The Pharmacological Activities of Licorice

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- licorice
- Leguminosae
- pharmacological activities

Abstract

Licorice is one of the oldest and most frequently used herbs in traditional Chinese medicine. It contains more than 20 triterpenoids and 300 flavonoids. In recent years, a lot of studies have reported that the active compounds isolated from licorice possess antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, and several other activities that contribute to the recovery and protection of the nervous, alimentary, respiratory, endocrine, and cardiovascular systems. In this paper, nine different pharmacological activities of licorice are summarized. The active compounds responsible for these pharmacological activities, the molecular mechanisms, and *in vivo* and *in vitro* studies are listed in detail. Furthermore, the clinical therapeutics and toxicity studies of licorice are also discussed. We hope this work can provide a basis for further studies concerning with the safe and effective use of licorice.

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Bibliography
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Abbreviations

ABCA1:	ATP-binding cassette transporter A1
ABTS:	2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate) radical dot+
BACE1:	beta-site amyloid precursor protein cleaving enzyme 1
CDK:	cyclin-dependent kinase
COX:	cyclooxygenase
DGC:	dehydroglyasperin C
DHV:	duck hepatitis virus
11-DOGA:	11-deoxyglycyrrhetinic acid
DPPH:	1,1-diphenyl-2-picrylhydrazyl
EC:	echinatin
ERK:	extracellular signal-regulated kinase
FAK:	focal adhesion kinase
GA:	glycyrrhetinic acid
GC:	glycyrrhizin
GLD:	glabridin
GP:	glycyrrhiza polysaccharides
GSH:	glutathione
HCV:	hepatitis C virus
HMGB1:	high-mobility group box 1
HMGP:	high-mobility group protein
HSV:	herpes simplex virus
IAV:	influenza A virus
IFN:	interferon
iNOS:	inducible nitric oxide synthase
ISL:	isoliquiritigenin
ISOA:	isoangustone A
IL:	interleukin
JNK:	Jun N-terminal kinases
LCA:	licochalcone A
LCB:	licochalcone B
LCC:	licochalcone C
LCD:	licochalcone D
LCE:	licochalcone E
LIA:	licorisoflavan A
LID:	licoricidin
LPS:	lipopolysaccharide
LTG:	liquiritigenin
MHC:	major histocompatibility complex
MKP:	mitogen-activated protein kinase phosphatase
MMP:	matrix metalloproteinase
NF-κB:	nuclear factor-kappa B
PGE2:	prostaglandin E2
PI3K:	phosphatidyl inositol 3-kinase
PMN:	polymorph nuclear
PPARγ:	peroxisome proliferator-activated receptor gamma
PON2:	paraoxonase 2
PrV:	pseudorabies virus
PTP1B:	protein tyrosine phosphatase 1B
ROS:	reactive oxygen species
Smac:	second mitochondria-derived activator of caspases
SOD:	superoxide dismutase
TDC:	2,2′,4′-trihydroxychalcone
TGF:	transforming growth factor

TNF: tumor necrosis factor

TPA: 12-*O*-tetradecanoylphorbol-13-acetate

Introduction

Three original plants, *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat., and *Glycyrrhiza glabra* L., are prescribed as licorice in the Chinese Pharmacopoeia [1]. They belong to the family Leguminosae and are widespread in Gansu, Shanxi, Inner Mongolia Autonomous Region, Hebei, Heilongjiang, Ningxia, Qinghai, and many other provinces in China [2]. Among them, the first three are believed to be authentic regions of licorice since ancient times in China [3]. It is also widespread in Spain, Persia, India, Afghanistan, Kazakhstan, Kyrghyzstan, Tajikistan, and Russia. As shown in **Fig. 1**, licorice is a kind of dwarf shrub and has oval leaflets, white or purplish flower clusters, flat pods, a main taproot, and numerous runners [2].

In China, the earliest written reference about licorice is Shen Nong Ben Cao Jing, the first Chinese dispensary. Since then, the roots and rhizomes of licorice have been widely used in traditional Chinese medicine for their effects of nourishing *qi*, alleviating pain, tonifying the spleen and stomach, eliminating phlegm, and relieving coughing. Licorice is honored as the reconciler in Chinese herbal compound prescriptions. With the development of modern pharmacology, many valuable and important pharmacological activities of licorice have been discovered. The main reasons that licorice has potent effects and wide applications are due to its various natural active compounds. To date, more than 20 triterpenoids and 300 flavonoids have been isolated from licorice. Many researches have reported that these active compounds possess antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, and several other activities that contribute to the recovery and protection of the nervous, alimentary, respiratory, endocrine, and cardiovascular systems. Nowadays, licorice extract, active compounds, and preparations have been used for the treatment of gastric ulcers [4], liver diseases [5], Addison's disease [6], and many other diseases. In this paper, nine pharmacological activities of licorice, the active compounds, and the molecular mechanisms are summarized. The clinical use and toxicity of licorice is also discussed.

Main Compounds Isolated from Licorice and Their Pharmacological Activities

To date, more than 20 triterpenoids, such as GC and GA, and 300 flavonoids, such as ISL, ISOA, LCA, LCB, LCC, LCD, LCE, GLD, and GP, have been isolated from licorice. Many pharmacological researches have demonstrated that they possess various pharmacological activities. The main compounds with different pharmacological activities are listed in **Figs. 2** and **3**.

Antitumor activity

The high mortality of cancer is one of the leading causes of death in humans. Using natural compounds without side effects has attracted the attention of many researchers. Many studies have proven that various natural compounds in licorice possess effective antitumor activity, including three triterpenoids, GC [7,8], GA [9], and 11-DOGA [10], and six flavonoids, ISOA [11], GLD [12], ISL [13], LCA [14,15], LCB [16], and LCE [17]. The antitumor compounds, the possible mechanisms for cancer prevention, cancer types, and correlated references are listed in **Table 1**.

GC exerts its antitumor activity by attenuating the level of TNF-α, declining the depletion of the mucous layer, shifting sialomucin to sulphomucin, and inducing cancer cell apoptosis through the caspase- and mitochondria-dependent pathways [8,18]. GA induces apoptosis and cell cycle arrest in the G2 phase, and downregulates the expression of NF-κB, vascular endothelial growth factor, and MMP-9. 11-DOGA also induces apoptosis and cell cycle arrest in the G2 phase. However, it presents lower toxicity [10,19]. ISOA induces mitochondrial outer membrane permeabilization and inhibits CDK2 and the mammalian target of rapamycin to suppress cell cycle progression at the G1 phase [11,20,21]. LCA blocks cell cycle progression at the G2/M transition [23], inhibits the expression of uridylyl phosphate adenosine, phosphor-JNK, and phosphor-map kinase kinase 4 [22], reactives the ROS-dependent pathway, and induces cancer cell apoptosis by an endoplasmic reticulum stressor through a caspase-dependent FasL-mediated death receptor pathway [25,26]. LCB leads to S phase arrest, enhances Bax expression, activates caspase-3, cleaves the poly ADP-ribose polymerase protein, and decreases the expression of cyclin A, CDK1 and CDK2 mRNA, cell division cycle 25 (Cdc25A and Cdc25B) protein, Bcl-2, and survivin [16]. ISL and LCE inhibit upstream signaling pathways [17,27]. GLD inhibits

Fig. 1 *Glycyrrhiza uralensis* Fisch. (Color figure available online only.)

