

# The Pharmacological Activities of Licorice

## Authors

Rui Yang, Li-qiang Wang, Bo-chuan Yuan, Ying Liu

## Affiliation

School of Chinese Pharmacy, Beijing University of Chinese Medicine, Beijing, China

## Key words

- licorice
- Leguminosae
- pharmacological activities

**received** Sept. 13, 2014  
**revised** July 17, 2015  
**accepted** July 23, 2015

## Bibliography

**DOI** <http://dx.doi.org/10.1055/s-0035-1557893>  
 Published online September 14, 2015  
 Planta Med 2015; 81:  
 1654–1669 © Georg Thieme  
 Verlag KG Stuttgart · New York ·  
 ISSN 0032-0943

## Correspondence

**Dr. Ying Liu**  
 School of Chinese Pharmacy  
 Beijing University of Chinese  
 Medicine  
 Wangjing Zhonghuan South  
 Street  
 Chaoyang District  
 Beijing, 100102  
 China  
 Phone: + 86 10 84 73 86 46  
 Fax: + 86 10 84 73 86 11  
 liuyliwd@vip.sina.com

## 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.

## 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-deoxyglycyrrhetic acid  
 DPPH: 1,1-diphenyl-2-picrylhydrazyl  
 EC: echinatin  
 ERK: extracellular signal-regulated kinase  
 FAK: focal adhesion kinase  
 GA: glycyrrhetic 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: phosphatidylinositol 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, Kyrgyzstan, 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**.

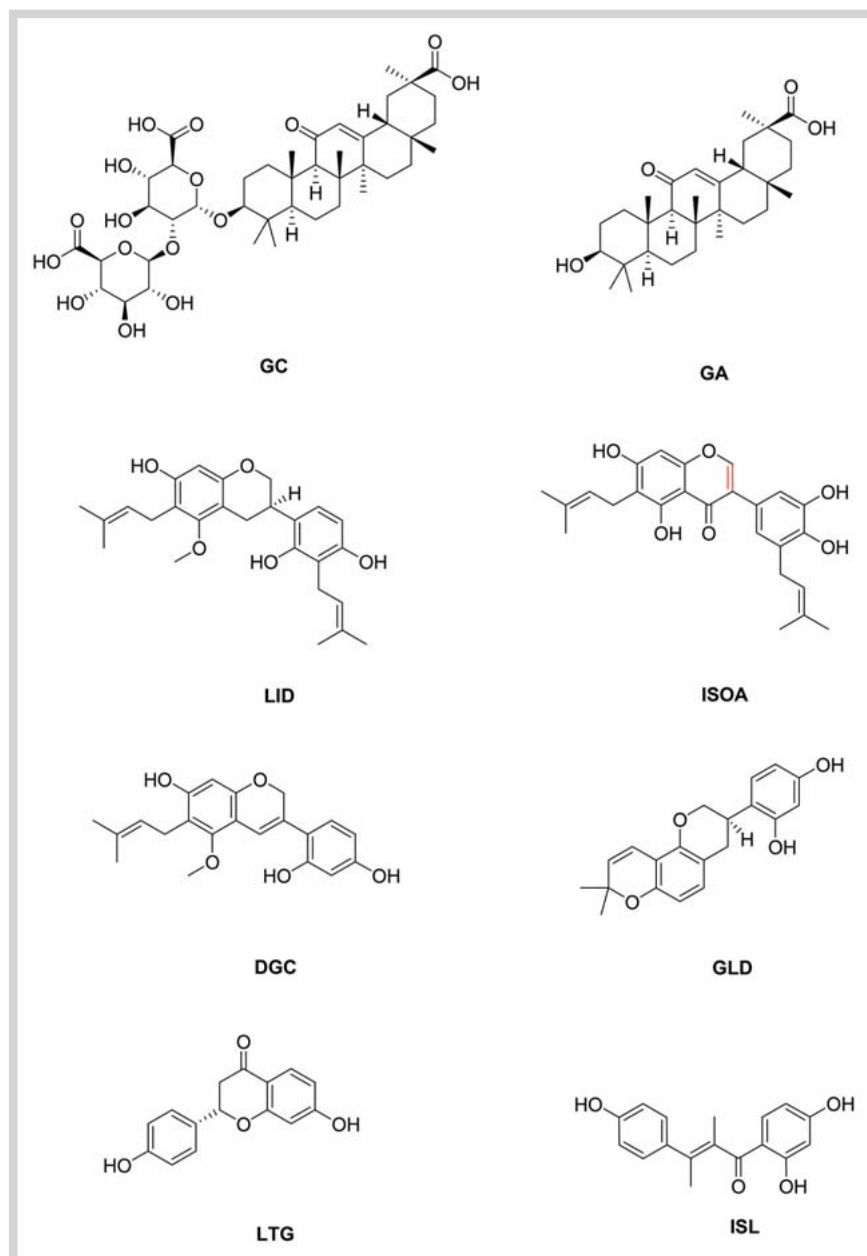
### Antitumor activity

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- $\alpha$ , 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 down-regulates the expression of NF- $\kappa$ B, 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], reactivates 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.)

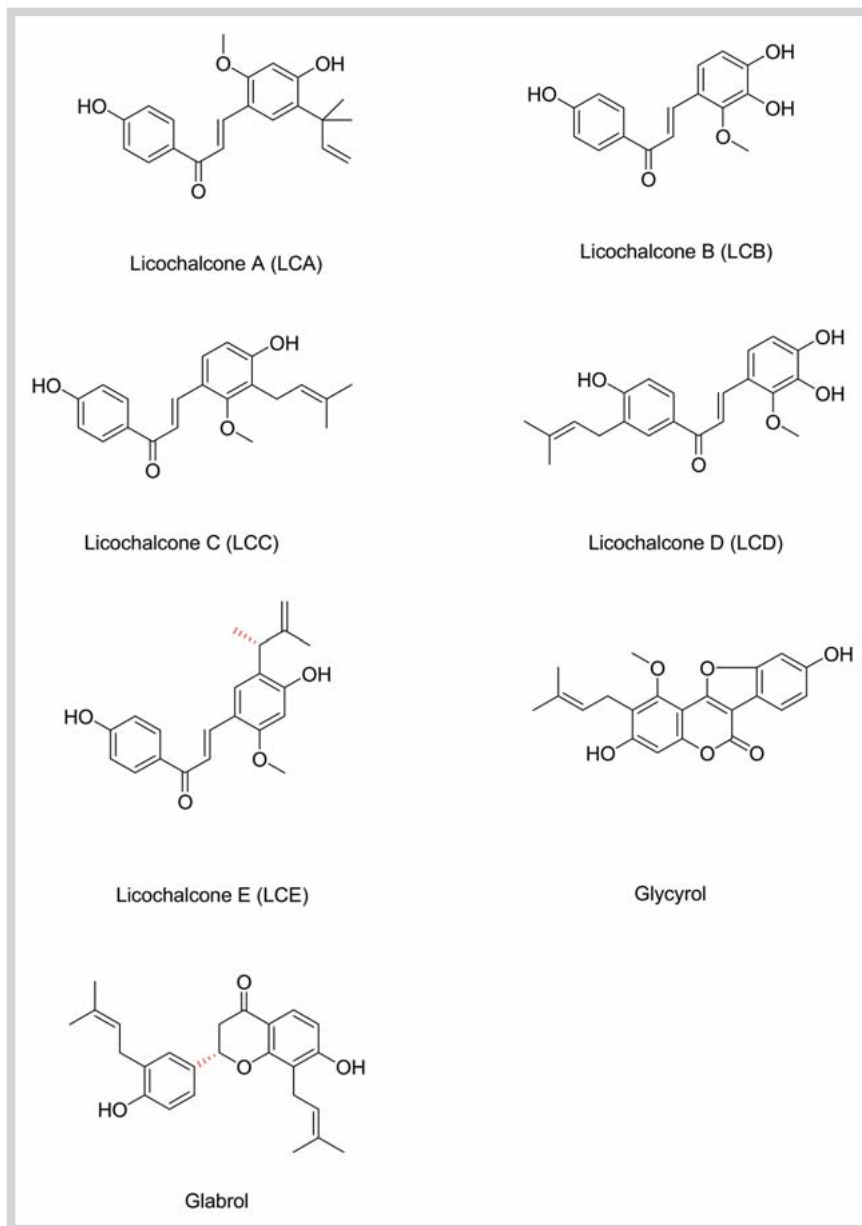


**Fig. 2** Chemical structures of GC, GA, LID, ISOA, DGC, GLD, LTG, and ISL. (Color figure available online only.)

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-dimethylhydrazine-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 melanoma 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 18 $\beta$ -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 18 $\beta$ -GA suppress proinflammatory cytokine COX-2, iNOS, TNF- $\alpha$ , HMGP 1, PGE2, myeloperoxidase, DPPH radicals, IL-6, IL-10, TGF- $\beta$ , and NF- $\kappa$ B, 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-1 $\beta$  [39], and LID and LIA inhibit the activation of NF- $\kappa$ B 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- $\kappa$ B 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- $\alpha$ , 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.

