to promote its sustainable utilization and development across diverse fields.

Main chemical constituents of licorice

Triterpenoid saponins

Triterpenoids is a class of 30 carbon atoms polymerized into six isoprene units (C_5H_8) and are structurally diverse. Free triterpenoids are almost insoluble or insoluble in water. In contrast, triterpenoid glycosides are mostly soluble in water, and their aqueous solution can produce a large number of persistent soap-like bubbles after shaking; thus, they are known as triterpenoid saponins[10]. Triterpenoid saponins are the main active components of licorice, and more than 60 triterpenoid saponin compounds have been isolated from licorice[11]. The most abundant compound is glycyrrhizic acid, also known as glycyrrhizin, which is the main source of sweetness in licorice. Glycyrrhizic acid is an oleanolane-type pentacyclic triterpenoid that exists mostly in the form of water-soluble potassium or calcium salts[7]. Studies have found that glycyrrhizic acid has a variety of pharmacological properties, including anti-inflammatory, antiviral, antitumor, antioxidant, and anti-allergic activities that contribute to the recovery and protection of the alimentary, respiratory, nervous, endocrine, and cardiovascular systems. In the human body, glycyrrhizic acid is broken down into glycyrrhizinic acid by intestinal bacteria, which possesses various pharmacological activities and has been widely researched and used for the treatment of various diseases[12,13].

Flavonoids

Flavonoids are derivatives of benzopyran, referring to the two benzene rings (A ring and B ring) connected to each other through three-carbon atoms. Flavonoids differ according to the degree of oxidation of the central three-carbon chain. The location of the B ring connection, as well as whether the three-carbon chain forms a ring structure, categorizes the chemicals as flavonoids, isoflavonoids, flavonoids, dihydroflavonoids, dihydroisoflavonoids, chalcones, dihydrochalcones, etc. To date, more than 300 flavonoids have been isolated and identified from licorice in China and elsewhere, of which more than 150 have been given structures and names, with dihydroflavonoids and chalcones being the main types[14]. Licorice varieties also differ in species specificity and content of certain chemical constituents. Flavonoids of *Glycyrrhiza glabra L.* include hispaglabridinA, isoliquiritigenin (ISL), and glabridin, etc, of which glabridin is a species-specific hallmark constituent[15,16]. Flavonoids in *Glycyrrhiza inflata Bat.* include licochalcone A, liquiritigenin, ISL, and Echinatin, etc, licochalcone A is a species-specific component of *Glycyrrhiza inflata Bat*[17]. Studies have shown that the flavonoid components of licorice have significant antiviral, antioxidant, antitumor, and antidiabetic properties[18–20].

Polysaccharides

Polysaccharides are found in plants, microorganisms, algae, and animals and are biological macromolecules that are widely distributed in nature[21]. Glycyrrhiza polysaccharides (GPS) are natural polysaccharides extracted from licorice. Their structure is complex, and they are mainly polymers composed of many monosaccharides connected by glycosidic bonds. These monosaccharides typically include mannose, galactose, rhamnose, glucose, and arabinose. Among them, glucose accounts for a relatively high proportion and is more important[22]. Studies have shown that licorice polysaccharides have antitumor, anti-inflammatory, antibacterial, antioxidant, and immunomodulatory effects[23,24].

Other chemicals

In addition to the above chemical composition, licorice contains a variety of fatty acids, amino acids, alkaloids, volatile oils, and coumarin compounds, as well as other trace elements and minerals such as magnesium, calcium, and potassium[25,26]. According to previous studies, coumarin-like active ingredients are mainly found in *Glycyrrhiza uralensis Fisch.*, and the basic parent nucleus is benzo-α-pyrone, which is typically characterized by substitution only on one side of the benzene ring[27,28]. Licorice contains a variety of compounds, and Table 1 demonstrates the basic information of some of the compounds of licorice. Figure 1 summarizes the chemical structures of the most important compounds in Licorice.

Extraction and separation of substances

Licorice mainly contains saponins, flavonoids, and polysaccharides; glycyrrhizic acid, glycyrrhetinic acid, and other saponins; liquiritigenin and liquiritin and other flavonoids as the main active ingredients, which are mainly extracted by solvent extraction, ultrasound-assisted extraction, supercritical carbon dioxide extraction, microwave-assisted extraction, enzyme-assisted extraction, and other methods[25,29,30]. The more widely used is the solvent extraction method, which is based on the principle of "similar solubility." The selection of appropriate solvents, such as ethanol, methanol, acetone, water, and other polar organic solvents induce leaching of chemical components from the raw material. Although the solvent extraction method is lengthy, requires a high extraction temperature, and specific solvent dosages and has other shortcomings, the required equipment is simple, easy to operate, and the extraction rate is high. At present, it is still the main method for the industrial production of licorice compounds. Other methods for extracting licorice compounds are polyamide column chromatography, the macroporous resin method, high-performance liquid chromatography, thin-layer chromatography, and column chromatography[31–33]. However, most of the components are isolated individually from licorice compounds at present, and the isolation of all the components is the focus of future research. Exploring efficient isolation methods suitable for large-scale industrial applications is also one of the key objectives of future research.