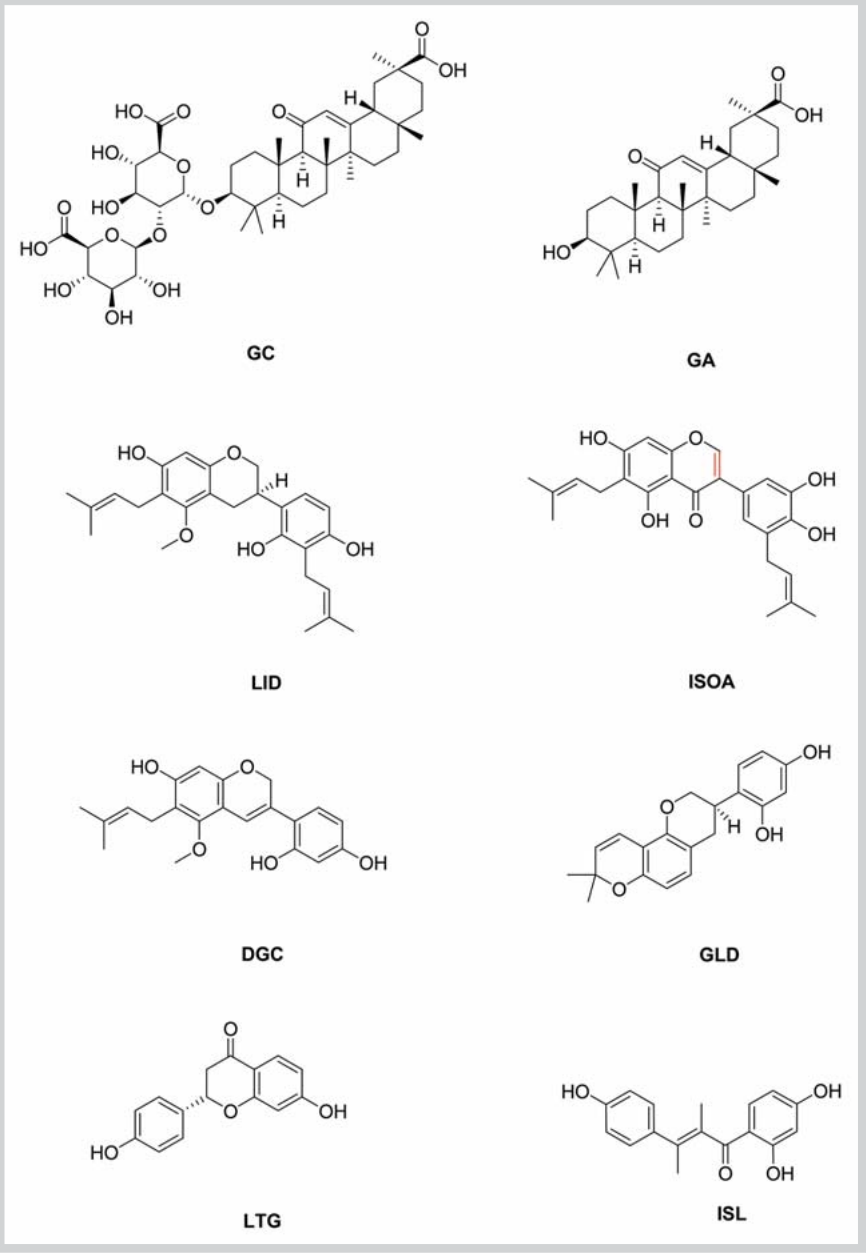

Fig. 2 Chemical structures of GC, GA, LID, ISOA, DGC, GLD, lLTG, and ISL. (Color figure available online only.)

the FAK/Rho signaling pathway [12]. In summary, the compounds of licorice exert their antitumor activities mainly by attenuating the level of cytokines, blocking cell cycle progression, and inducing cancer cell apoptosis. In addition to several single compounds isolated from licorice, some researchers also found that the ethanol extract and hexane/ethanol extract of roasted licorice had antitumor activity [28,29].

In vitro studies have shown that ISOA has been applied to SW480 human colorectal adenocarcinoma cells, DU145 human prostate cancer cells, and 4T1 murine breast cancer cells [11,29], ISL has been applied to HeLa human cervical cancer cells and MDA-MB-231 human breast cancer cells [13,27], GC has been applied to WEHI-3 mouse leukemia cells [18], GA has been applied to DU-145 prostate cancer cells [19], and LCA has been applied to MKN-28, AGS, MKN-45 gastric cancer cells, HA22T/VGH, SK-Hep-1, HepG2 human hepatocellular cancer cells, KB human oral cancer cells, and T24 bladder cancer cells [22–26,30].

In vivo studies have shown that GC has been applied to inhibit 1,2-dimethyhydrazine-induced colon precancerous lesions of Wistar rats [8], while GA has been applied to gastric cancer and inhibits tumor growth in a nude mouse model [10]. Glabridin inhibits MDA-MB-231 breast cancer angiogenesis in a nude mouse model [12]. LCB inhibited MB49 bladder tumor growth in a C57BL/6 mouse model [16]. LCE suppressed 4T1 mammary tumor growth and lung metastasis in the mammary fat pads in a syngeneic BALB/c mouse model [17]. ISOA significantly suppressed PTEN-deleted human prostate tumor growth and SK-MEL-28 human melanomay tumor growth in xenograft mice models [20,21]. All these indicate that licorice represents interesting and important hits for antitumor drug discovery and development.

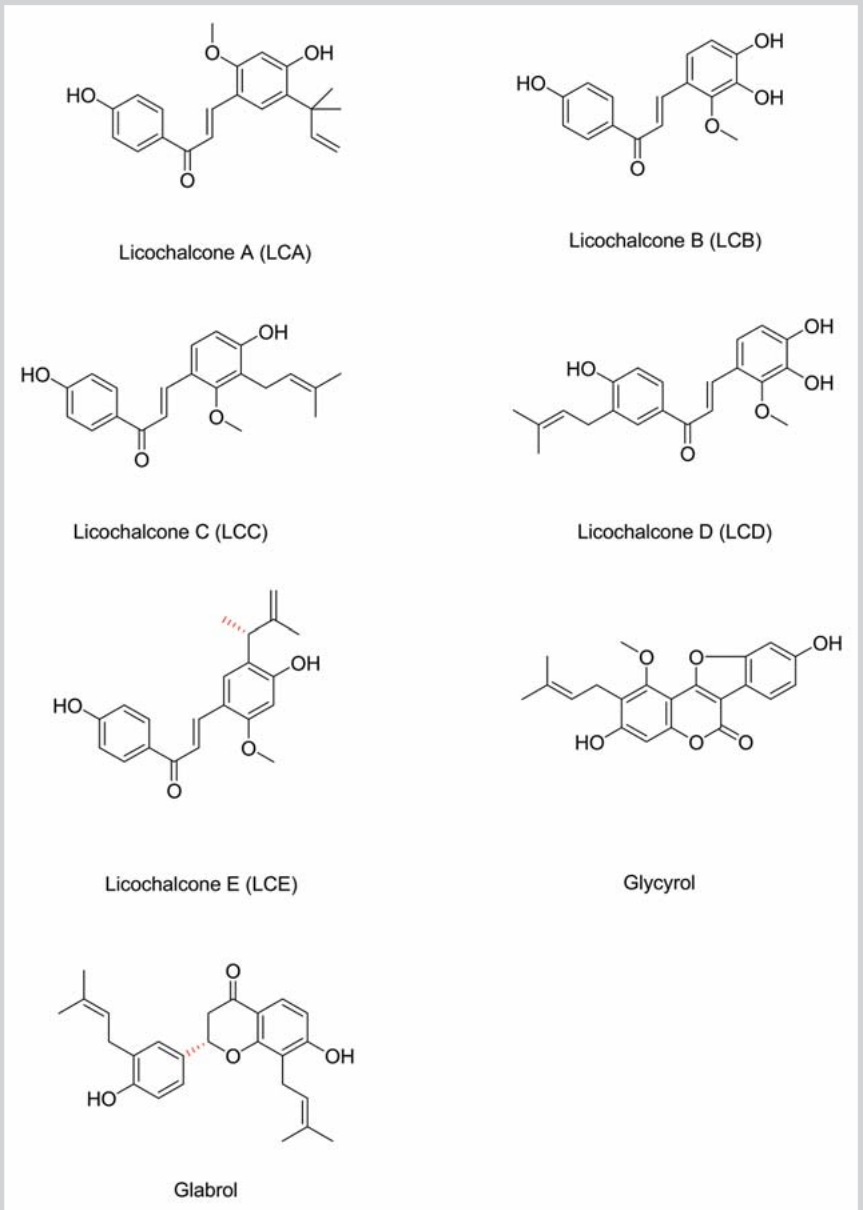

Fig. 3 Chemical structures of LCA, LCB, LCC, LCD), LCE, glycyrol, and glabrol. (Color figure available online only.)