Com-pounds	The possible mechanisms for cancer prevention	Cancer types	References
GC	GC attenuates the level of TNF- $\alpha$ and declines the depletion of the mucous layer and the shifting of sialomucin to sulphomucin. GC induces apoptosis through the caspase- and mitochondria-dependent pathways.	Colon carcinogenesis Leukemia	[8] [18]
18 $\beta$ -GA	18 $\beta$ -GA induces apoptosis and prevents the invasion of DU-145 cells on Matrigel-coated transwells via the downregulation of NF- $\kappa$ B, vascular endothelial growth factor, and NMP-9 expression. 18 $\beta$ -GA induces apoptosis and cell cycle arrest in the G2 phase.	Prostate cancer Gastric cancer	[19] [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. As a potent molecular inhibitor of CDK2 and mammalian target of rapamycin. ISOA suppresses cell cycle progression at the G1 phase and blocks the expression of G1 phase regulatory proteins.	Colorectal cancer Prostate cancer Human melanoma	[11] [20] [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. LCA blocks cell cycle progression at the G2/M transition and induces apoptosis. LCA increases intracellular rROS levels resulting in an oxidative stress status. LCA induces apoptosis by endoplasmic reticulum stress via a phospholipase C $\gamma$ 1-, Ca $^{2+}$ -, and reactivates ROS-dependent pathway. LCA induces apoptosis by a caspase-dependent FasL-mediated death receptor pathway.	Liver cancer Gastric cancer Bladder cancer Liver cancer Oral cancer	[22] [23] [24] [25] [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 18 $\beta$ -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 controlling 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.

Com-pounds	The possible mechanisms for inflammation prevention	Inflammatory types	Refer-ences
GC	GC suppresses proinflammatory COX-2, iNOS, and TNF- $\alpha$ , 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- $\alpha$ , IL-6, and NF- $\kappa$ B, 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- $\kappa$ B 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- $\beta$ .	<i>Leishmania donovani</i> -infected macrophages	[36]
18 $\beta$ -GA	18 $\beta$ -GA reduces mRNA expression of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6.	Indomethacin-induced small intestinal damage	[37]
	18 $\beta$ -GA attenuates the generation of excessive NO, PGE2, and ROS by suppressing the expression of proinflammatory genes through the inhibition of NF- $\kappa$ B and PI3K activity. It also reduces the protein and mRNA levels of iNOS and COX-2.	LPS-induced inflammatory response	[35]
	18 $\beta$ -GA increases antioxidant defense systems and decreases lipid peroxidations.	Ischemia/reperfusion	[38]
GLD	GLD inhibits the release of NO and IL-1 $\beta$ .	LPS-induced J774A.1 murine macrophages	[39]
ISL	ISL inhibits the production of NO, IL-1 $\beta$ , 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- $\kappa$ B 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- $\kappa$ B 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- $\alpha$ , and decreases NF- $\kappa$ B 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]
LCB	LCA exhibits potent inhibition of lipid peroxidation.	In rat liver microsomes	[41]
	LCB inhibits the LPS-induced activation of PKA, and reduces the LPS-induced production of NO, TNF- $\alpha$ 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]
LCC	LCB inhibits LPS-induced ROS production.	LPS-induced RAW 264.7 cell	[41]
	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 inhibits mast cell degranulation.	Allergic inflammation	[48]
LCE	LCD inhibits the LPS-induced activation of PKA, and reduces the LPS-induced production of NO, TNF- $\alpha$ , and MCP-1.	LPS-induced inflammatory response	[46]
	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- $\kappa$ B.	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 spe-

cific immune functions and activates immune cells [68,69]. In addition, GC, 18 $\beta$ -GA, LCA, LTC, 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- $\gamma$ , and

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

Com-pounds	The possible mechanisms for viral prevention	Virus types	Refer-ences
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 $\beta$ -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]
18 $\beta$ -GA	18 $\beta$ -GA reduces the levels of viral proteins VP2, VP6, and NSP2.	Rotavirus	[66]
	18 $\beta$ -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.

Com-pounds	The possible mechanisms for immunoregulatory activity	Therapeutic effect	References
GC	GC inhibits OVA-induced increases in airway resistance and eosinophil count, recovers the level of IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid, and increases the IFN- $\gamma$ 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]
18 $\beta$ -GA	18 $\beta$ -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]
	18 $\beta$ -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 IFN $\gamma$ 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 inhibits H <sub>2</sub> O <sub>2</sub> , NO, IFN- $\gamma$ , TNF- $\alpha$ , 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- $\gamma$ , and TNF- $\alpha$ 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- $\gamma$ 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- $\gamma$  and IL-2 via the CD4+ Th1 immune response [72]. LCA inhibits H<sub>2</sub>O<sub>2</sub>, NO, IFN- $\gamma$ , TNF- $\alpha$ , and IL-17 production, and modulates the immune re-

sponse on both Th1 and Th17 cells [73]. GP promotes  $\gamma\delta$ T cell proliferation and IFN- $\gamma$  and TNF- $\alpha$  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.	<i>C. albicans</i>	[96]
LCE	LCE reduces the production of $\alpha$ -toxin.	<i>S. aureus</i>	[97]
LCA	LCA inhibits the biofilm formation and prevents the yeast-hyphal transition.	<i>C. albicans</i>	[96]
LTG	LTG decreases the production of $\alpha$ -hemolysin.	<i>S. aureus</i>	[98]
18 $\beta$ -GA	18 $\beta$ -GA reduces the expression of key virulence genes, including <i>saeR</i> and <i>hla</i> .	<i>S. aureus</i>	[83]
	18 $\beta$ -GA exerts Th1-immunological adjuvant activity.	<i>C. albicans</i>	[99]
	Not mentioned.	<i>M. bovis</i>	[100]
LIA	Not mentioned.	<i>S. mutans</i> , <i>S. sobrinus</i> , <i>P. gingivalis</i> and <i>Prevotella intermedia</i>	[101]
LID	Not mentioned.	<i>S. mutans</i> , <i>S. sobrinus</i> , <i>P. gingivalis</i> , <i>P. intermedia</i> and <i>Fusobacterium nucleatum</i>	[101]
Glycyrrhizol A	Not mentioned.	Cariogenic bacteria like <i>S. mutans</i>	[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 immunomodulatory 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 supercritical 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 *Alternaria solani*, *Botrytis cinerea*, and *Phytophthora* [95].

Several compounds isolated from licorice, such as 18 $\beta$ -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*  $\alpha$ -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- $\kappa$ B 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 PPAR $\gamma$  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- $\kappa$ B pathway by increasing SOD activity, decreasing the peroxide degradation product malondialdehyde level, and decreasing proinflammatory cytokine TGF- $\beta$ 1 expression, AGEs-induced RAGE, and NF- $\kappa$ B 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 PPAR $\gamma$ 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]
Licoagron, licoagro-din, 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- $\beta$  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<sub>4</sub> [117,118], and hepatotoxicity induced by xanthium [119],  $\alpha$ -naphthyliso-

thiocyanates [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 hepatoprotective 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- $\kappa$ B [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-3 and 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 reduces the expression level of Smac, which inhibits c-IAP1 activity, ultimately inhibiting the activity of caspase-3. It inhibits CCl <sub>4</sub> -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- $\alpha$ -induced chronic liver inflammation by attenuating NF- $\kappa$ B 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- $\kappa$ B.	[129]
DGC	DGC possesses hepatoprotective effects against centrilobular injury caused by CCl <sub>4</sub> 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, glutathione 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 adrenocorticotrophic hormone formation, stimulated steroidogenesis directly in mice adrenal glands, and also stimulated the secretion of glucocorticoids, mineralocorticoids, and anterior pituitary corticotroph-releasing hormone and vasopressin from the adrenal cortex [132, 133].