Table 1

Information on the chemical composition of licorice

Number	Classification	Compound	Molecular formula	MW	CAS
1	Triterpenoids	Glycyrrhetinic acid	$C_{30}H_{46}O_4$	470.69	471-53-4
2		Glycyrrhizic acid	$C_{42}H_{62}O_{16}$	822.94	1405-86-3
3		18β-Glycyrrhetinic acid	$C_{30}H_{46}O_4$	470.69	471-53-4
4		18β-Glycyrrhizic acid	$C_{42}H_{62}O_{16}$	822.94	1405-86-3
5		18α-Glycyrrhizic acid	$C_{42}H_{62}O_{16}$	822.93	83896-44-0
6		18α-Glycyrrhetinic acid	$C_{30}H_{46}O_4$	470.68	1449-05-4
7		Uralsaponin C	$C_{42}H_{64}O_{16}$	824.95	1262326-46-4
8		Licorice saponin G2	$C_{42}H_{62}O_{17}$	838.93	118441-84-2
9		Licoricesaponin E2	$C_{42}H_{60}O_{16}$	820.9162	119417-96-8
10		24-Hydroxy-licorice-saponin A3	$C_{48}H_{72}O_{22}$	1,001.07	1262326-47-5
11		Glycyrrhetic acid 3-O-β-D-glucuronide	$C_{36}H_{54}O_{10}$	646.81	34096-83-8
12		Licoricesaponin A3	$C_{48}H_{72}O_{21}$	985.07	118325-22-7
13		Licorice glycoside C2	$C_{36}H_{38}O_{16}$	726.68	202657-55-4
14		22-Beta-Acetoxyglycyrrhizin	$C_{44}H_{64}O_{18}$	880.97	938042-17-2
15		Uralsaponin D	$C_{42}H_{58}O_{18}$	850.899	1262489-44-0
16	Flavonoids	Liquiritin	$C_{21}H_{22}O_9$	418.4	551-15-5
17		Isoliquiritin	$C_{21}H_{22}O_9$	418.39	5041-81-6
18		Liquiritigenin	$C_{15}H_{12}O_4$	256.25	578-86-9
19		Isoliquiritigenin	$C_{15}H_{12}O_4$	256.25	961-29-5
20		Licoflavonol	$C_{20}H_{18}O_6$	354.35	60197-60-6
21		Isolicoflavonol	$C_{20}H_{18}O_6$	354.35	94805-83-1
22		Echinatin	$C_{16}H_{14}O_4$	270.28	34221-41-5
23		Licochalcone A	$C_{21}H_{22}O_4$	338.4	58749-22-7
24		Licochalcone B	$C_{16}H_{14}O_5$	286.28	58749-23-8
25		Licochalcone C	$C_{21}H_{22}O_4$	338.4	144506-14-9
26		Licochalcone D	$C_{21}H_{22}O_5$	354.4	144506-15-0
27		Licochalcone E	$C_{21}H_{22}O_4$	338.4	864232-34-8
28		Licoricone	$C_{22}H_{22}O_6$	382.41	51847-92-8
29		Glabridin	$C_{20}H_{20}O_4$	324.37	59870-68-7
30		Glabrene	$C_{20}H_{18}O_4$	322.35	60008-03-9
31		Glabranin	$C_{20}H_{20}O_4$	324.37	41983-91-9
32		Quercetin	$C_{15}H_{10}O_7$	302.24	117-39-5
33		Formononetin	$C_{16}H_{12}O_4$	268.26	485-72-3
34		Liquiritin apioside	$C_{26}H_{30}O_{13}$	550.51	199796-12-8
35		Glabrol	$C_{25}H_{28}O_4$	392.49	59870-65-4
36		Neoliquiritin	$C_{21}H_{22}O_9$	418.39	5088-75-5
37		Neoisoliquiritin	$C_{21}H_{22}O_9$	418.4	7014-39-3
38		Licuraside	$C_{26}H_{30}O_{13}$	550.51	29913-71-1
39		3-Hydroxyglabrol	$C_{25}H_{28}O_5$	408.49	74148-41-7
40		Licoricidin	$C_{26}H_{32}O_5$	424.53	30508-27-1
41		Hispaglabridin A	$C_{25}H_{28}O_4$	392.49	68978-03-0
42		Licoflavone A	$C_{20}H_{18}O_4$	322.35	61153-77-3
43		Licoflavone B	$C_{25}H_{26}O_4$	390.47	91433-17-9
44		Licoflavonol	$C_{20}H_{18}O_6$	354.35	60197-60-6
45		Isolicoflavonol	$C_{20}H_{18}O_6$	354.35	94805-83-1

(*Continued*)

Table 1

(Continued)

Number	Classification	Compound	Molecular formula	MW	CAS
46		Licoisoflavanone	$C_{20}H_{18}O_6$	354.35	66067-26-3
47		Glycyrrhisoflavone	$C_{20}H_{18}O_6$	354.35	116709-70-7
48		Semilicoisoflavone B	$C_{20}H_{16}O_6$	352.34	129280-33-7
49		Glabrone	$C_{20}H_{16}O_5$	336.34	60008-02-8
50		Isoangustone A	$C_{25}H_{26}O_6$	422.47	129280-34-8
51		Glycyrol	$C_{21}H_{18}O_6$	366.36	23013-84-5
52		Glycyrin	$C_{22}H_{22}O_6$	382.41	66056-18-6
53		7,4'-Dihydroxyflavone	$C_{15}H_{10}O_4$	254.24	2196-14-7
54		4'-Hydroxychalcone	$C_{15}H_{12}O_2$	224.25	2657-25-2
55		Glabranine	$C_{20}H_{20}O_4$	324.37	41983-91-9
56		Isoliquiritin apioside	$C_{26}H_{30}O_{13}$	550.51	120926-46-7
57	Coumarins	Licopyranocoumarin	$C_{21}H_{20}O_7$	384.38	117038-80-9
58		Glycycoumarin	$C_{21}H_{20}O_6$	368.38	94805-82-0
59		Glabrocoumarin	/	/	/
60		Licocoumarin A	$C_{25}H_{26}O_5$	406.471	/

Pharmacological properties

Anti-inflammatory activity

Inflammation is the first line of physiological defense in biological systems and prevents the damaging effects of harmful stimuli such as pathogens and poisons. Macrophages can be activated by lipopolysaccharide (LPS), and their activation in turn increases phosphatidylinositol-3-kinase (PI3K) and nuclear factor-kB (NF-κB) expression, which leads to the production of inflammatory mediators such as reactive oxygen species (ROS), nitric oxide (NO), prostaglandins (PG), cytokines, and tumor necrosis factor-α (TNF-α) and promotes inflammatory responses. Wang et al.[34] found that in a LPS-induced macrophage inflammation model, glycyrrhizic acid and 18β glycyrrhetinic acid (18βGA) significantly reduced the protein levels of inducible nitric oxide synthase (iNOS) and cyclooxygenas-2 (COX-2), inhibited NF-κB activation and expression of PI3K p110δ and p110γ isoforms, and exerted anti-inflammatory effects