Anti-inflammatory activity

Inflammation plays an important role in epidemic diseases among populations. Licorice is an excellent alternative choice for the treatment of inflammation, especially for children. To date, many reports have shown that two triterpenoids, GC and 18β-GA, and several flavonoids isolated from licorice, such as GLD, ISL, LCA, LCB, LCC, LCD, LCE, ISOA, DGC, LID, LIA, EC, and glyurallin B, all possess anti-inflammatory activity. The anti-inflammatory compounds, the possible mechanisms for inflammation prevention, inflammatory types, and correlated references are listed in **Table 2**.

The mechanisms of the anti-inflammatory activity of licorice have been explored deeply. It has been widely accepted that GC and 18β-GA suppress proinflammatory cytokine COX-2, iNOS, TNF-α, HMGP 1, PGE2, myeloperoxidase, DPPH radicals, IL-6, IL-10, TGF-β, and NF-κB, inhibit the translocation of toll-like receptor 4 to lipid rafts, and activate ABCA1 [31–38]. GLD and ISL inhibit the release of NO and IL-1β [39], and LID and LIA inhibit the activation of NF-κB p65 and the secretion of IL-6, chemokine (C-C motif) ligand 5, MMP-7, MMP-8, and MMP-9 [40]. EC scavenges ABTS+ [41]. DGC increases the expression of MKP-1 and hemeoxygenase-1, and decreases DPPH, ABTS+, singlet oxygen radicals, NF-κB DNA binding activity, and the production of ROS [42,43]. LCA reduces the mRNA expression of acidic mammalian chitinase, chitinase 3-like protein 4, E-selectin, Muc5ac, CCl11, CCR3, and the serum levels of ovalbumin-specific immunoglobulin E and G. It also inhibits the production of NO, IL-6, PGE2, and ROS [41,45]. LCB and LCD inhibit the activation of PKA, and reduce NO, TNF-α, MCP-1, ABTS+, ROS, IL-6, and PGE2 [46,48]. LCC decreases the expression and activity of iNOS and modulates the antioxidant network activity of SOD, catalase, and glutathione peroxidase activity [47]. LCE inhibits the expression of iNOS, COX-2, AKT, p38 MAPK, IL-12p40, and the phosphorylation of protein kinase C-JNK and extracellular ERK 1/2 [49,50]. In other words, the compounds isolated from licorice exert their anti-inflammatory activity through the inhibition of COX, PGE2, cytokines and their receptors, and nuclear transcription factor as well as through the removal of oxygen free radicals.

Table 1 The antitumor compounds isolated from licorice and their possible mechanisms for cancer prevention.

Compounds	The possible mechanisms for cancer prevention	Cancer types	References
GC	GC attenuates the level of TNF-α and declines the depletion of the mucous layer and the shifting of sialomucin to sulphomucin.	Colon carcinogenesis	[8]
	GC induces apoptosis through the caspase- and mitochondria-dependent pathways.	Leukemia	[18]
18β-GA	18β-GA induces apoptosis and prevents the invasion of DU-145 cells on Matrigel-coated transwells via the downregulation of NF-κB, vascular endothelial growth factor, and NMP-9 expression.	Prostate cancer	[19]
	18β-GA induces apoptosis and cell cycle arrest in the G2 phase.	Gastric cancer	[10]
11-DOGA	11-DOGA induces apoptosis and cell cycle arrest in the G2 phase.	Gastric cancer	[10]
ISOA	ISOA induces mitochondrial outer membrane permeabilization and the release of cytochrome c.	Colorectal cancer	[11]
	As a potent molecular inhibitor of CDK2 and mammalian target of rapamycin.	Prostate cancer	[20]
	ISOA suppresses cell cycle progression at the G1 phase and blocks the expression of G1 phase regulatory proteins.	Human melanoma	[21]
LCA	LCA induces a dose-dependent inhibition of uridylyl phosphate adenosine activity and expression, reduces mRNA levels, and inhibits the expression of phosphor-JNK and phosphor-map kinase kinase 4 in SK-Hep-1 cells.	Liver cancer	[22]
	LCA blocks cell cycle progression at the G2/M transition and induces apoptosis.	Gastric cancer	[23]
	LCA increases intracellular rROS levels resulting in an oxidative stress status.	Bladder cancer	[24]
	LCA induces apoptosis by endoplasmic reticulum stress via a phospholipase Cγ1-, Ca2+-, and reactives ROS-dependent pathway.	Liver cancer	[25]
	LCA induces apoptosis by a caspase-dependent FasL-mediated death receptor pathway.	Oral cancer	[26]
LCB	LCB inhibits T24 or EJ cell line proliferation in a concentration-dependent and time-dependent manner.	Bladder cancer	[16]
LCE	LCE inhibits the migration and invasion of both MDA-MB-231 human breast cancer cells and 4T1 cells by inhibiting the upstream signaling pathways.	Breast cancer	[17]
ISL	ISL inhibits the migration and invasion of MDA-MB-231 cells by inhibiting the upstream signaling pathways.	Breast cancer	[27]
GLD	GLD inhibits migration, invasion, and angiogenesis of MDA-MB-231 human breast adenocarcinoma cells by inhibiting the FAK/Rho signaling pathway.	Breast cancer	[12]

Many *in vitro* studies have shown that GC has been used in *Leishmania donovani*-infected macrophages [36]. GA, GLD, and ISL have been used in LPS-stimulated macrophage models [35,39]. LID and LIA have been used in *Antinobacillus actinomycetemcomitans* LPS-treated macrophages [40]. LCA, LCB, and LCE have been used in LPS-induced RAW 264.7 macrophage cells [41,50], and DGC has been used in LPS-induced BV-2 microglia and mice hippocampal cells [42,43].

In vivo and clinical studies have shown that GC has been used in the postischemic brain with a middle cerebral artery occlusion mouse model [31], in an LPS-induced acute lung injury mouse model, and in a mastitis mouse model [33,34]. GA has been used to treat oxidative and neuronal damage in brain tissue caused by global cerebral ischemia/reperfusion in a C57BL/J6 mouse model [38]. LCA has been used in childhood atopic dermatitis and in a murine model of asthma [44,45]. LCE has been used in TPA-induced mice ear edema [49]. Many other studies have also shown that licorice extracts have benefits in the treatment of acute and chronic inflammatory conditions [51,52]. All of the above indicates that it is very important and meaningful to study the anti-inflammatory activity of licorice.

