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REVIEW

Pharmacological Effects of *Glycyrrhiza* spp. and Its Bioactive Constituents: Update and Review

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The roots and rhizomes of various species of the perennial herb licorice (*Glycyrrhiza*) are used in traditional medicine for the treatment of several diseases. In experimental and clinical studies, licorice has been shown to have several pharmacological properties including antiinflammatory, antiviral, antimicrobial, antioxidative, antidiabetic, antiasthma, and anticancer activities as well as immunomodulatory, gastroprotective, hepatoprotective, neuroprotective, and cardioprotective effects. In recent years, several of the biochemical, molecular, and cellular mechanisms of licorice and its active components have also been demonstrated in experimental studies. In this review, we summarized the new phytochemical, pharmacological, and toxicological data from recent experimental and clinical studies of licorice and its bioactive constituents after our previous published review.

Keywords: licorice; *Glycyrrhiza*; antidiabetic; antiasthma; nephroprotective.

INTRODUCTION

The genus *Glycyrrhiza*, commonly known as licorice, comprises approximately 30 species including *Glycyrrhiza glabra*, *Glycyrrhiza uralensis*, *Glycyrrhiza inflata*, *Glycyrrhiza aspera*, and *Glycyrrhiza korshinskii* (Nomura *et al*., 2002). Licorice contains chemical compounds such as triterpene saponins, flavonoids, coumarins, and other phenolics (Qiao *et al*., 2014; Zhang and Ye, 2009) (Table 1). Of these compounds, flavonoids contain a diverse structure, which includes flavanones, chalcones, isoflavans, isoflavenes, flavones, and isoflavones (Zhang and Ye, 2009). Some of the active constituents of *Glycyrrhiza* spp. that belong to these flavonoid structures have been summarized in Table 1. Also, the chemical structures of some important constituents of licorice were shown in Fig. 1.

Several traditional herbal medicines contain *Glycyrrhiza* spp., including Yokukansan (Nakagawa *et al*., 2012), Choi-joki-to, and Daio-kanzo-to (Fujimaki *et al*., 2014) from Japan as well as Lizhong pill (Zhao *et al*., 2011), Xiaoyaosan (Dai *et al*., 2010), and Sini Tang (Liu *et al*., 2014) from China.

Our previous review of *Glycyrrhiza* spp. was published in *Phytotherapy Research* (Asl and Hosseinzadeh, 2008). The current review is an update of this work, including a review of new research published after the original review.

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PHARMACOLOGICAL EFFECTS

Antiinflammatory activities

In one study, *G. glabra* and its active component glabridin significantly inhibited the effects of prostaglandin E_2 (PGE_2) and leukotriene B production; however, isoliquiritigenin only effectively suppressed PGE_2 and thromboxane 2 levels, whereas glycyrrhizin, up to a concentration of 50 μg/mL, did not have inhibitory effects in murine macrophages (J774A.1) and human neutrophil (HL-60) cells. It seems that inhibitory effects of *G. glabra* on production of cyclooxygenase and lipoxygenase may be related to glabridin and isoliquiritigenin (Chandrasekaran *et al*., 2011). However, it should mentioned that glycyrrhizin at a concentration of 100 μg/mL could inhibit PGE_2 production (Ohuchi *et al*., 1981). Some of the antiinflammatory effects of *Glycyrrhiza* spp. and its active components have been summarized in Table 2.

Antimicrobial, antiviral, and antiprotozoal activities

Two constituents of licorice, isoliquiritigenin [half maximal inhibitory concentration (IC_{50}) = 9 μM] and glycyrol (IC_{50} = 3.1 μM), have shown neuroaminidase inhibitory activity. Neuroaminidase is an enzyme, and both viruses of influenza A and B have it. This enzyme has an important role in virus proliferation (Ryu *et al*., 2010). Because of the toxicity of neuroaminidase inhibitors such as oseltamivir in treatment, studies need to focus more on the inhibitory effects of these active compounds on neuroaminidase activity for treatment or prophylaxis of influenza A and B (Ryu *et al*., 2010).