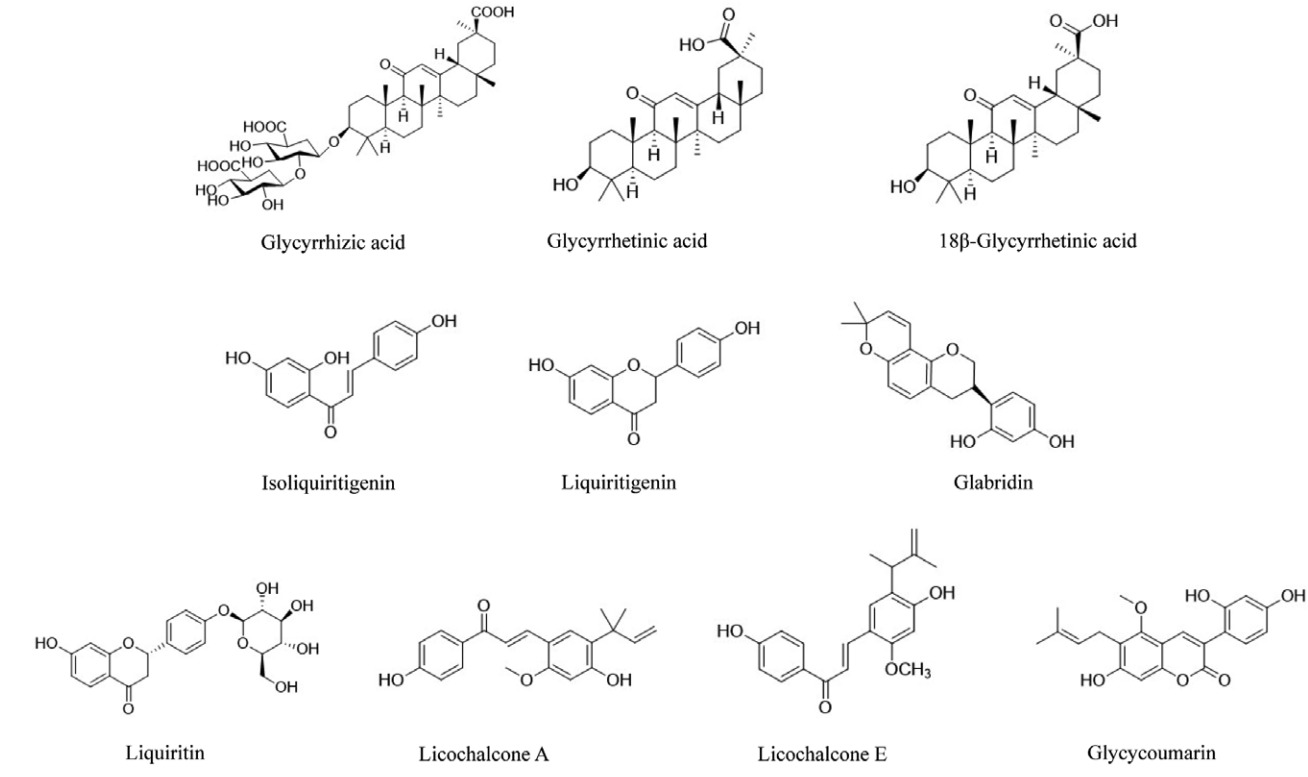

Figure 1. Chemical structures of the main components of licorice.

by reducing TNF-α, interleukin (IL)-6, and IL-1β production and inhibiting the expression of pro-inflammatory genes in a dose-dependent manner. Sepsis is a systemic inflammatory condition in which various inflammatory mediators and enzymes are involved in damage to the body. Zhao et al.[35] demonstrated the anti-inflammatory effect of glycyrrhizic acid by modulating inflammatory mediators and proteins such as TNF-α, MCP-1, intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in septic rats *in vivo* and in LPS-induced HBZY-1 cells *in vitro*. ISL is a flavonoid extracted from licorice that possesses a variety of biological activities, such as anti-inflammatory, antitumor, and antioxidant activities. Sun et al.[36] found that ISL inhibited IL-1β secretion and activation of gasdermin D (GSDMD) by suppressing *Mycobacterium tuberculosis* (Mtb) infection-induced activation of NLPR3 inflammatory vesicles. In addition, ISL has been shown to have favorable inhibitory effects on inflammatory factors such as TNF-α, IL-6, iNOS, and COX2. ISL exerts its anti-inflammatory effects by inhibiting the activation of Notch1/NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways. Wei et al.[37] used different concentrations of GPS to study its effect on the inflammatory response in mice with LPS-induced acute colitis. Expression levels of inflammatory factors, such as TNF-α, IL-1β, and IL-6, in the serum and colonic tissues were significantly decreased after treatment with GPS. In addition, GPS was effective in preventing LPS-induced acute colitis and exerted a beneficial effect on the health of the intestinal tract.

Anti-oxidant activity

Haleagrahara et al.[38] found that different doses of glycyrrhizic acid significantly increased isoproterenol (ISO)-induced total superoxide dismutase (SOD) and total glutathione (GSH) expression and decreased myocardial lipid hydroperoxide (LPO) and 8-isoprostane (IP) levels in rats. These antioxidant effects of glycyrrhizic acid encouraged maintenance and improved the proliferative potential of neural stem cells in the subventricular zone of adult mice. GA is the aglycone of glycyrrhizic acid, and a study by Agarwal et al.[39] demonstrated that glycyrrhizic acid was able to attenuate oxidative stress damage induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse skin. Licorice flavonoids also exhibit significant antioxidant activity[40,41]. Zeng et al.[42] investigated the protective effect of licorice flavonoids against kainate (KA)-induced seizures in mice and found that treatment with licorice flavonoids after seizures reduced KA-induced SOD activity and malondialdehyde (MDA) content on the seventh as well as 28th day, indicating that licorice flavonoids have a protective effect against epilepsy-induced neuronal cell death and cognitive deficits, probably through their antioxidant effects. Hong et al.[43] used Kunming mice as a high-fat diet model, and GPS significantly increased immune and antioxidant activities and reduced oxidative stress in these mice in a dose-dependent manner. In addition, licochalcones B and D in licorice show strong scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals and inhibit microsomal lipid peroxidation[44,45].

Antimicrobial activity

Deoxynivalenol (DON), a toxic metabolite produced mainly by *Fusarium graminearum* and *F. culmorum*, is commonly found in contaminated grains, food, and animal feed and poses a serious threat to animal and human health[46]. Studies have shown that the addition of glycyrrhizic acid to pig feed can significantly reduce DON residues in the serum, liver, and feces, improve the growth performance of DON-infected piglets, and reduce intestinal damage caused by DON. Licorice flavonoids, isoflavonoids, and chalcone compounds exhibit good antibacterial activities. It has been shown that glabridin can induce ROS accumulation, loss of mitochondrial membrane potential, and cell membrane disruption by affecting the expression level of phosphatidylserine decarboxylase, which possesses significant bactericidal activity against *Sclerotinia sclerotiorum*[47]. Zhou et al.[48] showed that Licochalcone E had effective antibacterial activity against methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), and Licochalcone E exerted its bacteriostatic effect by decreasing hemolysis of *S. aureus* through reduction of the production of α-toxin.

Anti-viral activity

According to a screening study on the antiviral effects of plant extracts, glycyrrhizic acid, a constituent of licorice root, has significant antiviral activity[49]. Cinatl et al.[50] evaluated the antiviral activity of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of coronaviruses (FFM-1 and FFM-2) from patients with SARS admitted to the Clinical Center of the University of Frankfurt, Germany, and of all the compounds, glycyrrhizic acid was the most active in inhibiting SARS-associated virus replication. Michaelis et al.[51] investigated the effect of glycyrrhizic acid against the highly pathogenic H5N1 influenza A virus *in vitro* and found it effectively reduced the expression of the pro-inflammatory cytokine IL-6 and chemokines C-X-C ligand 10 (CXCL10) and C-C chemokine ligand 5 (CCL5) in H5N1-induced macrophages. In one study, highly biocompatible glycyrrhizic acid carbon dots (Gly-CDs) were prepared using a hydrothermal method. In a model of porcine reproductive and respiratory syndrome virus (PRRSV) infection, Gly-CDs were found to inactivate PRRSV, inhibit its invasion and replication, stimulate the production of interferons in cells, and inhibit ROS generation induced by PRRSV infection, thus exerting a good antiviral effect[52]. GPS also exerted significant pharmacological effects by inhibiting PRRSVs. Yang et al.[53] found that glycyrrhizobium polysaccharides significantly inhibited the invasion and proliferation of PRRSV at early stages of infection in a dose-dependent manner. In addition, GPS also had significant inhibitory effects on pseudorabies virus (PRV) and showed good antiviral effects in the early stage of PRV infection. Its antiviral mechanism is to inhibit the binding and internalization of the virus[54].