Antiviral activity

Licorice preparations have been used to treat viral hepatitis since the late 1970s. In recent years, many studies have shown that licorice extract has significant antiviral activity against HIV, severe acute respiratory syndrome-coronavirus (SARS), HSV, influenza virus (H3N2), rotavirus, respiratory syncytial virus, varicella zoster virus, coxsackie virus, and enterovirus [53–56]. However, as far as a single compound is concerned, although many compounds have been isolated from licorice, only two triterpenoids, GC and 18β-GA, have been reported to possess antiviral activity. They were found to have a significant positive impact on HIV, H3N2, HSV, DHV, HCV, PrV, and IAV. The antiviral compounds, the possible mechanisms for antiviral activity, virus types, and correlated references are listed in **Table 3**.

Many *in vitro* experiments have shown that GC inhibits HCV by suppressing the release of infectious particles [57], inhibits HSV by depressing the cellular adhesion [58], inhibits influenza virus by reducing HMGB1 binding to DNA and suppressing interactions between viral macromolecules and host proteins [64], inhibits HIV by preventing the virus from replication [61], and inhibits H5N1 not by interfering with H5N1 replication, but by controling H5N1-induced proinflammatory gene expression [60]. The dispute about whether GC inhibits virus replication still needs further study. GC also interacts with the cell membrane and reduces endocytic activity [30], and causes deregulation of generating the mature forms of viral mRNA encoding, which is a process important for viral stability [62]. GA shows significant antiviral activity against rotavirus replication by reducing the amounts of viral proteins VP2, VP6, and NSP2 at a step or steps subsequent to virus entry [66]. It also effectively inhibits HIV-1 by reducing the accumulation of virus antigen p24 and protects cells from the cytopathogenic action of the virus [67].

In vivo studies have shown that GC demonstrates a pronounced lymphocytic proliferation response on white Pekin ducklings, and reveals a good immune stimulant and antiviral effect against DHV [59]. A combination of glutamyl-tryptophan and GC exerts a protective effect in reducing the death of H3N2 virus-infected mice [63].

In summary, GC and GA exert antiviral activity mainly by inhibiting the replication and release of the virus, suppressing interactions between the virus and host cells, activating immune re-

Table 2 The anti-inflammatory compounds isolated from licorice and their possible mechanisms for inflammation prevention.

Compounds	The possible mechanisms for inflammation prevention	Inflammatory types	References
GC	GC suppresses proinflammatory COX-2, iNOS, and TNF-α, and inhibits phosphorylation and secretion of HMGP 1.	Postischemic brain with middle cerebral artery occlusion	[31]
	GC scavenges DPPH radicals.	Chronic liver diseases	[32]
	GC attenuates myeloperoxidase activity, the expression of TNF-α, IL-6, and NF-κB, and the levels of cholesterol of lipid rafts. Inhibits the translocation of toll-like receptor 4 to lipid rafts. Activates ABCA1.	Mastitis	[33]
	GC inhibits the myeloperoxidase activity and the release of NO as well as the expression of COX-2 and iNOS.	Acute lung injury	[34]
	GC suppresses NF-κB via the PI3K pathway, inhibits the production of NO, PGE2, and ROS, and reduces the protein and mRNA levels of iNOS and COX-2.	LPS-induced inflammatory response	[35]
	GC enhances the expression of iNOS2 along with the inhibition of COX-2 and down-regulates IL-10 and TGF-β.	*Leishmania donovani*-infected macrophages	[36]
18β-GA	18β-GA reduces mRNA expression of TNF-α, IL-1β, and IL-6.	Indomethacin-induced small intestinal damage	[37]
	18β-GA attenuates the generation of excessive NO, PGE2, and ROS by suppressing the expression of proinflammatory genes through the inhibition of NF-κB and PI3K activity. It also reduces the protein and mRNA levels of iNOS and COX-2.	LPS-induced inflammatory response	[35]
	18β-GA increases antioxidant defense systems and decreases lipid peroxidations.	Ischemia/reperfusion	[38]
GLD	GLD inhibits the release of NO and IL-1β.	LPS-induced J774A.1 murine macrophages	[39]
ISL	ISL inhibits the production of NO, IL-1β, and IL-6.	LPS-induced J774A.1 murine macrophages	[39]
LID	LID inhibits the secretion of IL-6, chemokine (C-C motif) ligand 5, and the secretion of MMP-7, -8, and − 9. It also reduces the activation of NF-κB p65.	Periodontitis	[40]
LIA	LIA inhibits the secretion of IL-6 and chemokine (C-C motif) ligand 5, and the secretion of MMP-7, -8, and − 9. It also reduces the activation of NF-κB p65.	Periodontitis	[40]
EC	EC scavenges the ABTS radical dot+.	Lipid peroxidation in rat liver microsomes	[41]
DGC	DGC increases MKP-1 expression, suppresses the inflammation-mediated neurodegeneration and the production of TNF-α, and decreases NF-κB DNA binding activity.	LPS-induced BV-2 microglia	[42]
	DGC scavenges DPPH, ABTS+, and singlet oxygen radicals, reduces ROS generation and cytotoxicity, and increases the expression of hemeoxygenase-1.	Glutamate-induced hippocampal HT22 cells	[43]
LCA	LCA decreases transepidermal water loss.	Childhood atopic dermatitis	[44]
	LCA reduces the mRNA expression of acidic mammalian chitinase, chitinase 3-like protein 4, E-selectin, Muc5ac, CCl11, and CCR3 in lung tissues, and serum levels of ovalbumin-specific immunoglobulin E and G. It also inhibits cytokine release.	Allergic airway inflammation	[45]
	LCA inhibits LPS-induced ROS production.	LPS-induced RAW 264.7 cell	[41]
	LCA inhibits the production of NO, IL-6, and PGE2.	LPS-induced macrophage cells	[41]
	LCA exhibits potent inhibition of lipid peroxidation.	In rat liver microsomes	[41]
LCB	LCB inhibites the LPS-induced activation of PKA, and reduces the LPS-induced production of NO, TNF-α and MCP-1.	LPS-induced inflammatory response	[46]
	LCB shows strong scavenging activity toward the ABTS radical dot+ radical.	In rat liver microsomes	[41]
	LCB inhibits the production of NO, IL-6, and PGE2.	LPS-induced macrophage cells	[41]
	LCB inhibits LPS-induced ROS production.	LPS-induced RAW 264.7 cell	[41]
LCC	LCC decreases the expression and activity of iNOS, and modulates the antioxidant network activity of SOD, catalase, and glutathione peroxidase activity.	LPS and interferon-gamma-induced inflammatory response	[47]
LCD	LCD inhibits mast cell degranulation.	Allergic inflammation	[48]
	LCD inhibites the LPS-induced activation of PKA, and reduces the LPS-induced production of NO, TNF-α, and MCP-1.	LPS-induced inflammatory response	[46]
LCE	LCE inhibits the phosphorylation of protein kinase C – JNK, ERK 1/2, and the expression of iNOS and COX-2 proteins.	TPA-induced mouse ear edema	[49]
	LCE dose-dependently inhibites IL-12p40 production and decreases binding to NF-κB.	LPS-induced RAW 264.7 cells	[50]

sponses in host cells, and attenuating a virus-induced anti-inflammatory response.

Immunoregulatory activity

In the last five years, a lot of researches demonstrated the immunoregulatory activity of licorice. Among the compounds of licorice, GP is believed to play an important role in stimulating the body's immune ability. It affects the body's nonspecific and specific immune functions and activates immune cells [68, 69]. In addition, GC, 18β-GA, LCA, LTG, and glycyrol also showed immunoregulatory activity [9, 70–74]. The compounds with immunoregulatory activity, the possible mechanisms for the immunoregulatory activity, the potential therapeutic effects, and the correlated references are listed in **Table 4**.