Among the compounds isolated from licorice, 18 $\beta$ -GA, GC, and ISL exert the adrenal cortical hormone like function. ISL has significant estrogenic activities due to its estrogen responsive  $\beta$  selectivity, partial estrogen agonist activity, and the nonenzymatic transformation between ISL and LTG [134]. 18 $\beta$ -GA and GC play a very important role in the treatment of glucocorticoid-dependent diseases as a well-known inhibitor of 11 $\beta$ -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 anti-amnesic 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 demonstrate 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 chronic, 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 Pharmacopoeia. 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 saprodonia [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 se-

verity 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 has 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  $11\beta$ -hydroxysteroid dehydrogenase deficiency. Harahap et al. [162] believed that licorice ingestion, as well as mutations in the HSD11B2 gene, inhibited  $11\beta$ -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 evaluation 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.

## Acknowledgements

This work was supported by the Beijing Project for Young Talents (YETP0819) and National Science Foundation of China (81503181).

## Conflict of Interest

All authors declare that they have no competing interests.

## References

- National Pharmacopoeia Committee. Pharmacopoeia of the People's Republic of China. Part 1. Beijing: Chemical Industry Press; 2010: 80–81
- Delectis Flora Reipublicae Popularis Sinicae Agendae Academiae Sinicae Edita. Flora Reipublicae Popularis Sinicae, Vol. 42 (2). Beijing: Science Press; 1998: 169
- Xie JB. Researches on the therapeutic basis and system of evaluation target of genuineness of liquorice [dissertation]. Beijing: Beijing University of Chinese Medicine; 2009: 11–12
- Mukherjee M, Bhaskaran N, Srinath R, Shivaprasad HN, Allan JJ, Shekhar D, Agarwal A. Anti-ulcer and antioxidant activity of GutGard. Indian J Exp Biol 2010; 48: 269–274
- Li JY, Cao HY, Liu P, Cheng GH, Sun MY. Glycyrrhizic acid in the treatment of liver diseases: literature review. Biomed Res Int 2014; 2014: 872139
- Methlie P, Husebye EE, Hustad S, Lien EA, Lovas K. Grapefruit juice and licorice increase cortisol availability in patients with Addison's disease. Eur J Endocrinol 2011; 165: 761–769
- Li J, Xu H, Ke X, Tian J. The anti-tumor performance of docetaxel liposomes surface-modified with glycyrrhetic acid. J Drug Target 2012; 20: 467–473
- Khan R, Khan AQ, Lateef A, Rehman MU, Tahir M, Ali F, Hamiza OO, Sultana S. Glycyrrhizic acid suppresses the development of precancerous lesions via regulating the hyperproliferation, inflammation, angiogenesis and apoptosis in the colon of Wistar rats. PLoS One 2013; 8: e56020
- Kim ME, Kim HK, Kim DH, Yoon JH, Lee JS. 18beta-Glycyrrhetic acid from licorice root impairs dendritic cells maturation and Th1 immune responses. Immunopharmacol Immunotoxicol 2013; 35: 329–335
- Lin D, Zhong W, Li J, Zhang B, Song G, Hu T. Involvement of BID translocation in glycyrrhetic acid and 11-deoxy glycyrrhetic acid-induced attenuation of gastric cancer growth. Nutr Cancer 2014; 66: 463–473
- Huang W, Tang S, Qiao X, Ma W, Ji S, Wang K, Ye M, Yu S. Isoangustone A induces apoptosis in SW480 human colorectal adenocarcinoma cells by disrupting mitochondrial functions. Fitoterapia 2014; 94: 36–47
- Hsu YL, Wu LY, Hou MF, Tsai EM, Lee JN, Liang HL, Jong YJ, Hung CH, Kuo PL. Glabridin, an isoflavan from licorice root, inhibits migration, invasion and angiogenesis of MDA-MB-231 human breast adenocarcinoma cells by inhibiting focal adhesion kinase/Rho signaling pathway. Mol Nutr Food Res 2011; 55: 318–327
- Park I, Park KK, Park JH, Chung WY. Isoliquiritigenin induces G2 and M phase arrest by inducing DNA damage and by inhibiting the metaphase/anaphase transition. Cancer Lett 2009; 277: 174–181
- Kim YH, Shin EK, Kim DH, Lee HH, Park JH, Kim JK. Antiangiogenic effect of licochalcone A. Biochem Pharmacol 2010; 80: 1152–1159
- Szliszka E, Jaworska D, Ksek M, Czuba ZP, Krol W. Targeting death receptor TRAIL-R2 by chalcones for TRAIL-induced apoptosis in cancer cells. Int J Mol Sci 2012; 13: 15343–15359
- Yuan X, Li T, Xiao E, Zhao H, Li Y, Fu S, Gan L, Wang Z, Zheng Q, Wang Z. Licochalcone B inhibits growth of bladder cancer cells by arresting cell cycle progression and inducing apoptosis. Food Chem Toxicol 2014; 65: 242–251
- Kwon SJ, Park SY, Kwon GT, Lee KW, Kang YH, Choi MS, Yun JW, Jeon JH, Jun JG, Park JH. Licochalcone E present in licorice suppresses lung metastasis in the 4T1 mammary orthotopic cancer model. Cancer Prev Res (Phila) 2013; 6: 603–613
- Chueh FS, Hsiao YT, Chang SJ, Wu PP, Yang JS, Lin JJ, Chung JG, Lai TY. Glycyrrhizic acid induces apoptosis in WEHI-3 mouse leukemia cells through the caspase- and mitochondria-dependent pathways. Oncol Rep 2012; 28: 2069–2076
- Shetty AV, Thirugnanam S, Dakshinamoorthy G, Samyuktty A, Zheng G, Chen A, Bosland MC, Kajdacsy-Balla A, Gnanasekar M. 18alpha-glycyrrhetic acid targets prostate cancer cells by down-regulating inflammation-related genes. Int J Oncol 2011; 39: 635–640
- Lee E, Son JE, Byun S, Lee SJ, Kim YA, Liu K, Kim J, Lim SS, Park JH, Dong Z, Lee KW, Lee HJ. CDK2 and mTOR are direct molecular targets of isoangustone A in the suppression of human prostate cancer cell growth. Toxicol Appl Pharmacol 2013; 272: 12–20
- Song NR, Lee E, Byun S, Kim JE, Mottamal M, Park JH, Lim SS, Bode AM, Lee HJ, Lee KW, Dong Z. Isoangustone A, a novel licorice compound, inhibits cell proliferation by targeting PI3K, MKK4, and MKK7 in human melanoma. Cancer Prev Res (Phila) 2013; 6: 1293–1303
- Tsai JP, Hsiao PC, Yang SF, Hsieh SC, Bau DT, Ling CL, Pai CL, Hsieh YH. Licochalcone A suppresses migration and invasion of human hepatocellular carcinoma cells through downregulation of MKK4/JNK via NF-kappaB mediated urokinase plasminogen activator expression. PLoS One 2014; 9: e86537
- Xiao XY, Hao M, Yang XY, Ba Q, Li M, Ni SJ, Wang LS, Du X. Licochalcone A inhibits growth of gastric cancer cells by arresting cell cycle progression and inducing apoptosis. Cancer Lett 2011; 302: 69–75
- Jiang J, Yuan X, Zhao H, Yan X, Sun X, Zheng Q. Licochalcone A inhibiting proliferation of bladder cancer T24 cells by inducing reactive oxygen species production. Biomed Mater Eng 2014; 24: 1019–1025
- Choi AY, Choi JH, Hwang KY, Jeong YJ, Cho W, Yoon KS, Ha J, Kim SS, Yoon JH, Yeo EJ, Kang I. Licochalcone A induces apoptosis through endoplasmic reticulum stress via a phospholipase Cgamma1-1-, Ca(2+)-, and reactive oxygen species-dependent pathway in HepG2 human hepatocellular carcinoma cells. Apoptosis 2014; 19: 682–697
- Kim JS, Park MR, Lee SY, Kim DK, Moon SM, Kim CS, Cho SS, Yoon G, Im HJ, You JS, Oh JS, Kim SG. Licochalcone A induces apoptosis in KB human oral cancer cells via a caspase-dependent FasL signaling pathway. Oncol Rep 2014; 31: 755–762
- Wang KL, Hsia SM, Chan CJ, Chang FY, Huang CY, Bau DT, Wang PS. Inhibitory effects of isoliquiritigenin on the migration and invasion of human breast cancer cells. Expert Opin Ther Targets 2013; 17: 337–349
- Lee SK, Park KK, Park JH, Lim SS, Chung WY. The inhibitory effect of roasted licorice extract on human metastatic breast cancer cell-induced bone destruction. Phytother Res 2013; 27: 1776–1783
- Seon MR, Park SY, Kwon SJ, Lim SS, Choi HJ, Park H, Lim DY, Kim JS, Lee CH, Kim J, Park JH. Hexane/ethanol extract of *Glycyrrhiza uralensis* and its active compound isoangustone A induce G1 cycle arrest in DU145 human prostate and 4T1 murine mammary cancer cells. J Nutr Biochem 2012; 23: 85–92