Moreover, isolated chalcones from *G. inflata* such as echinantin (5 μM) were shown to be novel inhibitors of

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Table 1. Major constituents of *Glycyrrhiza* sp

Structure	Compounds
Saponins	18β-Glycyrrhetinic acid (Qiao *et al.*, 2014; Xu *et al.*, 2013), glycyrrhizic acid (Xu *et al.*, 2013), licorice-saponin A3 (Xu *et al.*, 2013; Qiao *et al.*, 2014), licorice-saponin G2 (Qiao *et al.*, 2014), licorice-saponin E2 (Qiao *et al.*, 2014)
Flavanones	Liquiritigenin, liquiritin (Xu *et al.*, 2013), liquiritin apioside (Xu *et al.*, 2013)
Chalcones	Isoliquiritigenin (Simmler *et al.*, 2014), isoliquiritigenin apioside (Simmler *et al.*, 2014), isoliquiritin (Simmler *et al.*, 2014), neoisoliquiritin (Zhang and Ye, 2009), licochalcone A and B (Zhang and Ye, 2009)
Flavones (flavonols)	Licoflavonol (Qiao *et al.*, 2014; Zhang and Ye, 2009), isolicoflavonol (Qiao *et al.*, 2014; Zhang and Ye, 2009)
Isoflavones	Licoisoflavone (Zhang and Ye, 2009; Qiao *et al.*, 2014), licoricone (Zhang and Ye, 2009; Qiao *et al.*, 2014), gancaonin (Zhang and Ye, 2009; Qiao *et al.*, 2014), angustone (Zhang and Ye, 2009; Qiao *et al.*, 2014), isoangustone (Zhang and Ye, 2009; Qiao *et al.*, 2014), glabrone (Zhang and Ye, 2009)
Isoflavans	Glabridin (Zhang and Ye, 2009), hispaglabridin A and B (Zhang and Ye, 2009)
Isoflavenes	Glabrene (Zhang and Ye, 2009)
Coumarins	Glycycoumarin (Qiao *et al.*, 2014), licopyranocoumarin (Qiao *et al.*, 2014), glycyrin, glycyrol (Wang *et al.*, 2015)

new H1N1 swine influenza by inhibiting neuroaminidase activity (i.e., novel influenza) (Dao *et al.*, 2010). Furthermore, chalcones such as licochalcone A alter the ultrastructure of parasite mitochondria and inhibit their function by selectively inhibiting fumarate reductase in the respiratory chain of the parasite (Zhai *et al.*, 1995; Chen *et al.*, 2001). It seems that this enzyme only exists in *Leishmania* parasites. Then, it will be a good target for antileishmanial drugs (Chen *et al.*, 2001).

Table 3 summarizes some of the antimicrobial, antiviral, and antiprotozoal effects of *Glycyrrhiza* spp. and its active components.

Antioxidative activities

The ethanolic extract of *G. glabra* and its fractions were found to increase plasma levels of high-density lipoprotein cholesterol in dyslipidemia hamsters that were fed high-fructose diets (Maurya *et al.*, 2009). Moreover, glabridin, an isoflavan of *G. glabra*, was a potent antioxidant toward low-density lipoprotein (LDL) oxidation in healthy subjects (Carmeli and Fogelman, 2009). It seems that polyphenols of *G. glabra* could decrease serum total cholesterol, LDL cholesterol (LDL-C), triglyceride, and very-LDL-C levels through reducing the susceptibility of LDLs to oxidation by binding to LDL, scavenging free radicals, and inhibiting cellular cholesterol biosynthesis (Hasani-Ranjbar *et al.*, 2010). However, more studies are needed to develop further the mechanism of action and structure–activity relationship of *G. glabra* extract and its active components such as glabridin, hispaglabridin A and hispaglabridin B, 4′-*O*-methyl glabridin, isoprenyl chalcone, and isoliquiritigenin.

Glycyrrhiza glabra polysaccharides have also shown antioxidant activity and reduced oxidative stress in mice with high-fat diets (Hong *et al.*, 2009). Isoliquiritigenin protects cells from the toxicity of arachidonic acid plus