GC shows a pronounced lymphocytic proliferation response and increases the level of IL-4, IL-5, IL-10, IL-12, IL-13, and IFN-γ, and

Table 3 The antiviral compounds isolated from licorice and their possible mechanisms for viral prevention.

Compounds	The possible mechanisms for viral prevention	Virus types	References
GC	GC affects the release of infectious HCV particles, inhibits HCV full-length viral particles and HCV core gene expression.	HCV	[57]
	GC reduces adhesion force and stress between cerebral capillary vessel endothelial and PMN.	HSV	[58]
	GC activates T lymphocyte proliferation.	DHV	[59]
	GC weakens chemokine ligand 10, IL-6, and CCL5 production and suppresses H5N1-induced apoptosis.	H5N1	[60]
	GC induces the production of β-chemokines.	HIV	[61]
	GC deregulates the multicistronic latency transcript.	Herpes virus	[62]
	GC exerts an effect on the innate immunity to fight against a pathogenic virus.	H3N2	[63]
	GC reduces HMGB1 binding to DNA and inhibits influenza virus polymerase activity.	Influenza virus	[64]
	GC reduces endocytotic activity and reduces virus uptake.	IAV	[30]
	GC inhibits cell infection by PrV.	PrV	[65]
18β-GA	18β-GA reduces the levels of viral proteins VP2, VP6, and NSP2.	Rotavirus	[66]
	18β-GA effectively inhibits HIV-1 and the accumulation of virus antigen p24 and protects cells from the cytopathogenic action of the virus.	HIV	[67]

Table 4 The compounds with an immunoregulatory activity isolated from licorice and their possible mechanisms for immunoregulatory activity.

Compounds	The possible mechanisms for immunoregulatory activity	Therapeutic effect	References
GC	GC inhibits OVA-induced increases in airway resistance and eosinophil count, recoveries the level of IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid, and increases the IFN-γ level in bronchoalveolar lavage fluid.	It effectively ameliorates the progression of asthma	[70]
	GC demonstrates a pronounced lymphocytic proliferation response.	It reveals an antiviral effect against DHV	[59]
	GC causes increased production of IL-10	It downregulates liver inflammation	[75]
	GC shows a dose-dependent priming effect on LPS-induced IL-12 p40 and IL-12 p70 (heterodimer of p40 and p35) protein production by peritoneal macrophages.	It exhibits an effect in interferon-gamma knockout (IFN-gamma−/−) mice	[76]
18β-GA	18β-GA significantly suppresses the expression of cell surface molecules CD80, CD86, MHC class I, and MHC class II and the levels of IL-12 production.	It impairs dendritic cell maturation and Th1 immune responses	[9]
	18β-GA increases CD19(+) B cells in the lamina propria and B220(+) B cell aggregates framed by CD11c(+) dendritic cells in structures resembling isolated lymphoid follicles.	It reduces the duration of viral antigen shedding, and increased the end point serum antibody titers	[74]
Glycyrol	Glycyrol inhibits calcineurin activity, suppresses IL-2 production, and regulates T lymphocytes.	It can be developed as a novel drug	[71]
LTG	LTG produces IFNγ and IL-2 when dominantly compared to IL-4 and IL-10 by the CD4+ Th1 immune response.	It inhibits disseminated candidiasis	[72]
LCA	LCA inhibites H_2O_2, NO, IFN-γ, TNF-α, and IL-17 production in splenocytes and peritoneal cells, and modulates the immune response in both Th1 and Th17 cells.	It reduces severity of experimental autoimmune encephalomyelitis in mice	[73]
GP	GP promotes $\gamma\delta$T cells proliferation, IFN-γ, and TNF-α secretion.	It significantly improves the cytotoxicity of $\gamma\delta$T cells to HepG2 cells	[77]
	GP enhances the expression of the cell surface molecules CD80, CD86, and MHC I-A/I-E, increases the production of IL-12 p70, and enhances both the proliferation and IFN-γ secretion of allogenic CD3+ T cells.	It induces the maturation of dendritic cells	[69]
	GP reduces the proportion of Treg cells, decreases lymph node Foxp3 and IL-10 mRNA expression, and upregulates the Th1/Th2 cytokine ratio in serum.	It partially inhibits tumor growth	[78]

the production of IL-12 p40 and IL-12 p70 proteins [59, 70, 75, 76]. GA significantly suppresses the expression of cell surface molecules CD80 and CD86, and MHC classes I and as well as the levels of IL-12 production [9]. It also increases CD19 (+) B cells in the lamina propria and B220 (+) B cell aggregates [74]. Glycyrol inhibits calcineurin activity, suppresses IL-2 production, and regulates T lymphocytes [71]. LTG produces IFN-γ and IL-2 via the CD4+ Th1 immune response [72]. LCA inhibits H_2O_2, NO, IFN-γ, TNF-α, and IL-17 production, and modulates the immune response on both Th1 and Th17 cells [73]. GP promotes $\gamma\delta$T cell proliferation and IFN-γ and TNF-α secretion, enhances the expression of CD80, CD86, and MHC I-A/I-E and the production of IL-12 p70, upregulates the Th1/Th2 cytokine ratio in serum, reduces the proportion of Treg cells, and decreases the expression of lymph node Foxp3 and IL-10 mRNA [69, 77, 78]. In summary, compounds isolated from licorice exert immunoregulatory activity by regulating the production of cytokines and interleukin as

Table 5 The antimicrobial compounds isolated from licorice and their possible mechanisms for antimicrobial activity.

Compounds	The possible mechanisms for antimicrobial activity	Microorganism types	References
GLD	Not mentioned.	Yeast and filamentous fungi	[90]
	GLD prevents the yeast-hyphal transition.	*C. albicans*	[96]
LCE	LCE reduces the production of α-toxin.	*S. aureus*	[97]
LCA	LCA inhibits the biofilm formation and prevents the yeast-hyphal transition.	*C. albicans*	[96]
LTG	LTG decreases the production of α-hemolysin.	*S. aureus*	[98]
18β-GA	18β-GA reduces the expression of key virulence genes, including *sae*R and *hla*.	*S. aureus*	[83]
	18β-GA exerts Th1-immunological adjuvant activity.	*C. albicans*	[99]
	Not mentioned.	*M. bovis*	[100]
LIA	Not mentioned.	*S. mutans, S. sobrinus, P. gingivalis* and *Prevotella intermedia*	[101]
LID	Not mentioned.	*S. mutans, S. sobrinus, P. gingivalis, P. intermedia* and *Fusobacteriu nucleatum*	[101]
Glycyrrhizol A	Not mentioned.	Cariogenic bacteria like *S. mutans*	[102]

well as the expression of cell surface molecules and immune responses.

According to many *in vivo* and clinical studies, these compounds protected mice against disseminated candidiasis [72], reduced the severity of experimental autoimmune encephalomyelitis in mice [73], increased the end point serum antibody titers [74], increased the production of IL-10 in mice with Con A-induced hepatitis [75], and acted as an immune stimulant against DHV [59]. All these reports affirm the immunoregulatory activity of licorice and indicate that it can be developed as a novel immnuomodulatory drug.