Anti-tumor activity

The immunosuppressive tumor microenvironment (TME) is a major barrier to the antitumor response in

melanoma, and studies have shown that the immunosuppressive TME is directly correlated with enhanced activation of the functions of T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Juin et al.[55] found that glycyrrhizic acid could circumvent the antitumor inhibitory function of Tregs and MDSCs by inhibiting pSTAT3, and glycyrrhizic acid not only exerted an anti-proliferative effect on melanoma cells but also significantly limited melanoma tumor progression. Through a series of *in vivo* and *in vitro* experiments, Wang et al.[56] found that 18βGA had a significant therapeutic effect on colorectal cancer and demonstrated, for the first time, that 18βGA may be effective in inhibiting colorectal cancer cell proliferation, invasion, and migration by inhibiting the PI3K and STAT3 signaling pathways. Licorice contains several prenylated flavonoids, including the diprenylated flavonoids lupalbigenin (LPB) and 6,8-diprenylgenistein (DPG). Shao et al.[57] reported for the first time that LPB and DPG isolated and purified from licorice could induce SW480 cell death by promoting autophagy through the protein kinase B (PKB, also known as Akt)/mammalian target of rapamycin (mTOR) signaling pathway, which could provide a basis for clinical drug research on therapeutic anticancer agents against colorectal cancer. Ayeka et al.[58] investigated the tumor growth and immunomodulatory anticancer activities of licorice polysaccharides in CT-26 loaded BALB/c mice, and the results showed that licorice polysaccharides, especially low-molecular-weight licorice polysaccharides, could significantly elevate the levels of IL-2, IL-6, and IL-7 related inflammatory factors and reduce the expression of TNF-α, which inhibited the growth of tumors significantly, increased the indexes of immune organs, and played a significant immunomodulatory role.

Hepatoprotective activity

Glycyrrhizic acid, the main component extracted from licorice root, has been widely reported to have significant hepatoprotective effects[59–61]. A study investigated the therapeutic effect of glycyrrhizic acid on hepatic fibrosis *in vivo* in a CCl4-induced mouse model of liver fibrosis as well as *in vitro* in transforming growth factor-β1 (TGF-β1)-activated human LX-2 cells and a primary hepatic stellate cells (HSCs) fibrosis model. The results showed that glycyrrhizic acid reduced hepatic fibrosis markers such as α-SMA, collagen α1, HA, COL-III, and LN in liver tissues, significantly increased the levels of IFN-γ, p-STAT1, and Smad7 *in vivo* and *in vitro* and decreased the expression level of CUG-binding protein 1 (CUGBP1), demonstrating for the first time that glycyrrhizic acid reduces liver fibrosis and HSC activation *in vivo* and *in vitro* by promoting the CUGBP1-mediated IFN-γ/STAT1/Smad7 signaling pathway. Wang et al.[62] investigated the protective effects of ISL in a mouse model of alcoholic liver disease (ALD) and revealed that ISL dose-dependently attenuated ALD through the miR-23a-3p/PGC-1α axis, thereby promoting fatty acid metabolism and inhibiting the expression of ROS, TNF-α, IL-1β, and IL-6 and exerting a hepatoprotective effect.

Immune-regulatory activity

The immune system is extremely complex and plays an important role in maintaining homeostasis and body health. Raphael and Kuttan[63] investigated the effects of naturally occurring triterpenoids such as glycyrrhizic acid, ursolic acid, oleanolic acid, and nomilin on the immune system using Balb/c mice, and found that these terpene treatments augmented bone marrow cells and α-esterase positive cells in mice, as well as significantly suppressing the delayed-type hypersensitivity reaction (DTH). Furthermore, in glycyrrhizic acid-treated animals, the total number of leukocytes increased to the highest level, and the inhibition of DTH by glycyrrhizic acid was close to 95%. These results provide clear evidence for the immunomodulatory activity of terpenoids such as glycyrrhizic acid, ursolic acid, oleanolic acid, and nomiline[63]. Ma et al.[64] used an ovalbumin (OVA)-induced mouse asthma model and showed that glycyrrhizic acid effectively suppressed the expression levels of inflammatory factors such as IL-4, IL-5, and IL-13, increased the expression level of IFN-γ, regulated the balance of T-helper 1 (Th1)/T-helper 2 (Th2) cytokines, and inhibited eosinophil recruitment and monocyte overproduction, reducing airway inflammation and bronchial hyperresponsiveness. In addition, glycyrrhizic acid effectively increased the number of Tregs, significantly enhancing the immune function of the body and exerting anti-asthmatic effects. Cyclophosphamide (CTX) is an alkylating agent and immunosuppressant that significantly damages the intestinal mucosal structure and decreases immune organ index, immune cells, and cytokine secretion[65]. Song et al.[66] used a model of CTX-induced immunosuppression and intestinal mucosal injury to study the immune function-promoting effects of GPS in mice and its regulatory functions on the intestinal microbiota. The results showed that GPS reversed C-induced intestinal structural damage; increased the number of cuprocytes, $CD4^+$ and $CD8^+$ T lymphocytes, and other immune cells; regulated the balance of Th1/Th2 cytokines; and regulated the structure and metabolites of the intestinal microflora that are involved in the immune response of the organism.

Neuroprotective activity

Akman et al.[67] constructed a model of middle cerebral artery occlusion in rats and intervened with glycyrrhizic acid, which significantly elevated the levels of SOD and NRF1 and decreased MDA levels. Histopathological analysis also showed that glycyrrhizic acid significantly ameliorated brain edema, vacuolization, degeneration, and neuronal damage. Photoglycyrrhizidine is the main active flavonoid in licorice, which improves learning and memory in mice and has various pharmacological effects on the central nervous system. Hasanein[68] investigated the effects of long-term treatment with different concentrations of photoglycodine on cognitive function in diabetic rats. The results showed that photoglycyrrhizidine in the medium- and high-dose groups (25 and 50 mg/kg) improved learning and memory in non-diabetic rats and was effective in reversing the learning and memory deficits induced by streptozotocin (STZ) in diabetic rats.

This benefit stems from the fact that glycyrrhizidine combines multiple effects of antioxidant action, neuronal defense mechanisms, and anticholinesterase activity, making it potentially useful in therapeutic regimens targeting patients with diabetes-associated dementia.