- 30 Wolkerstorfer A, Kurz H, Bachhofner N, Szolar OH. Glycyrrhizin inhibits influenza A virus uptake into the cell. *Antiviral Res* 2009; 83: 171–178
- 31 Luo L, Jin Y, Kim ID, Lee JK. Glycyrrhizin attenuates kainic Acid-induced neuronal cell death in the mouse hippocampus. *Exp Neurobiol* 2013; 22: 107–115
- 32 Imai K, Takagi Y, Iwazaki A, Nakanishi K. Radical scavenging ability of glycyrrhizin. *Free Radic Antioxid* 2013; 3: 40–42
- 33 Fu Y, Zhou E, Wei Z, Liang D, Wang W, Wang T, Guo M, Zhang N, Yang Z. Glycyrrhizin inhibits the inflammatory response in mouse mammary epithelial cells and a mouse mastitis model. *FEBS J* 2014; 281: 2543–2557
- 34 Ni YF, Kuai JK, Lu ZF, Yang GD, Fu HY, Wang J, Tian F, Yan XL, Zhao YC, Wang YJ, Jiang T. Glycyrrhizin treatment is associated with attenuation of lipopolysaccharide-induced acute lung injury by inhibiting cyclooxygenase-2 and inducible nitric oxide synthase expression. *J Surg Res* 2011; 165: e29–e35
- 35 Wang CY, Kao TC, Lo WH, Yen GC. Glycyrrhizic acid and 18beta-glycyrrhetic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF-kappaB through PI3K p110delta and p110gamma inhibitions. *J Agric Food Chem* 2011; 59: 7726–7733
- 36 Bhattacharjee S, Bhattacharjee A, Majumdar S, Majumdar SB, Majumdar S. Glycyrrhizic acid suppresses Cox-2-mediated anti-inflammatory responses during Leishmania donovani infection. *J Antimicrob Chemother* 2012; 67: 1905–1914
- 37 Ishida T, Miki I, Tanahashi T, Yagi S, Kondo Y, Inoue J, Kawachi S, Nishiumi S, Yoshida M, Maeda H, Tode C, Takeuchi A, Nakayama H, Azuma T, Mizuno S. Effect of 18beta-glycyrrhetic acid and hydroxypropyl gamma-cyclodextrin complex on indomethacin-induced small intestinal injury in mice. *Eur J Pharmacol* 2013; 714: 125–131
- 38 Oztanir MN, Ciftci O, Cetin A, Durak MA, Basak N, Akyuva Y. The beneficial effects of 18beta-glycyrrhetic acid following oxidative and neuronal damage in brain tissue caused by global cerebral ischemia/reperfusion in a C57BL/6J mouse model. *Neuro Sci* 2014; 35: 1221–1228
- 39 Thiyagarajan P, Chandrasekaran CV, Deepak HB, Agarwal A. Modulation of lipopolysaccharide-induced pro-inflammatory mediators by an extract of *Glycyrrhiza glabra* and its phytoconstituents. *Inflammopharmacology* 2011; 19: 235–241
- 40 La VD, Tanabe S, Bergeron C, Gafner S, Grenier D. Modulation of matrix metalloproteinase and cytokine production by licorice isolates licoridin and licorisoflavan A: potential therapeutic approach for periodontitis. *J Periodontol* 2011; 82: 122–128
- 41 Fu Y, Chen J, Li YJ, Zheng YF, Li P. Antioxidant and anti-inflammatory activities of six flavonoids separated from licorice. *Food Chem* 2013; 141: 1063–1071
- 42 Kim J, Kim J, Shim J, Lee S, Kim J, Lim SS, Lee KW, Lee HJ. Licorice-derived dehydroglyasperin C increases MKP-1 expression and suppresses inflammation-mediated neurodegeneration. *Neurochem Int* 2013; 63: 732–740
- 43 Kim HJ, Lim SS, Park IS, Lim JS, Seo JY, Kim JS. Neuroprotective effects of dehydroglyasperin C through activation of heme oxygenase-1 in mouse hippocampal cells. *J Agric Food Chem* 2012; 60: 5583–5589
- 44 Wananukul S, Chatproedprai S, Chunharas A, Limpongsanuruk W, Singalavanija S, Nitiyaram R, Wisuthasarewong W. Randomized, double-blind, split-side, comparison study of moisturizer containing licochalcone A and 1% hydrocortisone in the treatment of childhood atopic dermatitis. *J Med Assoc Thai* 2013; 96: 1135–1142
- 45 Chu X, Jiang L, Wei M, Yang X, Guan M, Xie X, Wei J, Liu D, Wang D. Attenuation of allergic airway inflammation in a murine model of asthma by Licochalcone A. *Immunopharmacol Immunotoxicol* 2013; 35: 653–661
- 46 Furusawa J, Funakoshi-Tago M, Mashino T, Tago K, Inoue H, Sonoda Y, Kasahara T. Glycyrrhiza inflata-derived chalcones, Licochalcone A, Licochalcone B and Licochalcone D, inhibit phosphorylation of NF-kappaB p65 in LPS signaling pathway. *Int Immunopharmacol* 2009; 9: 499–507
- 47 Wang Z, Cao Y, Paudel S, Yoon G, Cheon SH. Concise synthesis of licochalcone C and its regioisomer, licochalcone H. *Arch Pharm Res* 2013; 36: 1432–1436
- 48 Tanifuji S, Aizu-Yokota E, Funakoshi-Tago M, Sonoda Y, Inoue H, Kasahara T. Licochalcones suppress degradation by decreasing the intracellular Ca<sup>2+</sup> level and tyrosine phosphorylation of ERK in RBL-2H3 cells. *Int Immunopharmacol* 2010; 10: 769–776
- 49 Lee HN, Cho HJ, Lim DY, Kang YH, Lee KW, Park JH. Mechanisms by which licochalcone e exhibits potent anti-inflammatory properties: studies with phorbol ester-treated mouse skin and lipopolysaccharide-stimulated murine macrophages. *Int J Mol Sci* 2013; 14: 10926–10943
- 50 Cho YC, Lee SH, Yoon G, Kim HS, Na JY, Choi HJ, Cho CW, Cheon SH, Kang BY. Licochalcone E reduces chronic allergic contact dermatitis and inhibits IL-12p40 production through down-regulation of NF-kappa B. *Int Immunopharmacol* 2010; 10: 1119–1126
- 51 Nirmala P, Selvaraj T. Anti-inflammatory and anti-bacterial activities of *Glycyrrhiza glabra* L. *Int J Agric Technol* 2011; 7: 815–823
- 52 Wu TY, Khor TO, Saw CL, Loh SC, Chen AI, Lim SS, Park JH, Cai L, Kong AN. Anti-inflammatory/Anti-oxidative stress activities and differential regulation of Nrf2-mediated genes by non-polar fractions of tea *Chrysanthemum zawadskii* and licorice *Glycyrrhiza uralensis*. *AAPS J* 2011; 13: 1–13
- 53 Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P, Ephantimos IE, Kitai I, Mederski BD, Shadowitz SB, Gold WL, Hawryluck LA, Rea E, Chenkin JS, Cescon DW, Poutanen SM, Detsky AS. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; 289: 2801–2809
- 54 Wang J, Chen X, Wang W, Zhang Y, Yang Z, Jin Y, Ge HM, Li E, Yang G. Glycyrrhizic acid as the antiviral component of *Glycyrrhiza uralensis* Fisch. against coxsackievirus A16 and enterovirus 71 of hand foot and mouth disease. *J Ethnopharmacol* 2013; 147: 114–121
- 55 Kwon HJ, Kim HH, Ryu YB, Kim JH, Jeong HJ, Lee SW, Chang JS, Cho KO, Rho MC, Park SJ, Lee WS. In vitro anti-rotavirus activity of polyphenol compounds isolated from the roots of *Glycyrrhiza uralensis*. *Bioorg Med Chem* 2010; 18: 7668–7674
- 56 Shebl RI, Amin MA, Emad-Eldin A, Bin DS, Mostafa AS, Ibrahim EH, Mohamed AF. Antiviral activity of liquorice powder extract against varicella zoster virus isolated from Egyptian patients. *Chang Gung Med J* 2012; 35: 231–239
- 57 Matsumoto Y, Matsuura T, Aoyagi H, Matsuda M, Hmwe SS, Date T, Watanabe N, Wataishi K, Suzuki R, Ichinose S, Wake K, Suzuki T, Miyamura T, Wakita T, Aizaki H. Antiviral activity of glycyrrhizin against hepatitis C virus in vitro. *PLoS One* 2013; 8: e68992
- 58 Huang W, Chen X, Li Q, Li P, Zhao G, Xu M, Xie P. Inhibition of intercellular adhesion in herpes simplex virus infection by glycyrrhizin. *Cell Biochem Biophys* 2012; 62: 137–140
- 59 Soufy H, Yassein S, Ahmed AR, Khodier MH, Kutkat MA, Nasr SM, Okda FA. Antiviral and immune stimulant activities of glycyrrhizin against duck hepatitis virus. *Afr J Tradit Complement Altern Med* 2012; 9: 389–395
- 60 Michaelis M, Geiler J, Naczek P, Sithisarn P, Ogbomo H, Altenbrandt B, Leutz A, Doerr HW, Cinatl jr. J. Glycyrrhizin inhibits highly pathogenic H5N1 influenza A virus-induced pro-inflammatory cytokine and chemokine expression in human macrophages. *Med Microbiol Immunol* 2010; 199: 291–297
- 61 Sasaki H, Takei M, Kobayashi M, Pollard RB, Suzuki F. Effect of glycyrrhizin, an active component of licorice roots, on HIV replication in cultures of peripheral blood mononuclear cells from HIV-seropositive patients. *Pathobiology* 2002; 70: 229–236
- 62 Kang H, Lieberman PM. Mechanism of glycyrrhizic acid inhibition of Kaposi's sarcoma-associated herpesvirus: disruption of CTCF-cohesin-mediated RNA polymerase II pausing and sister chromatid cohesion. *J Virol* 2011; 85: 11159–11169
- 63 Smirnov VS, Zarubaev VV, Anfimov PM, Shtro AA. [Effect of a combination of glutamyl-tryptophan and glycyrrhizic acid on the course of acute infection caused by influenza (H3H2) virus in mice]. *Vopr Virusol* 2012; 57: 23–27
- 64 Moisy D, Avilov SV, Jacob Y, Laoide BM, Ge X, Baudin F, Naffakh N, Jestin JL. HMGb1 protein binds to influenza virus nucleoprotein and promotes viral replication. *J Virol* 2012; 86: 9122–9133
- 65 Sui X, Yin J, Ren X. Antiviral effect of diammonium glycyrrhizinate and lithium chloride on cell infection by pseudorabies herpesvirus. *Antiviral Res* 2010; 85: 346–353
- 66 Hardy ME, Hendricks JM, Paulson JM, Faunce NR. 18beta-glycyrrhetic acid inhibits rotavirus replication in culture. *Virology* 2012; 9: 96
- 67 Baltina jr. LA, Chistoedova ES, Baltina LA, Kondratenko RM, Plysunova OA. Synthesis and anti-HIV-1 activity of new conjugates of 18β- and 18α-glycyrrhizic acids with aspartic acid esters. *Chem Nat Compd* 2012; 48: 262–266
- 68 Hong YK, Wu HT, Ma T, Liu WJ, He XJ. Effects of *Glycyrrhiza glabra* polysaccharides on immune and antioxidant activities in high-fat mice. *Int J Biol Macromol* 2009; 45: 61–64