Antimicrobial activity

Increasing antibiotic resistance has resulted in an urgent need for alternative therapies to treat diseases. In recent years, many clinical and pharmacological researches have demonstrated the antimicrobial activities of licorice aqueous extract [79,80], ethanol extract [79,81], and superctitical fluid extract [82]. Many reports have shown that licorice has potent effects in inhibiting the activities of gram-positive and gram-negative bacteria such as *Staphylococcus aureus* [83–85], *Porphyromonas gingivalis* [86], *Streptococcus mutans* [87,88], *Candida albicans* [89,90], *Escherichia coli* [91], *Enterococcus faecalis* [92], *Pseudomonas aeruginosa* [93], *Helicobacter pylori* [94], and *Bacillus subtilis* [89]. It also has effects in inhibiting the activities of pathogenic fungi such as *Alternariasolani, Botrytis cinerea*, and *Phytophthora* [95].

Several compounds isolated from licorice, such as 18β-GA, LTG, GLD, LCA, LCE, LIA, LID, and glycyrrhizol A, have been reported to possess antimicrobial effects against *S. aureus, C. albicans, Mycobacterium bovis*, yeast, and several cariogenic bacteria like *S. mutans* and *Streptococcus sobrinus*. The antimicrobial compounds, the possible mechanisms for the antimicrobial effects, and the microorganism types are listed in detail in ◉ **Table 5**.

GA inhibits *S. aureus* by reducing the expression of key virulence genes [83], and induces a greater Th1 immune response for the treatment of Th1-disordered disease due to *C. albicans* [99]. Both LCA and GLD inhibit hyphal formation and LCA inhibits biofilm formation. Since hyphae and biofilm have been reported to be key virulence factors, the application of these two compounds may be a new strategy to treat *C. albicans*, the main causal agent of candidiasis [96]. LTG and LCE remarkably decrease the production of *S. aureus* α-hemolysin and play an important role in *S. aureus*-mediated lung cell injury [97,98]. In summary, these compounds exert their antimicrobial activities by inhibiting the formation of bacteria, the production of exotoxins, and activating an immune response. However, researches about the mechanisms are still in the initial stage and need further study.

Based on the above, licorice has great application prospects as an alternative therapy in treating dental caries, periodontal disease, digestive anabrosis, and tuberculosis. At the same time, it is also being considered as a potential alternative to synthetic fungicides, or as a lead compound for new classes of synthetic fungicides.

Inhibitory effect on diabetes

Licorice has been shown to inhibit a series of pathological and physiological changes induced by D-galactose, such as insulin resistance and oxidative stress/free radical damage, so as to delay the development of diabetes. Several compounds isolated from licorice, such as GL, GA, LTG, ISL, GLD, LCA, LCE, and some other flavonoids, have been reported to possess an inhibitory effect in diabetes. The antidiabetic compounds, the possible mechanisms for an inhibitory effect in diabetes, and correlated references are listed in ◉ **Table 6**.

GC and GA show multiple biological activities on glucose absorption, glucose uptake, insulin secretion, diabetic vascular dysfunction, retinopathy, and nephropathy [104]. GC also inhibits the RAGE/NF-κB pathway [103], reduces diabete-induced abnormalities of pancreas and kidney tissues, counteracts free iron, iron-mediated free radical reactions and carbonyl formations in hemoglobin, and normalizes oxidative stress parameters [105]. Many flavonoids isolated from licorice exhibit a significant blood glucose lowering effect with different mechanisms. LCA selectively inhibits JNK1 activity, resulting in G1 phase arrest and apoptosis [106]. LCE increases the levels of PPARγ expression, enhances adipocyte differentiation, and increases the population of small adipocytes [107]. Glabrol shows a noncompetitive type of inhibition against diacylglycerol acyltransferase [111]. GLD increases body weight and glucose tolerance, and decreases fasting blood glucose levels and MDA content in the liver, kidney, and pancreas. It also strengthens the antioxidant defense mechanism by increasing PON2 activity, upregulates the mRNA expression of PON2 and the expression of manganese superoxide dismutase and catalase in monocytes [112,113]. Glycybenzofuran and several other flavonoids selectively inhibit the activity of PTP1B in different models and with different selectivities in the insulin-

Table 6 The antidiabetic compounds isolated from licorice and their possible mechanisms for inhibitory effect of diabetes.

Compounds	The possible mechanisms for inhibitory effect of diabetes	References
GC	GC inhibits the RAGE/NF-κB pathway by increasing SOD activity, decreasing the peroxide degradation product malondialdehyde level, and decreasing poinflammatory cytokine TGF-β1 expression, AGEs-induced RAGE, and NF-κB protein expression.	[103]
	GC shows multiple biological activities on glucose absorption, glucose uptake, insulin secretion, diabetic vascular dysfunction, retinopathy, and nephropathy.	[104]
	GC decreases the serum insulin level, and increases the levels of glycohemoglobin, cholesterol, and triglycerides. It also reduces diabetes-induced abnormalities of pancreas and kidney tissues, counteracts free iron, iron-mediated free radical reactions and carbonyl formation in hemoglobin. Oxidative stress parameters are reverted to normal values after GC administration.	[105]
GA	GA shows multiple biological activities on glucose absorption, insulin secretion, diabetic vascular dysfunction, retinopathy, and nephropathy.	[104]
LCA	LCA selectively inhibits JNK1 activity, which results in G1 phase arrest and apoptosis.	[106]
LCE	LCE increases the levels of PPARγ expression, enhances adipocyte differentiation, and increases the population of small adipocytes.	[107]
ISL	ISL exhibits a significant blood glucose lowering effect. The presence of ether and ester groups in ISL is important for this effect.	[108]
LTG	LTG exhibits a significant blood glucose lowering effect. The presence of ether and ester groups in LTG is important for this effect.	[108]
Licoagrone, licoagrodin, licoagroaurone, isobavachalcone	These compounds inhibit the activity of PTP1B in different modes and with different selectivities in the insulin-signaling pathway.	[109]
Glycybenzofuran	It selectively inhibits the activity of PTP1B and promotes insulin-stimulated Akt phosphorylation level in human hepatocellular liver carcinoma (HepG2) cells.	[109]
Semilicoisoflavone B	It inhibits sorbitol formation of the rat lens incubated with a high concentration of glucose.	[110]
Glabrol	It shows a noncompetitive type of inhibition against diacylglycerol acyltransferase.	[111]
GLD	GLD significantly increases body weight, glucose tolerance and SOD activities, while it decreases fasting blood glucose levels and MDA content in the liver, kidneys, and pancreas.	[112]
	GLD has the potential of strengthening the antioxidant defense mechanism by increasing PON2 activity, upregulating mRNA expression of PON2, and upregulating the expression of manganese SOD and catalase in monocytes.	[113]

signaling pathway [109]. Above all, after licorice administration, oxidative stress parameters are reverted to normal values, diabetes-induced abnormalities of liver, kidney, and pancreas are improved, and glucose absorption and insulin secretion are controlled and regulated.

Some researches also demonstrated that licorice extract would be a highly potent therapeutic agent for the prevention and treatment of diabetes nephropathy led by mesangial fibrosis and glomerulosclerosis through blocking Akt activation and TGF-β signaling [114]. It alleviated blood glucose levels, restored renal function, attenuated body weight loss, and modulated the adverse effect of diabetes on renal glutathione and malondialdehyde as well as the activity of catalase and superoxide dismutase. It also restored the total antioxidant capacity of diabetic rat kidneys. Above all, licorice extract has a potential therapeutic effect for diabetes due to its antioxidant and antihyperglycemic properties [115,116]. All these reports indicated that licorice was a highly potent therapeutic agent for diabetes treatment.