Other activities

Glycycoumarin (GCM) is a representative coumarin compound isolated from licorice that has good bioavailability[69,70]. Zhang et al.[71] evaluated the protective effect of GCM against hepatocyte lipoapoptosis using a palmitate-induced lipoapoptotic cell culture model and an animal model of non-alcoholic steatohepatitis (NASH), which demonstrated the ability of GCM to reactivate impaired autophagy due to lipid metabolism disorders, and the study showed for the first time that GCM efficiently inhibits hepatocyte lipoapoptosis both *in vitro* and *in vivo*. In addition, licorice coumarin analogs have been shown to inhibit tumor growth. In an *in vitro* study, Lu et al.[72] found that glycyrol (GC), a representative coumarin compound in licorice, had a highly potent inhibitory effect on several human non-small cell lung cancer (NSCLC) cell lines and significantly inhibited tumor growth *in vivo*. The mechanism involves the binding of GC to T-lymphokine-activated killer cell-originated protein kinase (TOPK) and the inhibition of its kinase activity, leading to the activation of the apoptotic signaling pathway, thus inhibiting tumor development. Different licorice compounds such as glycyrrhizin flavonoids, glycyrrhizic acid, and their derivatives also exhibit antidiabetic activity. Glycyrrhizic acid and its derivatives are promising candidates for the treatment of type 2 diabetes mellitus and its associated complications[73]. Akutagawa et al.[74] investigated the effects of glycyrrhizic acid on inflammation and blood glucose levels in diabetic mice. *Porphyromonas gulae* and periodontal ligation have been used to model oral inflammation and its effects in diabetes. Topical glycyrrhizic acid inhibited the periodontal and systemic inflammation and reduced the increase in blood glucose levels in a diabetic mouse periodontal disease model *via* the high mobility group box 1 (HMGB1)-receptor for advanced glycation end products (RAGE) axis. KK-Ay mice are animal models that mimic type 2 diabetes in humans. Licorice flavonoid oil (LFO) was found to lower blood glucose levels in these mice, and this hypoglycemic effect was associated with enhanced translocation of GLUT4 from the skeletal muscle to the cell membrane, which promoted glucose uptake and contributed to the lowering of blood glucose. This study suggests that LFO may be a beneficial natural substance that is effective in preventing and ameliorating type 2 diabetes mellitus[75].

In conclusion, the main chemical constituents of licorice, such as glycyrrhizic acid, 18βGA, Glabridin, ISL, Licochalcone A, GPS show significant pharmacological activities (Table 2). Figure 2 illustrates the six major compounds present in *Glycyrrhiza glabrata* and their corresponding pharmacological mechanisms of action.

Relevance and potential significance of licorice in clinical practice

Use in traditional and modern medicine

In China, the medicinal use of licorice has a rich historical background and extensive application. In ancient times, practitioners in China discovered and extensively utilized the medicinal potential of licorice. According to the 2020 edition of the Pharmacopoeia of the People's Republic of China, licorice exhibits various pharmacological actions, including tonifying the spleen qi, clearing heat and toxins, resolving phlegm, alleviating coughs, relieving tension and pain, and harmonizing with other herbal medicines. It is indicated for conditions such as spleen and stomach deficiencies, fatigue, palpitations, dyspnea, productive coughs with abundant sputum, limb hypertonicity, pain, abscesses, swelling, ulcers, and injuries. Additionally, it is used to moderate the harsh properties and toxicity of other herbal medicines[6]. Licorice also possesses a broad spectrum of historical and contemporary applications not only in China but worldwide. Since the 1820s, licorice has been officially recognized as a medicinal substance by the United States Pharmacopoeia. Currently, licorice is included in the pharmacopeias of Europe and Japan. In modern times, the utilization of licorice spans diverse industries, including food manufacturing, medicine and supplements, tobacco, daily chemical products, environmental protection, animal husbandry, and aquaculture[6]. Moreover, ongoing research and development is gradually uncovering the potential of the aerial parts of this plant.

Perspectives for drug development of licorice

The therapeutic potential and prospects for licorice-based drug development are extensive. First, as a natural botanical medicine, licorice possesses mild pharmacological effects and a wide range of applications, making it highly favored by consumers. Demand for licorice in the pharmaceutical market continues to grow, providing entrepreneurs with ample market opportunities. Second, licorice exhibits various pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, antiviral, antitumor, immune-regulatory, and neuroprotective effects. Its anti-inflammatory and antiviral properties make it an important ingredient for the treatment of chronic liver and respiratory diseases[76,77]. Due to their antitumor and immunomodulatory activities, licorice extracts also show potential for the development of cancer immunotherapy or complementary therapeutic agents[55]. In addition, the antioxidant properties make it promising for application on skin conditions, including dermatitis, eczema, itching, and cysts[78]. These active ingredients can serve as lead compounds for the development of novel drugs.

Glycyrrhizic acid has been clinically developed as a therapeutic drug. As the most important marker component in licorice, the development of glycyrrhizic acid preparations has a long history in China, from glycyrrhizic acid tablets to ammonium glycyrrhizinate, diammonium glycyrrhizinate, and magnesium isoglycyrrhizinate. All the above glycyrrhizic acid preparations possess antiviral

Table 2

Main chemical constituents of licorice and their pharmacological activities

Pharmacological activity	Compound	Concentration	Model	Main function	References
Anti-inflammatory activity	Glycyrrhizic acid and 18β-glycyrrhetinic acid	*In vitro*: 10–75 μM	*In vitro*: 1 μg/mL LPS-stimulated RAW 264.7 cells	Suppresses NF-κB through PI3K p110δ and p110γ inhibition, attenuating the generation of NO, PGE2, and ROS	[34]
	Glycyrrhizic acid	*In vivo*: 25, 50 mg/kg *In vitro*: 50, 100 μM	*In vivo*: Sepsis model was established by injection of 5 mg/kg LPS in rats *In vitro*: 1 μg/mL LPS-stimulated HBZY-1 cells	Inhibits activation of NF-κB signaling pathway	[35]
	Isoliquiritigenin	*In vitro*: 5–40 μM	*In vitro*: Mtb H37Ra stimulated RAW 264.7 cells, murine primary peritoneal macrophages	Notch1/NF-κB and MAPK signaling pathways	[36]
	Glycyrrhiza polysaccharides	*In vivo*: 100, 200, 400 mg/kg	*In vivo*: 10 mg/kg LPS-induced acute colitis mouse model	Promotes the growth and reproduction of beneficial bacteria such as Lactobacillus, Bacteroides, and SCFA-producing bacteria; increasing IL-10 levels; and inhibiting TLR4 activation	[37]
Antioxidant activity	Glycyrrhizic acid	*In vivo*: 5, 10, 20 mg/kg	*In vivo*: 85 mg/kg isoproterenol-induced acute myocardial infarction in Sprague-Dawley rats	Decreases lipid hydroperoxides and isoprostanes and to increase SOD and glutathione levels	[38]
	18β-glycyrrhetinic acid	*In vivo*: 1.25, 2.5 mg/animal	*In vivo*: 20 μg DMBA/2.0 μg TPA-mediated oxidative stress and tumor promotion in murine skin	Scavenges free radicals and inhibiting ODC induction	[39]
	Flavonoids extracted from licorice	*In vivo*: 10 mg/kg	*In vivo*: 25 mg/kg KA-induced seizure in mice	Reduces the expression level of SOD and MDA	[42]
	Glycyrrhiza polysaccharide	*In vivo*: 100, 300 mg/kg	*In vivo*: high-fat mice	Protects against immune function dysfunction and oxidative injury through such effects as promotion of spleen lymphocyte proliferation	[43]
Antimicrobial activity	Glycyrrhizic acid	*In vivo*: 400 mg/kg	*In vivo*: 1,040 μg/kg DON-induced intestinal injury model in piglets	Regulates gut microbiota, increases anti-inflammatory function, enhances the stability and integrity of intestinal barrier structure and nutrient transport functions	[46]
	Glabridin	*In vivo*: 50, 100, 200 μg/mL *In vitro*: 500 μg/mL	*In vivo*: against *Sclerotinia sclerotiorum* in leaves of rape *In vitro*: pathogenic fungi	Causes ROS accumulation, the loss of mitochondrial membrane potential, and cell membrane destruction by affecting the expression levels of phosphatidylserine decarboxylase	[47]
	Licochalcone E	*In vitro*: 0.25–1,024 μg/mL	*In vitro*: *Staphylococcus aureus*	Licochalcone E inhibits the transcription of agrA.	[48]