- 69 Li X, He X, Liu B, Xu L, Lu C, Zhao H, Niu X, Chen S, Lu A. Maturation of murine bone marrow-derived dendritic cells induced by Radix Glycyrrhizae polysaccharide. *Molecules* 2012; 17: 6557–6568
- 70 Ma C, Ma Z, Liao XL, Liu J, Fu Q, Ma S. Immunoregulatory effects of glycyrrhizic acid exerts anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4(+)CD25(+)Foxp3+ regulatory T cells in ovalbumin-sensitized mice. *J Ethnopharmacol* 2013; 148: 755–762
- 71 Li J, Tu Y, Tong L, Zhang W, Zheng J, Wei Q. Immunosuppressive activity of the murine immune responses of glycyrol from *Glycyrrhiza uralensis* via inhibition of calcineurin activity. *Pharm Biol* 2010; 48: 1177–1184
- 72 Lee JY, Lee JH, Park JH, Kim SY, Choi JY, Lee SH, Kim YS, Kang SS, Jang EC, Han Y. Liquiritigenin, a licorice flavonoid, helps mice resist disseminated candidiasis due to *Candida albicans* by Th1 immune response, whereas liquiritin, its glycoside form, does not. *Int Immunopharmacol* 2009; 9: 632–638
- 73 Fontes LB, Dos Santos Dias D, de Carvalho LS, Mesquita HL, da Silva Reis L, Dias AT, Da Silva Filho A, do Amaral Correa J. Immunomodulatory effects of licochalcone A on experimental autoimmune encephalomyelitis. *J Pharm Pharmacol* 2014; 66: 886–894
- 74 Hendricks JM, Hoffman P, Pascual DW, Hardy ME. 18beta-glycyrrhetic acid delivered orally induces isolated lymphoid follicle maturation at the intestinal mucosa and attenuates rotavirus shedding. *PLoS One* 2012; 7: e49491
- 75 Abe M, Akbar F, Hasebe A, Horiike N, Onji M. Glycyrrhizin enhances interleukin-10 production by liver dendritic cells in mice with hepatitis. *J Gastroenterol* 2003; 38: 962–967
- 76 Dai JH, Iwatani Y, Ishida T, Terunuma H, Kasai H, Iwakura Y, Fujiwara H, Ito M. Glycyrrhizin enhances interleukin-12 production in peritoneal macrophages. *Immunology* 2001; 103: 235–243
- 77 Sun S, He X, Chai W, Lv C, Lv A, Yu C. Immunoregulation function of Glycyrrhizae Radix et Rhizoma polysaccharide to  $\gamma\delta$ T cells from human peripheral blood. *Chinese J Exper Tradit Med Formulae* 2013; 6: 72
- 78 He X, Li X, Liu B, Xu L, Zhao H, Lu A. Down-regulation of Treg cells and up-regulation of TH1/TH2 cytokine ratio were induced by polysaccharide from Radix Glycyrrhizae in H22 hepatocarcinoma bearing mice. *Molecules* 2011; 16: 8343–8352
- 79 Jain E, Pandey RK, Khanna R. Liquorice root extracts as potent cariostatic agents in pediatric practice. *J Indian Soc Pedod Prev Dent* 2013; 31: 146–152
- 80 Al-Turki AI, El-Ziney MG, Abdel-Salam AM. Chemical and anti-bacterial characterization of aqueous extracts of oregano, marjoram, sage and licorice and their application in milk and labneh. *JFAE* 2008; 6: 39
- 81 Park I, Kim J, Lee Y, Shin S. *In vivo* fungicidal activity of medicinal plant extracts against six phytopathogenic fungi. *Int J Pest Manage* 2008; 54: 63–68
- 82 Bodet C, La VD, Gafner S, Bergeron C, Grenier D. A licorice extract reduces lipopolysaccharide-induced proinflammatory cytokine secretion by macrophages and whole blood. *J Periodontol* 2008; 79: 1752–1761
- 83 Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM. 18beta-Glycyrrhetic acid inhibits methicillin-resistant *Staphylococcus aureus* survival and attenuates virulence gene expression. *Antimicrob Agents Chemother* 2013; 57: 241–247
- 84 Snowden R, Harrington H, Morrill K, Jeane L, Garrity J, Orian M, Lopez E, Rezaie S, Hassberger K, Familoni D, Moore J, Virdee K, Alborno-Sanchez L, Walker M, Cavins J, Russell T, Guse E, Reker M, Tschudy O, Wolf J, True T, Ukaegbu O, Ahaghotu E, Jones A, Polanco S, Rochon Y, Waters R, Langland J. A comparison of the anti-*Staphylococcus aureus* activity of extracts from commonly used medicinal plants. *J Altern Complement Med* 2014; 20: 375–382
- 85 Lau D, Plotkin BJ. Antimicrobial and biofilm effects of herbs used in traditional Chinese medicine. *Nat Prod Commun* 2013; 8: 1617–1620
- 86 Wittschier N, Faller G, Hensel A. Aqueous extracts and polysaccharides from liquorice roots (*Glycyrrhiza glabra* L.) inhibit adhesion of *Helicobacter pylori* to human gastric mucosa. *J Ethnopharmacol* 2009; 125: 218–223
- 87 Ahn SJ, Cho EJ, Kim HJ, Park SN, Lim YK, Kook JK. The antimicrobial effects of deglycyrrhizinated Licorice root extract on *Streptococcus mutans* UA159 in both planktonic and biofilm cultures. *Anaerobe* 2012; 18: 590–596
- 88 Peters MC, Tallman JA, Braun TM, Jacobson JJ. Clinical reduction of *S. mutans* in pre-school children using a novel liquorice root extract lollipop: a pilot study. *Eur Arch Paediatr Dent* 2010; 11: 274–278
- 89 Irani M, Sarmadi M, Bernard F, Ebrahimi PG, Shaker BH. Leaves antimicrobial activity of *Glycyrrhiza glabra* L. Iran *J Pharm Res* 2010; 9: 425–428
- 90 Fatima A, Gupta VK, Luqman S, Negi AS, Kumar JK, Shanker K, Saikia D, Srivastava S, Darokar MP, Khanuja SP. Antifungal activity of *Glycyrrhiza glabra* extracts and its active constituent glabridin. *Phytother Res* 2009; 23: 1190–1193
- 91 Awandkar SP, Mendhe MS, Badukale DM, Kulkarni MB. Antimicrobial action of cold aqueous and cold ethanolic root extracts of *Glycyrrhiza glabra* against bovine mammary pathogens. *Anim Sci Rep* 2012; 6: 88–91
- 92 Badr AE, Omar N, Badria FA. A laboratory evaluation of the antibacterial and cytotoxic effect of Liquorice when used as root canal medication. *Int Endod J* 2011; 44: 51–58
- 93 Yoshida T, Yoshida S, Kobayashi M, Herndon DN, Suzuki F. Pivotal advance: glycyrrhizin restores the impaired production of  $\beta$ -defensins in tissues surrounding the burn area and improves the resistance of burn mice to *Pseudomonas aeruginosa* wound infection. *J Leukoc Biol* 2010; 87: 35–41
- 94 Asha MK, Debraj D, Prashanth D, Edwin JR, Srikanth HS, Muruganatham N, Detha SM, Anirban B, Jaya B, Deepak M, Agarwal A. *In vitro* anti-*Helicobacter pylori* activity of a flavonoid rich extract of *Glycyrrhiza glabra* and its probable mechanisms of action. *J Ethnopharmacol* 2013; 145: 581–586
- 95 Treutwein J, Cergel S, Runte J, Nowak A, Konstantinidou-Doltsinis S, Kleeborg H, Schmitt A. Efficacy of *Glycyrrhiza glabra* extract fractions against phytopathogenic fungi. *Julius-Kühn-Archiv* 2010; 428: 82
- 96 Messier C, Grenier D. Effect of licorice compounds licochalcone A, glabridin and glycyrrhizic acid on growth and virulence properties of *Candida albicans*. *Mycoses* 2011; 54: e801–e806
- 97 Zhou T, Deng X, Qiu J. Antimicrobial activity of licochalcone E against *Staphylococcus aureus* and its impact on the production of staphylococcal alpha-toxin. *J Microbiol Biotechnol* 2012; 22: 800–805
- 98 Dai XH, Li HE, Lu CJ, Wang JF, Dong J, Wei JY, Zhang Y, Wang X, Tan W, Deng XM, Zhao SH, Zhang MJ. Liquiritigenin prevents *Staphylococcus aureus*-mediated lung cell injury via inhibiting the production of alpha-hemolysin. *J Asian Nat Prod Res* 2013; 15: 390–399
- 99 Kim J, Joo I, Kim H, Han Y. 18beta-glycyrrhetic acid induces immunological adjuvant activity of Th1 against *Candida albicans* surface mannan extract. *Phytomedicine* 2013; 20: 951–955
- 100 Zhou X, Zhao L, Liu X, Li X, Jia F, Zhang Y, Wang Y. Antimycobacterial and synergistic effects of 18beta-glycyrrhetic acid or glycyrrhetic acid-30-piperazine in combination with isoniazid, rifampicin or streptomycin against *Mycobacterium bovis*. *Phytother Res* 2012; 26: 253–258
- 101 Gafner S, Bergeron C, Villinski JR, Godejohann M, Kessler P, Cardellina JH, Ferreira D, Feghali K, Grenier D. Isoflavonoids and coumarins from *Glycyrrhiza uralensis*: antibacterial activity against oral pathogens and conversion of isoflavans into isoflavan-quinones during purification. *J Nat Prod* 2011; 74: 2514–2519
- 102 Hu CH, He J, Eckert R, Wu XY, Li LN, Tian Y, Lux R, Shuffer JA, Gelman F, Menten J, Spackman S, Bauer J, Anderson MH, Shi WY. Development and evaluation of a safe and effective sugar-free herbal lollipop that kills cavity-causing bacteria. *Int J Oral Sci* 2011; 3: 13–20
- 103 Feng L, Zhu MM, Zhang MH, Wang RS, Tan XB, Song J, Ding SM, Jia XB, Hu SY. Protection of glycyrrhizic acid against AGEs-induced endothelial dysfunction through inhibiting RAGE/NF-kappaB pathway activation in human umbilical vein endothelial cells. *J Ethnopharmacol* 2013; 148: 27–36
- 104 Alqahtani A, Hamid K, Kam A, Wong KH, Abdelhak Z, Razmovski-Naumovski V, Chan K, Li KM, Groundwater PW, Li GQ. The pentacyclic triterpenoids in herbal medicines and their pharmacological activities in diabetes and diabetic complications. *Curr Med Chem* 2013; 20: 908–931
- 105 Sen S, Roy M, Chakraborti AS. Ameliorative effects of glycyrrhizin on streptozotocin-induced diabetes in rats. *J Pharm Pharmacol* 2011; 63: 287–296
- 106 Yao K, Chen H, Lee MH, Li H, Ma W, Peng C, Song NR, Lee KW, Bode AM, Dong Z, Dong Z. Licochalcone A, a natural inhibitor of c-Jun N-terminal kinase 1. *Cancer Prev Res (Phila)* 2014; 7: 139–149
- 107 Park HG, Bak EJ, Woo GH, Kim JM, Quan Z, Kim JM, Yoon HK, Cheon SH, Yoon G, Yoo YJ, Na Y, Cha JH. Licochalcone E has an antidiabetic effect. *J Nutr Biochem* 2012; 23: 759–767