Hepatoprotective effect

To date, only three compounds, GA, GC, and DGC, have been reported to possess hepatoprotective activity, especially GC, which has been shown to be effective in almost the whole process of liver diseases. Since a GC preparation was used for the clinical treatment of liver disease by Yamamoto saso in 1958, it has been widely used in the treatment of a variety of liver diseases, such as hepatitis B, hepatitis C, liver fibrosis, and cirrhosis of the liver. Different *in vivo* animal models have shown that GC has an obvious protective effect in liver injury induced by CCl_4 [117,118], and hepatotoxicity induced by xanthium [119], α-naphthylisothiocyanates [120], and liver fibrosis [121]. The hepatoprotective compounds, the mechanisms for the hepatoprotective effect, and correlated references are listed in **Table 7**.

Oxidative stress, lipid peroxidation, and transaminase reactions are some of the mechanisms that can lead to liver dysfunction. Recent reports have found that the downregulation of these factors may explain the hepatoprptective effect of licorice. GA has been reported to exert a hepatoprotective effect by restoring the expression of proliferating cell nuclear antigen, COX 2, inducible nitric oxide synthase, and NF-κB [127,129], stabilizing lysosomal membranes, inhibiting cathepsin B expression and enzyme activity, inhibiting mitochondrial cytochrome c release, and reducing free fatty acid-induced oxidative stress [128]. GC exerts the hepatoprotective effect by inhibiting the lytic pathway in which the membrane attack complex is formed [126], reducing the Bax/Bcl-2 ratio and the expression of cleaved caspase-3and cleaved caspase-9, inhibiting cytochrome c and Smac release from the mitochondria to cytoplasm [125], increasing CYP3A4 mRNA and protein levels through the activation of the PXR, inhibiting the expression of CYP7A1 through an increase in small heterodimer partner expression [122], inhibiting mitochondrial membrane depolarization [124], and downregulating both the mRNA and protein of MMP-9 [119]. DGC possesses hepatoprotective effects through the suppression of CYP2E1 expression [130]. In summary, licorice exerts its hepatoprotective effect by regulating the expression of CYP enzymes, attenuating oxidative stress, improving the stability of the cell structure and biological membrane systems, and inhibiting the cytolytic activity of the complement and apoptosis systems.

Table 7 Compounds with a hepatoprotective activity isolated from licorice and their possible mechanisms for hepatoprotective activity.

Compounds	The possible mechanisms for hepatoprotective activity	References
GC	GC regulates the expression of CYP3A and CYP7A to prevent the toxic accumulation of bile acids, and protects the liver from the harmful effects of lithocholic acid.	[122]
	GC significantly reduces alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and thiobarbituric acid reactive substance levels, and increases GSH, SOD, and catalase levels.	[123]
	GC protects hepatocytes against tert-butyl hydroperoxide-induced oxidative injury, and against cell death by preventing intracellular reduced GSH depletion, a decrease in ROS formation, and the inhibition of mitochondrial membrane depolarization.	[124]
	GC reduces the Bax/Bcl-2 ratio, the expression of cleaved caspase-3, cleaved caspase-9, and inhibits cytochrome c and Smac release from the mitochondria to cytoplasm. It reducs the expression level of Smac, which inhibits c-IAP1 activity, ultimately inhibiting the activity of caspase-3. It inhibits CCl_4-induced hepatocyte apoptosis through a p53-dependent mitochondrial pathway to reduce the ratio of the hepatic fibrotic region.	[125]
	GC inhibits the lytic pathway in which the membrane attack complex is formed.	[126]
	GC leads to a downregulation of both the mRNA and protein of MMP-9.	[119]
GA	GA protects hepatocytes against TNF-α-induced chronic liver inflammation by attenuating NF-κB activation.	[127]
	GA stabilizes lysosomal membranes, inhibits cathepsin B expression and enzyme activity, inhibits mitochondrial cytochrome c release, and reduces free fatty acid-induced oxidative stress.	[128]
	GA restores the expressions of proliferating cell nuclear antigen, COX 2, iNOS, and NF-κB.	[129]
DGC	DGC possesses hepatoprotective effects against centrilobular injury caused by CCl_4 injection through suppression of CYP2E1 expression.	[130]

In addition, licorice extract significantly inhibits the aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase activities, and decreases total protein, albumin, and globulin levels. It also enhances liver SOD, catalase, GSH peroxidase, gluthione reductase, and glutathione S-transferase activities as well as the GSH level [117, 118, 123, 131]. All these reports indicate that licorice is a highly potent therapeutic agent for the treatment of liver diseases.

Adrenal cortical hormone like function

Some reports demonstrated that licorice extracts and compounds had adrenal cortical hormone like function, increased adrenocorticotropic hormone formation, stimulated steroidogenesis directly in mice adrenal glands, and also stimulated the secretion of glucocorticoids, minernalocorticoids, and anterior pituitary corticotroph-releasing hormone and vasopressin from the adrenal cortex [132, 133].

Among the compounds isolated from licorice, 18β-GA, GC, and ISL exert the adrenal cortical hormone like function. ISL has significant estrogenic activities due to its estrogen responsive β selectivity, partial estrogen agonist activity, and the nonenzymatic transformation between ISL and LTG [134]. 18β-GA and GC play a very important role in the treatment of glucocorticoid-dependent diseases as a well-known inhibitor of 11β-hydroxysteroid dehydrogenases [133, 135, 136]. GA shows its mineralocorticoid actions by inhibiting the conjugation of deoxycorticosterone and dehydroepiandrosterone at a source within the adrenal cortex [137]. The above findings lend support to the reasonable use of licorice as a promising strategy for the treatment of hormone-dependent diseases.

Enhancing memory and nerve protective effect

The beneficial effects of licorice aqueous extract on learning and memory have been investigated by different researchers. Chakravarthi and Avadhani [138] investigated the function of licorice aqueous extract on the dendritic morphology of hippocampal cornu ammonis area three (CA3) neurons and found it, in the doses of 150 and 225 mg/kg, showed an obvious enhancement of dendritic arborization and dendritic intersections in hippocampal pyramidal neurons, which demonstrated its neuronal dendritic growth stimulating properties. He also found that all of the doses of licorice aqueous extracts significantly enhanced the memory, and in the doses of 150 and 225 mg/kg, it significantly enhanced both learning and memory [139]. Michel et al. [140] believed that the nootropic and antiamnestic effects of licorice extracts were mediated through augmenting monoaminergic transmission in the cortex, hippocampus, and striatum.

Among all of the kinds of compounds isolated from licorice, GLD and TDC are responsible for improving learning and memory and are commonly used in the treatment of cardiovascular and central nervous system diseases, especially the former. The higher doses of GLD significantly antagonize amnesia induced by scopolamine [141]. GLD also prevents the deleterious effects of diabetes on memory and learning in rats [142]. Inhibition of BACE1 is regarded as an effective strategy for anti-Alzheimer's disease drug discovery. While the research of Zhu et al. demonstrated that TDC was a new BACE1 inhibitor to ameliorate memory impairment in mice [143].

All of the above demonstrat that licorice appears to be a promising drug for improving memory, impaired learning, Alzheimer's disease, dementia, and other neurodegenerative disorders [141, 144].

Other activities

In addition to the above nine activities, GLD and glabrene have an estrogen-like effect that stimulates the synthesis of epithelial cell DNA and prevents postmenopausal women from vascular injury and atherosclerosis [145]. GA is effective in suppressing pain-related behaviors caused by sciatic nerve injury [146]. ISL has a spasmolytic effect on uterine contraction, an effective function in reducing pain [147], and an antiangiogenic property [148]. The traditional compound prescription "gancao wheat jujube soup" demonstrated a potential antidepressant-like effect of liquiritin treatment in choronic, variable, stress-induced depression in a rat model, which might be related to the defense of liquiritin against oxidative stress [149]. Licorice is also used to relieve menopausal symptoms in postmenopausal women [150].