(*Continued*)

Table 2
(Continued)

Pharmacological activity	Compound	Concentration	Model	Main function	References
Antiviral activity	Glycyrrhizic acid	*In vitro*: 1,000–4,000 mg/L	*In vitro*: Vero cells	/	[50]
	Glycyrrhizic acid	*In vitro*: 100 μg/mL	*In vitro*: H5N1-induced apoptosis in human monocyte-derived macrophages	Impairs H5N1-induced production of CXCL10, interleukin-6, and CCL5 and inhibits H5N1-induced apoptosis	[51]
	Glycyrrhizic acid	*In vitro*: 0.30 mg/mL	*In vitro*: PK-15, Vero and MARC-145 cells	Inhibition of PRRSV invasion and replication, stimulation of cells to produce interferon, inhibition of ROS production induced by PRRSV infection	[52]
	Glycyrrhiza polysaccharides	*In vitro*: 10, 20, 40 μg/mL	*In vitro*: Marc-145 cells	Reduces the expression of the CD163 and NF-κB p65 genes in cells, inhibits the binding of virus and receptor, reduces the activation of NF-κB, and blocks the nuclear transfer of p65 gene	[53]
	Glycyrrhiza polysaccharide	*In vitro*: 100, 200, 400, 600 μg/mL	*In vitro*: PK-15 cells, Vero cells	Interferes with virus attachment and internalization	[54]
Antitumor activity	Glycyrrhizic acid	*In vivo*: 45 mg/kg *In vitro*: 30 μg/mL	*In vivo*: B16F10 murine models *In vitro*: Murine B16F10 melanoma and human A375 melanoma cells	Inhibits B16F10 cell proliferation by inducing apoptosis and immunomodulation of the TME by STAT3; mediates downregulation of Tregs and MDSCs to restrain the progression of melanoma tumors	[55]
	18β-glycyrrhetinic acid	*In vivo*: 40 mg/kg *In vitro*: 12.5, 25, 50 μM	*In vivo*: LoVo cells implanted subcutaneously in nude mice *In vitro*: LoVo, SW480, SW620, and NCM460 cells	Inhibits colorectal cancer cell proliferation, invasion, and migration probably by suppressing the PI3K and STAT3 signaling pathways	[56]
	LPB 6,8-DPG	*In vitro*: 0–20 μM	*In vitro*: SW480 cells	Induces death of SW480 cells by promoting autophagy, probably through the Akt/mTOR signaling pathway	[57]
	Glycyrrhiza polysaccharides	*In vivo*: 50 mg/kg	*In vivo*: CT-26 tumor bearing BALB/c mice	Activates CD4+ and CD8+ immune cell groups, increases the levels of IL-2, IL-6, and IL-7, and decreases the level of TNF-α	[58]
Hepatoprotective activity	Glycyrrhizic acid	*In vivo*: 20, 40 mg/kg *In vitro*: 2, 4, 8 mg/mL	*In vivo*: CCl_4-induced mouse model of liver fibrosis *in vitro*: TGF-β1-activated human LX-2 cells and primary HSCs	Activates CUGBP1-mediated IFN-γ/STAT1/Smad7 pathway	[59]
	Licorice aqueous extract	*In vivo*: 100, 150, 300 mg/kg	*In vivo*: the CCl_4-induced liver injury in a rat model	Scavenges free radicals, stimulates activities of antioxidant enzymes, and arrests production of inflammatory cytokine	[60]
	Glycyrrhizic acid	*In vivo*: 0.2% GA solution in water (3 mL)	*In vivo*: CCl_4-induced liver injury in rats	Inhibiting hepatocyte apoptosis and hepatic stellate cell activation	[61]
	Isoliquiritigenin	*In vivo*: 10, 20, 40 mg/kg *In vitro*: 5, 10, 20 μM	*In vivo*: Mouse model of alcoholic liver disease *In vitro*: LO2 cells	Promotes lipid metabolism, ROS production, and ameliorates inflammatory response *via* miR-23a 3p/PGC-1α axis dose-dependently	[62]

(*Continued*)

Table 2

(Continued)

Pharmacological activity	Compound	Concentration	Model	Main function	References
Immune-regulatory activity	Glycyrrhizic acid	*In vivo*: 50 μmol/kg	*In vivo*: Balb/c mice	/	[63]
	Glycyrrhizic acid	*In vivo*: 10, 20, 40 mg/kg	*In vivo*: Ovalbumin-induced asthma model in mice	*Via* modulation of Th1/Th2 cytokines and enhancement of CD4 + CD25 + Foxp3 + regulatory T cells	[64]
	Glycyrrhiza polysaccharide	*In vivo*: 100, 200 mg/kg	*In vivo*: CTX-induced immunosuppressed and intestinal mucosal injury in a mouse model	Increases the number of immune cells and cytokine secretion, regulates the mRNA expression levels of immune-related pathways, and adjusts the structure and metabolites of the gut microbiota	[66]
Neuroprotective activity	Glycyrrhizic acid	*In vivo*: 80 mg/kg	*In vivo*: a MCAO model	Elevates SOD and NRF1 expression levels and decreases MDA expression levels	[67]
	Glabridin	*In vivo*: 5, 25, 50 mg/kg	*In vivo*: STZ-induced diabetic rats	Shows antioxidant, neuroprotective, and anticholinesterase properties	[68]
Other activities	Glycycoumarin	*In vivo*: 15 mg/kg *In vitro*: 10–40 μM	*In vivo*: MCD diet-induced mouse model of NASH *In vitro*: PA-induced lipotoxicity	Inhibits hepatocyte lipoapoptosis through activation of autophagy and inhibition of ER stress/GSK-3-mediated mitochondrial pathway	[71]
	Glycyrol	*In vivo*: 20 mg/kg *In vitro*: 5, 7.5, 10 μM	*In vivo*: Mouse xenograft models of human cancer *in vitro*: A549, HCC827, MRC-5, HCC827GR, PC9, and PC9GR10 cells	Binds to the TOPK protein and inhibits its kinase activity, leading to the activation of apoptotic signaling pathways	[72]
	Glycyrrhizic acid	*In vivo*: 1 mL/kg	*In vivo*: High-fat diet diabetic KK/TaJcl mice model	Suppresses periodontal and systemic inflammation and reduce blood glucose levels through the HMGB1-RAGE axis in diabetic mice	[74]
	Liquorice flavonoid oil	*In vivo*: 1.0, 1.5 g/kg	*In vivo*: High-fat diet diabetic KKAy mice model	Activates both the AMPK pathway and Akt pathway in muscles of KK-Ay mice	[75]