- 108 Gaur R, Yadav KS, Verma RK, Yadav NP, Bhakuni RS. *In vivo* anti-diabetic activity of derivatives of isoliquiritigenin and liquiritigenin. *Phyto-medicine* 2014; 21: 415–422
- 109 Li W, Li S, Higai K, Sasaki T, Asada Y, Ohshima S, Koike K. Evaluation of licorice flavonoids as protein tyrosine phosphatase 1B inhibitors. *Bio-org Med Chem Lett* 2013; 23: 5836–5839
- 110 Lee YS, Kim SH, Jung SH, Kim JK, Pan CH, Lim SS. Aldose reductase inhibitory compounds from *Glycyrrhiza uralensis*. *Biol Pharm Bull* 2010; 33: 917–921
- 111 Choi JH, Choi JN, Lee SY, Lee SJ, Kim K, Kim YK. Inhibitory activity of diacylglycerol acyltransferase by glabrol isolated from the roots of licorice. *Arch Pharm Res* 2010; 33: 237–242
- 112 Wu F, Jin Z, Jin J. Hypoglycemic effects of glabridin, a polyphenolic flavonoid from licorice, in an animal model of diabetes mellitus. *Mol Med Rep* 2013; 7: 1278–1282
- 113 Yehuda I, Madar Z, Szuchman-Sapir A, Tamir S. Glabridin, a phytoestrogen from licorice root, up-regulates manganese superoxide dismutase, catalase and paraoxonase 2 under glucose stress. *Phytother Res* 2011; 25: 659–667
- 114 Li J, Lee YS, Choi JS, Sung HY, Kim JK, Lim SS, Kang YH. Roasted licorice extracts dampen high glucose-induced mesangial hyperplasia and matrix deposition through blocking Akt activation and TGF-beta signaling. *Phytomedicine* 2010; 17: 800–810
- 115 Kataya HH, Hamza AA, Ramadan GA, Khasawneh MA. Effect of licorice extract on the complications of diabetes nephropathy in rats. *Drug Chem Toxicol* 2011; 34: 101–108
- 116 Saleem MMNM, Mohammad AAW, Al-Tameemi JA, Sulaiman GM. Biological study of the effect of licorice roots extract on serum lipid profile, liver enzymes and kidney function tests in albino mice. *Afr J Biotechnol* 2011; 10: 12702–12706
- 117 Huo HZ, Wang B, Liang YK, Bao YY, Gu Y. Hepatoprotective and antioxidant effects of licorice extract against CCl(4)-induced oxidative damage in rats. *Int J Mol Sci* 2011; 12: 6529–6543
- 118 Yin G, Cao L, Xu P, Jeney G, Nakao M, Lu C. Hepatoprotective and antioxidant effects of *Glycyrrhiza glabra* extract against carbon tetrachloride (CCl(4))-induced hepatocyte damage in common carp (*Cyprinus carpio*). *Fish Physiol Biochem* 2011; 37: 209–216
- 119 Abe K, Ikeda T, Wake K, Sato T, Sato T, Inoue H. Glycyrrhizin prevents of lipopolysaccharide/D-galactosamine-induced liver injury through down-regulation of matrix metalloproteinase-9 in mice. *J Pharm Pharmacol* 2008; 60: 91–97
- 120 Zhai D, Zhao Y, Chen X, Guo J, He H, Yu Q, Yang J, Davey AK, Wang J. Protective effect of glycyrrhizin, glycyrrhetic acid and matrine on acute cholestasis induced by alpha-naphthyl isothiocyanate in rats. *Planta Med* 2007; 73: 128–133
- 121 Sharifzadeh M, Shamsa F, Shiran S, Karimfar MH, Miri AH, Jalalizadeh H, Gholizadeh S, Salar F, Tabrizian K. A time course analysis of systemic administration of aqueous licorice extract on spatial memory retention in rats. *Planta Med* 2008; 74: 485–490
- 122 Wang YG, Zhou JM, Ma ZC, Li H, Liang QD, Tan HL, Xiao CR, Zhang BL, Gao Y. Pregnane X receptor mediated-transcription regulation of CYP3A by glycyrrhizin: a possible mechanism for its hepatoprotective property against lithocholic acid-induced injury. *Chem Biol Interact* 2012; 200: 11–20
- 123 Rasool M, Iqbal J, Malik A, Ramzan HS, Qureshi MS, Asif M, Qazi MH, Kamal MA, Chaudhary AG, Al-Qahtani MH, Gan SH, Karim S. Hepatoprotective effects of *Silybum marianum* (Silymarin) and *Glycyrrhiza glabra* (Glycyrrhizin) in combination: a possible synergy. *Evid Based Complement Alternat Med* 2014; 2014: 641597
- 124 Tripathi M, Singh BK, Kakkar P. Glycyrrhizic acid modulates t-BHP induced apoptosis in primary rat hepatocytes. *Food Chem Toxicol* 2009; 47: 339–347
- 125 Guo XL, Liang B, Wang XW, Fan FG, Jin J, Lan R, Yang JH, Wang XC, Jin L, Cao Q. Glycyrrhizic acid attenuates CCl(4)-induced hepatocyte apoptosis in rats via a p53-mediated pathway. *World J Gastroenterol* 2013; 19: 3781–3791
- 126 Fujisawa Y, Sakamoto M, Matsushita M, Fujita T, Nishioka K. Glycyrrhizin inhibits the lytic pathway of complement-possible mechanism of its anti-inflammatory effect on liver cells in viral hepatitis. *Microbiol Immunol* 2000; 44: 799–804
- 127 Chen HJ, Kang SP, Lee IJ, Lin YL. Glycyrrhetic acid suppressed NF-kappaB activation in TNF-alpha-induced hepatocytes. *J Agric Food Chem* 2014; 62: 618–625