Licorice Applications in Traditional Chinese Medicine Therapeutics

Licorice is officially listed in the Chinese Pharmacopeia. In traditional applications, it is used for the treatment of gastro and respiratory diseases, and is also used to alleviate the toxicity of other drugs. Licorice is honored as the "excellent coordinator" in traditional Chinese medicine since it can harmonize the activities of all of the other ingredients and promote their rapid absorption into the bloodstream, organs, and target cells. In Shang han za bing lun, one of the most authoritative medical formularies in ancient China, which contains 112 traditional prescriptions, licorice shows up 70 times. Monkshood [roots of *Aconitum carmichaelii* Debx. (Ranunculaceae), Fu zi in Chinese], pinelliae [tubers of *Pinellia ternata* (Thunb.) Breit. (Araceae), Ban xia in Chinese], and cinnabaris (mercuric sulphide, Zhu sha in Chinese) are the top three toxics that are most frequently combined with licorice. Ginseng [roots of *Panax ginseng* C. A. Mey. (Araliaceae), Ren shen in Chinese], Poria [sclerotium of *Poria cocos* (Schw.) Wolf. (Polyporaceae), Fu ling in Chinese], and Chinese angelica [roots of *Angelica sinensis* (Oliv.) Diels. (Alpiaceae), Dang gui in Chinese] are the top three nontoxic herbs that are most frequently combined with licorice. Licorice is seldom used with seaweed [*Sargassum pallidum* (Turn.) C. Ag. or *Sargassum fusiforme* (Harv.) Setch. (Sargassaceae), Hai Zao in Chinese], *Euphorbia pekinensis* [the ground part of *Cirsium japonicum* (Thunb.) Fisch. ex DC (Asteraceae), Da ji in Chinese], *Euphorbia kansui* [root of *Euphorbia kansui* T. N. Liou ex T. P. Wang. (Euphorbiaceae), Gan sui in Chinese], and *Daphne genkwa* [flower of *Daphne genkwa* Sieb. et Zucc. (Thymelaeaceae), Yuan Hua in Chinese] in traditional clinic application [151]. It has been applied to nourishing *qi*, alleviating pain, tonifying the spleen and stomach, eliminating phlegm, and relieving coughing.

Clinical Therapeutics

With the development of modern pharmacology and clinical trials, there are many reports about the clinical applications of licorice ingredients and preparations. Among all of the active compounds isolated from licorice, the development of GC preparations, which are mostly used to treat liver diseases, has a long history in Asia [5]. GC preparation has developed four generations so far, from GC tablets to ammonium glycyrrhizinate, diammonium glycyrrhizinate, and magnesium isoglycyrrhizinate. Compared with the first three GC preparations, magnesium isoglycyrrhizinate has a better lipotropy, higher targeting, and fewer adverse reactions. It has been used in protecting hepatic L02 cells from ischemia/reperfusion-induced injury [152], slowing down the process of pulmonary fibrosis [153], inhibiting ethanol-induced testicular injury [154], and restoring hepatic impairments caused by paclitaxel in other cancer treatments [155].

Furthermore, licorice and its active compounds have been applied to Addison's disease [6], allergic rhinitis [156], postoperative sore throat [157], and saprodontia [79]. The addition of licorice to oral cortisone acetate increased the amount of cortisol available to tissues in Addison's disease [6]. A double-blind clinical trial study conducted on patients with allergic rhinitis showed that the rate of allergic rhinitis symptoms including sever rhinorrhea, sneeze, pruritus, and congestion were lowered significantly after using GC nasal drops [156]. Agarwal et al. [157] found that licorice gargle was effective in attenuating the incidence and severity of postoperative sore throat. Jain et al. [79] found that both aqueous and ethanolic licorice extracts exerted cariostatic activities through a clinical trial carried out among 60 pediatric patients aged 7–14 years.

With the discovery of more and more pharmacology activities, licorice has shown a great potential for acting as a novel drug or complement agent to treat different diseases.

Toxicity Studies

It have been reported that large doses or long-term injections of licorice sometimes produce an acquired form of apparent mineralocorticoid excess syndrome, expressed as sodium retention, hypokalemia, and high blood pressure [158, 159].

According to a recent report, the medical records of patients treated with herbal complexes containing licorice from January 1, 2010 to December 31, 2010 were examined. The changes in the levels of creatinine, potassium, and blood urea nitrogen before and after herbal complex intake were recorded, and the prevalence of hypokalemia among these patients were investigated. Three hundred and sixty patients did not show significant changes in the levels of potassium and creatinine ($p = 0.815$ and 0.289, respectively) and hypokalemia was observed in six patients. However, in five patients, the hypokalemia did not appear to be related to the licorice. This investigation suggested that herbal complexes containing licorice did not significantly influence the potassium levels in routine clinical herbal therapies [160]. In another study, 4T1 mammary carcinoma cells were injected into the mammary fat pads of syngeneic BALB/c mice. Seven days after the injection, the mice received LCE (7 or 14 mg/kg body weight/day) via oral gavage for 25 days. LCE suppressed solid tumor growth and lung metastasis, but did not exhibit kidney or liver toxicity [17]. Russo et al. [161] proposed that some people could be susceptible to low doses of GC because of an 11β-hydroxysteroid dehydrogenase deficiency. Harahap et al. [162] believed that licorice ingestion, as well as mutations in the HSD11B2 gene, inhibited 11β-hydroxysteroid dehydrogenase type 2 enzyme activity and caused the syndrome of apparent mineral corticoid excess, which supposed that licorice ingestion was an environmental risk factor for hypertension or an apparent mineral corticoid excess state in patients with a mutation in HSD11B2.

Future Directions of Research

In recent years, the triterpene compounds of licorice, such as GC and GA, have been studied most frequently and deeply for their various activities, such as anti-inflammatory, antitumor, antiviral, antidiabetic, immune-stimulating, and hepatoprotective activities. The antiviral effects of GC and GA cannot be replaced by other compounds in licorice. Flavonoids, especially chalcones, play an important role in the treatment of cancer, inflammation, diabetes, and diseases caused by bacteria. Licorice polysaccharides have an effective and important function on enhancing immunity, which is worth studying more deeply.

In the Chinese Pharmacopoeia, GC is stipulated to be one of the marker compounds to evaluate the quality of licorice. Since many other compounds have been found to have excellent pharmacological activities so far, we propose that the quality evalution method be updated to meet the need of clinical therapy. In addi-

tion, the active ingredients and their proportion vary a lot in the three official species (*G. uralensis, G. inflata*, and *G. glabra*) [163], but the research about the differences in their clinical applications is infrequent. Furthermore, different medicinal parts of licorice, main roots, adventitious roots, and lateral roots, contain different levels of active ingredients, which might lead to the differences in pharmacological activities. Plus, functional genes can influence the biosynthesis of metabolites, and finally cause the differences in a pesticide effect, which is also worth studying.

It has been reported that licorice extract inhibited NO production and iNOS expression in LPS-stimulated RAW264 murine macrophage cells, while treatment of GC alone could not show this activity. Interestingly, the inhibitory effect of the GC knockout extract was significantly attenuated compared with the extract. Furthermore, the combined treatment with GC knockout extract and GC could improve the attenuated inhibition [164]. It appears that some biological activities may be due to the combined effects of several licorice constituents rather than a specific active ingredient. The synergistic activity can also be a future research direction.

Recently, the clinical safety of licorice has been evaluated. There is apparently a great individual variation in the susceptibility to GC and other compounds. A special strategy should be developed to evaluate the possible adverse effects of licorice. Multidose pharmacokinetics should be characterized more fully.

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Conflict of Interest

All authors declare that they have no competing interests.

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