Akt: Protein kinase B, PKB; AMPK: Adenosine monophosphate-activated protein kinase; CCl4: Carbon tetrachloride; CCL5: C-C chemokine ligand 5; CUGBP1: CUG-binding protein 1; CXCL10: C-X-C ligand 10; CXTX: Cyclophosphamide; DMBA: 7,12-dimethyl benz(a)anthracene; DON: Deoxynivalenol; DPG: Diprenylgenistein; ER: Endoplasmic reticulum; GSK-3: Glycogen synthase kinase 3; HMGB1: High mobility group box 1; H5N1: Highly pathogenic avian influenza; HSC: Hepatic stellate cells; IFN-γ: Interferon-γ; IL: Interleukin; KA: Kainate; LPB: Lupalbigenin; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MCAO: Middle cerebral artery occlusion; MCD: Methionine-choline-deficient; MDA: Malondialdehyde; MDSC: Myeloid-derived suppressor cell; mRNA: Messenger RNA; mTOR: Mammalian target of rapamycin; NASH: Non-alcoholic steatohepatitis; NF-κB: Nuclear factor-κB; NO: Nitric oxide; NRF1: Homo sapiens nuclear respiratory factor 1; ODC: Ornithine decarboxylase; PA: Palmitate; PGC-1α: Peroxisome proliferative activated receptor-γ coactivator 1 alpha; PGE2: Prostaglandin E2; PI3K: Phosphatidylinositol-3-kinase; PRRSV: Porcine reproductive and respiratory syndrome virus; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; SCFA: Short-chain fatty acids; SOD: Superoxide dismutase; STAT3: Signal transducer and activator of transcription 3; STZ: Streptozotocin; TGF-β1: Transforming growth factor-β1; Th1/Th2: T-helper 1 (Th1)/T-helper 2 (Th2); TLR4: Toll-like receptor 4; TME: Tumor microenvironment; TNF-α: Tumor necrosis factor-α; TOPK: T-lymphokine-activated killer cell-originated protein kinase; TPA: 12-O-tetradecanoylphorbol-13-acetate.

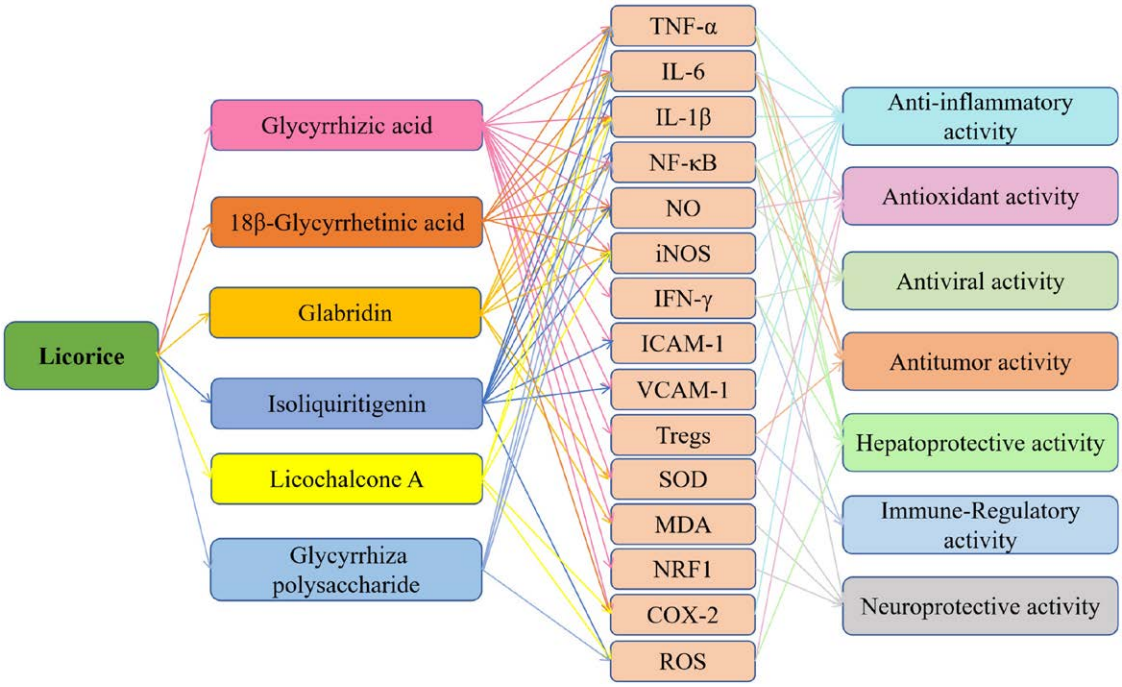

Figure 2. Chemical composition and pharmacological properties of licorice. ICAM-1: Intercellular cell adhesion molecule-1; IFN-γ: Interferon-γ; IL-1β: Interleukin-1β; IL-6: Interleukin-6; iNOS: Inducible nitric oxide synthase; MDA: Malondialdehyde; NF-κB: Nuclear factor-κB; NO: Nitric oxide; NRF1: Homo sapiens nuclear respiratory factor 1; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-α; Tregs: T regulatory cells; VCAM-1: Vascular cell adhesion molecule-1.

and antimicrobial activities[12]. Glycyrrhizic acid has been used to treat chronic hepatitis in Japan for more than 20 years. 18βGA is the main active metabolite of glycyrrhizic acid. The identification of potent anti-hepatitis C drugs has been achieved by making structural modifications to 18βGA[79]. Furthermore, a series of novel fluorinated chalcone derivatives were synthesized using licorice chalcone as the parent nucleus and targeted MDM2-p53, thereby presenting a promising licochalcone derivative-based drug candidate with enhanced efficacy and reduced toxicity for the treatment of cervical cancer[80]. Although these compounds have shown promise in preclinical studies, they have not completed the necessary preclinical and clinical trials to establish their safety and effectiveness, specifically for a particular disease indication in humans. Therefore, any prospective medication derived from licorice necessitates extensive additional research and development before attaining the status of a lead drug. In addition to the pharmaceutical industry, licorice is widely used in the food industry as a natural sweetener and flavor enhancer[81]. In the cosmetics industry, the antioxidant, hyperpigmentation-reducing, and whitening properties of licorice have made it a popular ingredient in a variety of skincare products[80,82,83].