- 128 Wu X, Zhang L, Gurley E, Studer E, Shang J, Wang T, Wang C, Yan M, Jiang Z, Hylemon PB, Sanyal AJ, Pandak Jr. WM, Zhou H. Prevention of free fatty acid-induced hepatic lipotoxicity by 18beta-glycyrrhetic acid through lysosomal and mitochondrial pathways. *Hepatology* 2008; 47: 1905–1915
- 129 Hasan S, Khan R, Ali N, Khan A, Rehman M, Tahir M, Lateef A, Nafees S, Mehdi S, Rashid S, Shahid A, Sultana S. 18-beta Glycyrrhetic acid alleviates 2-acetylaminofluorene-induced hepatotoxicity in Wistar rats: Role in hyperproliferation, inflammation and oxidative stress. *Hum Exp Toxicol*, advance online publication 28 Oct 2014; DOI: 10.1177/0960327114554045
- 130 Seo JY, Han JH, Kim YJ, Lim SS, Kim J. Protective effects of dehydroglyasperin c against carbon tetrachloride-induced liver damage in mice. *Food Sci Biotechnol* 2014; 23: 547–553
- 131 Al-Razuqi RAM, Al-Jawwad FH, Al-Hussaini JA, Al-Jeboori A. Hepatoprotective effect of *Glycyrrhiza glabra* in carbon tetrachloride-induced model of acute liver injury. *J Phys Pharm Adv* 2012; 2: 259–263
- 132 Lee HY, Jung DY, Ha H, Kang SS, Kim JS, Kim C. Induction of growth hormone release by *Glycyrrhizae Radix* on rat. *J Biochem Mol Biol* 2007; 40: 979–985
- 133 Kratschmar DV, Vuorinen A, Da Cunha T, Wolber G, Classen-Houben D, Doblhoff O, Schuster D, Odermatt A. Characterization of activity and binding mode of glycyrrhetic acid derivatives inhibiting 11beta-hydroxysteroid dehydrogenase type 2. *J Steroid Biochem Mol Biol* 2011; 125: 129–142
- 134 Hajirahimkhan A, Simmler C, Yuan Y, Anderson JR, Chen SN, Nikolic D, Dietz BM, Pauli GF, van Breemen RB, Bolton JL. Evaluation of estrogenic activity of licorice species in comparison with hops used in botanicals for menopausal symptoms. *PLoS One* 2013; 8: e67947
- 135 Raikkonen K, Seckl JR, Heinonen K, Pyhala R, Feldt K, Jones A, Pesonen AK, Phillips DI, Lahti J, Jarvenpaa AL, Eriksson JG, Matthews KA, Strandberg TE, Kajantie E. Maternal prenatal licorice consumption alters hypothalamic-pituitary-adrenocortical axis function in children. *Psychoneuroendocrinol* 2010; 35: 1587–1593
- 136 Sasaki H, Suzuki N, Alshwaimi E, Xu Y, Battaglini R, Morse L, Stashenko P. 18beta-glycyrrhetic acid inhibits periodontitis via glucocorticoid-independent nuclear factor-kappaB inactivation in interleukin-10-deficient mice. *J Periodontol Res* 2010; 45: 757–763
- 137 Al-Dujaili EA, Kenyon CJ, Nicol MR, Mason JJ. Licorice and glycyrrhetic acid increase DHEA and deoxycorticosterone levels *in vivo* and *in vitro* by inhibiting adrenal SUL2A1 activity. *Mol Cell Endocrinol* 2011; 336: 102–109
- 138 Chakravarthi KK, Avadhani R. Enhancement of hippocampal ca3 neuronal dendritic arborization by *Glycyrrhiza glabra* root extract treatment in Wistar albino rats. *J Nat Sci Biol Med* 2014; 5: 25–29
- 139 Chakravarthi KK, Avadhani R. Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: An experimental study. *J Nat Sci Biol Med* 2013; 4: 420–425
- 140 Michel HE, Tadros MG, Abdel-Naim AB, Khalifa AE. Prepulse inhibition (PPI) disrupting effects of *Glycyrrhiza glabra* extract in mice: a possible role of monoamines. *Neurosci Lett* 2013; 544: 110–114
- 141 Cui YM, Ao MZ, Li W, Yu LJ. Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. *Planta Med* 2008; 74: 377–380
- 142 Hasanein P. Glabridin as a major active isoflavan from *Glycyrrhiza glabra* (licorice) reverses learning and memory deficits in diabetic rats. *Acta Physiol Hung* 2011; 98: 221–230
- 143 Zhu Z, Li C, Wang X, Yang Z, Chen J, Hu L, Jiang H, Shen X. 2, 2', 4'-trihydroxychalcone from *Glycyrrhiza glabra* as a new specific BACE1 inhibitor efficiently ameliorates memory impairment in mice. *J Neurochem* 2010; 114: 374–385
- 144 Yu XY, Lin SG, Zhou ZW, Chen X, Liang J, Yu XQ, Chowbay B, Wen JY, Duan W, Chan E, Li XT, Cao J, Li CG, Xue CC, Zhou SF. Role of P-glycoprotein in limiting the brain penetration of glabridin, an active isoflavan from the root of *Glycyrrhiza glabra*. *Pharm Res* 2007; 24: 1668–1690
- 145 Kwon HS, Oh SM, Kim JK. Glabridin, a functional compound of licorice, attenuates colonic inflammation in mice with dextran sulphate sodium-induced colitis. *Clin Exp Immunol* 2008; 151: 165–173
- 146 Akasaka Y, Sakai A, Takasu K, Tsukahara M, Hatta A, Suzuki H, Inoue H. Suppressive effects of glycyrrhetic acid derivatives on tachykinin receptor activation and hyperalgesia. *J Pharmacol Sci* 2011; 117: 180–188
- 147 Shi Y, Wu D, Sun Z, Yang J, Chai H, Tang L, Guo Y. Analgesic and uterine relaxant effects of isoliquiritigenin, a flavone from *Glycyrrhiza glabra*. *Phytother Res* 2012; 26: 1410–1417