In view of the wide range of biological activities demonstrated by licorice and its broad application prospects, scientific research institutions and related enterprises in China and elsewhere have invested in in-depth research and taken active intellectual property protection measures for the research results obtained. The national patent search system was searched for patent applications in various fields involving licorice and its active ingredients. The data analysis showed that in the past 10 years, there were more than 14,000 patent applications involving licorice, of which more than 9,000 were authorized, related to Chinese veterinary medicine, avian disease prevention and treatment, quality control of TCM, TCM preparation technology, regenerative medicine, biomedical technology, plant extract technology, chemical purification technology, skin care technology, cosmetic technology, health care technology, food technology, planting technology, active composition technology, marine biomedical technology, and other fields. Licorice and its constituents are mostly applied in the form of TCM compositions and their preparations in the fields of TCM technology and TCM compound preparation technology, accounting for approximately 30% of the total number of applications, among which, raw licorice and roasted licorice are mostly involved in the preparation. Licorice contains a variety of active ingredients, and the search revealed that glycyrrhizic acid was the most studied, accounting for 45% of the total, followed by licorice and its extracts, accounting for 21% of the total, and then licorice flavonoids, GA, etc, and other active ingredients were relatively less researched.

With the increasing use of this herb worldwide, cultivation areas dedicated to licorice production have expanded. However, the development and utilization of licorice are subject to certain limitations. For example, cultivating and harvesting licorice requires significant labor and time investment, processing and transportation procedures involve substantial financial resources along with technological expertise, and some regions have depleted their existing reserves of licorice, necessitating exploration for new sources[84]. In conclusion, licorice shows great promise for treatment and drug development. In the future, it is believed that licorice will

play an even more significant role in the advancement of new drugs and clinical applications, as scientific progress deepens our understanding of the properties of this plant.

Regulatory oversight and safety of licorice use

Adverse effects associated with the consumption of licorice

In recent years, several cases of licorice toxicity have been reported due to the high consumption of glycyrrhizic acid, the dominant reactive component in licorice. The most commonly described clinical mechanism of licorice toxicity is linked to its aldosterone-like activity. The predominant pathogenic mechanism associated with licorice toxicity is pseudo-hyperaldosteronism (PsA)[6], characterized by the typical features of arterial hypertension, hypokalemia, and metabolic alkalosis[85]. Although infrequent, arrhythmias, skeletal muscle paralysis, rhabdomyolysis, and impaired consciousness are the fatal manifestations of licorice toxicity[86]. In addition to its effects on PsA, GA was found to affect sexual activity and reproduction in male rats, whereas it elicits a mild inhibition of androgenic hormones in humans[45,84]. In addition to GA, licorice appears to have an estrogenic effect on flavonoids and isoflavonoids. Liquiritigenin, a flavonoid component, exhibits good binding affinity for the bovine uterine estrogen receptor[45], whereas glabridin and glabrene mimic estrogen activity and maintain calcium balance[84]. Moreover, GA has been shown to induce miscarriages and should be avoided in patients taking oral contraceptives, hydrocortisone, and prednisone. In terms of gastrointestinal function, isoliquitigenin, a flavonoid component of licorice, may decrease bowel mobility, independent of cholinergic inhibition or adrenergic and/or nitrergic exacerbation[45]. In addition, the consumption of licorice may potentially contribute to the development of hypertension, hypertensive encephalopathy, and posterior reversible encephalopathy syndrome[87].

Biochemical mechanism of licorice toxicity

Licorice toxicity is mainly triggered by an imbalance in the cortisol and aldosterone pathways, leading to PsA. Under physiological conditions, aldosterone and cortisol compete to activate mineralocorticoid receptors (MRs) in the cortical collecting duct cells of the kidney because of their similar molecular structures and receptor affinities. Aldosterone regulates Na-K exchangers, epithelial Na channels, renal outer medullary K channels, aquaporins, and bicarbonate-chloride antiporters *via* MR activation. *In vitro* studies revealed that both glycyrrhizic acid and GA exhibit inhibitory effects on 11β-hydroxysteroid dehydrogenase-type 2 (11β-HSD2), which leads to an excessive production of mineralocorticoids[87], with the potency of GA inhibition being approximately 200 times greater than that of glycyrrhizic acid[13]. Within the renal glomeruli, this event elicits a pronounced aldosterone-like response, resulting in enhanced Na reabsorption and K excretion[85,88,89]. In adults, the expression of 11β-HSD2 is also observed in cardiac tissues, neural structures, and vascular systems[88]. When mineralocorticoids accumulate to a certain extent, they can bind to MRs, resulting in enhanced sodium retention and potassium excretion, leading to decreased blood potassium levels and increased blood volume. Disruption of this mechanism may result in a range of adverse reactions including fatigue, thirst, irritability, excessive urination, edema, hypertension, hypokalemia, and alkalosis. However, preclinical evidence suggests that glycyrrhizic acid or GA may potentially restrict hepatic degradation of aldosterone by inhibiting 5β-reductase and 3β-hydroxysteroid dehydrogenase, thereby preserving systemic hormone levels[90].

Suggested dosage and limits

The toxicity threshold of glycyrrhizic acid as defined by the World Health Organization is 100 mg/day. However, significant variability exists based on factors such as age, sex, concomitant medication use, and comorbidities (eg, essential arterial hypertension, chronic renal failure, and hepatic failure)[13]. After oral intake, licorice is converted into glycyrrhizic acid in the gut, which is hydrolyzed to GA by the β-glucuronidase in gut microbiota. According to the Food and Drug Administration, smoking accounts for approximately 90% of consumption, whereas the dietary intake of GA is negligible[91]. However, the potential for surpassing the safety threshold and experiencing signs or symptoms of toxicity can be associated with excessive daily consumption of readily available products (eg, flavored candies or beverages). In this regard, de-glycyrrhizinated licorice was recently developed to mitigate licorice toxicity as a possible adverse effect[92].

Conclusion and perspective

Licorice, a valuable resource in TCM, not only possesses a rich history and extensive applications within China but also garners significant global attention. Its unique pharmacological activity and diverse chemical composition make it an essential raw material in various fields, such as medicine, food, and cosmetics. The pharmacological effects of licorice include anti-inflammatory, antioxidant, antiviral, and antitumor effects. This review summarizes the abundant research resources and promising directions for drug development of licorice in modern medicine.

However, licorice research faces challenges in understanding the complex composition and interactions among its numerous constituents, ensuring quality control owing to uncertain factors in planting and harvesting, determining consistent dosage and administration methods across studies, addressing potential adverse effects from prolonged usage, and elucidating its mechanism of action and structure-activity relationship for developing novel therapeutics. Future research should focus on investigating the pharmacological mechanisms of licorice, improving quality control and standardization, exploring new drug development possibilities, expanding clinical research, enhancing international collaboration, and prioritizing conservation efforts.

In conclusion, the research value and potential for the development of licorice as a TCM with broad applications and substantial pharmacological activities cannot be overlooked. Looking ahead, we anticipate further breakthroughs and advancements in the research and application of licorice to significantly enhance human health and quality of life.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Lingling Dang, Rui Shao wrote the manuscript. Yajing Jin, Ye Yuan contributed to performing the literature search. Yu Wang and Rui Shao revised the manuscript. All the authors have read and approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

All data generated or analyzed during this study are included in this published articles.

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