- 148 Jhanji V, Liu H, Law K, Lee VY, Huang SF, Pang CP, Yam GH. Isoliquiritigenin from licorice root suppressed neovascularisation in experimental ocular angiogenesis models. *Br J Ophthalmol* 2011; 95: 1309–1315
- 149 Zhao Z, Wang W, Guo H, Zhou D. Antidepressant-like effect of liquiritin from *Glycyrrhiza uralensis* in chronic variable stress induced depression model rats. *Behav Brain Res* 2008; 194: 108–113
- 150 Menati L, Khaleghinezhad K, Tadayon M, Siahpoosh A. Evaluation of contextual and demographic factors on licorice effects on reducing hot flashes in postmenopause women. *Health Care Women Int* 2014; 35: 87–99
- 151 Guo J, Shang E, Zhao J, Fan X, Duan J, Qian D, Tao W, Tang Y. Data mining and frequency analysis for licorice as a “two-face” herb in Chinese Formulae based on Chinese Formulae database. *Phytomedicine* 2014; 21: 1281–1286
- 152 Huang X, Qin J, Lu S. Magnesium isoglycyrrhizinate protects hepatic L02 cells from ischemia/reperfusion induced injury. *Int J Clin Exp Pathol* 2014; 7: 4755–4764
- 153 Xiao ZW, Zhang W, Ma L, Qiu ZW. Therapeutic effect of magnesium isoglycyrrhizinate in rats on lung injury induced by paraquat poisoning. *Eur Rev Med Pharmacol Sci* 2014; 18: 311–320
- 154 He Y, Zeng F, Liu Q, Ju W, Fu H, Hao H, Li L, Xie Y. Protective effect of magnesium isoglycyrrhizinate on ethanol-induced testicular injuries in mice. *J Biomed Res* 2010; 24: 153–160
- 155 Chen KJ, Chen WY, Chen X, Jia YM, Peng GQ, Chen L. Increased elimination of paclitaxel by magnesium isoglycyrrhizinate in epithelial ovarian cancer patients treated with paclitaxel plus cisplatin: a pilot clinical study. *Eur J Drug Metab Pharmacokinet* 2014; 39: 25–31
- 156 Akhavan A, Saberi M, Saberi F. Topical effects of Glycyrrhizic acid on allergic rhinitis in comparison to the beclomethazone treatment. *J Med Plants* 2012; 11: 120–129
- 157 Agarwal A, Gupta D, Yadav G, Goyal P, Singh PK, Singh U. An evaluation of the efficacy of licorice gargle for attenuating postoperative sore throat: a prospective, randomized, single-blind study. *Anesth Analg* 2009; 109: 77–81
- 158 Shen X, Xiao P, Liu C. Research and application of Radix Glycyrrhizae. *Asian J Pharmacodyn Pharmacokinet* 2007; 7: 181–200
- 159 Wang ZY, Nixon DW. Licorice and cancer. *Nutr Cancer* 2001; 39: 1–11
- 160 Jung W, Kwon S, Im J, Park S, Moon S, Park J, Ko C, Cho K. Influence of herbal complexes containing licorice on potassium levels: a retrospective study. *Evid Based Complement Alternat Med* 2014; 2014: 970385
- 161 Russo S, Mastropasqua M, Mosetti MA, Persegani C, Paggi A. Low doses of liquorice can induce hypertension encephalopathy. *Am J Nephrol* 2000; 20: 145–148
- 162 Harahap IS, Sasaki N, Gunadi, Yusoff S, Lee MJ, Morikawa S, Nishimura N, Sasaki T, Usuki S, Hirai M, Ohta M, Takaoka Y, Nishimoto T, Nishio H. Herbal medicine containing licorice may be contraindicated for a patient with an HSD11B2 mutation. *Evid Based Complement Alternat Med* 2011; 2011: 646540
- 163 Simmler C, Jones T, Anderson JR, Nikolić DC, van Breemen RB, Soejarto DD, Chen SN, Pauli GF. Species-specific standardisation of licorice by metabolomic profiling of flavanones and chalcones. *Phytochem Anal* 2014; 25: 378–388
- 164 Uto T, Morinaga O, Tanaka H, Shoyama Y. Analysis of the synergistic effect of glycyrrhizin and other constituents in licorice extract on lipopolysaccharide-induced nitric oxide production using knock-out extract. *Biochem Biophys Res Commun* 2012; 417: 473–478