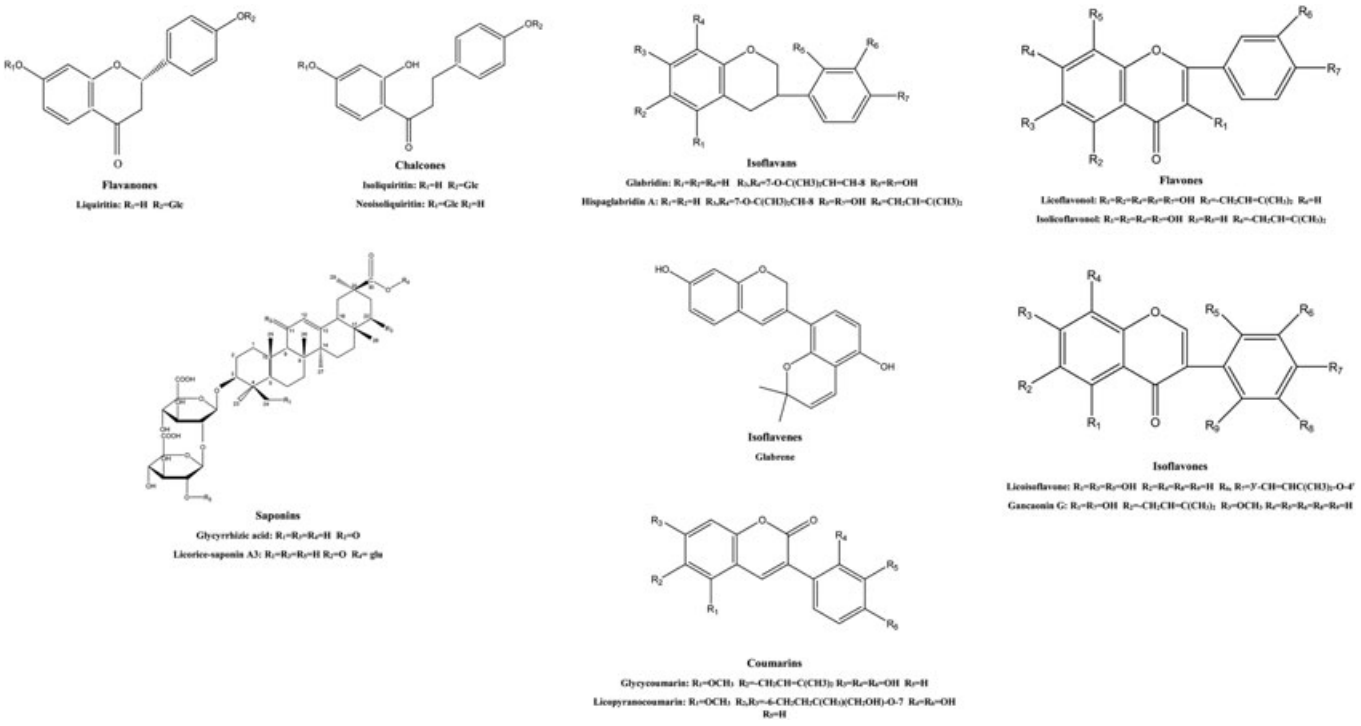

Figure 1. Chemical structure of some active constituents of licorice.

iron, which produces reactive oxygen species (ROS) and causes mitochondrial dysfunction (Choi *et al*., 2010b). This effect was produced via adenosine monophosphate-activated protein kinase-dependent inactivation of glycogen synthase kinase 3β. In recent studies, three phenylflavonoids of *G. uralensis*, namely, dehydroglyasperin C (DGC), dehydroglyasperin D, and isoangustone A, were shown to have antioxidant activity (Kim *et al*., 2012b; Lee *et al*., 2010b), with DGC apparently producing the strongest activity (Kim *et al*., 2012b). In another study, an extract of *G. glabra* (100 mg/kg) had protective effects against ochratoxin-induced damage of the testis (Malekinejad *et al*., 2011). Specifically, the extract enhanced total antioxidant power and total thiol molecule production levels in serum, which was confirmed by histopathological examination. Administration of licorice extract (50 mg/kg) also reportedly improves testicular damage induced by carbendazim by decreasing lipid peroxidation and increasing the enzymatic testicular oxidative biomarkers superoxide dismutase and catalase (Sakr and Shalaby, 2014).

Hepatoprotective studies

In one study, nano-sized oil-in-water emulsion encapsulating glycyrrhizin was shown to be useful as a new sustained-release formulation that could be administrated subcutaneously for prolonged chronic hepatitis therapy (Koga *et al*., 2011). In another study, 18α-glycyrrhetinic acid inhibited the growth of the human hematopoietic stem cells cell line LX-2 and cirrhotic fat-storing cells by reducing proliferation and inducing apoptosis (Zong *et al*., 2013). These effects may be caused by the stimulation of peroxisome proliferator-activated receptor γ (PPARγ) and inhibition of nuclear factor (NF)-κB activity. Table 4 summarizes some of the hepatoprotective effects of glycyrrhizin and the other active components of *Glycyrrhiza* spp.

Diabetes and related diseases

Licochalcone E can increase the expression of PPARγ in white adipose tissues, which could enhance adipocyte differentiation and the population of small adipocytes and thereby improve hyperglycemia and hyperlipidemia associated with diabetes (Park *et al*., 2012).

A recent study on phenolic compounds isolated from *G. glabra* roots, including glabrol and glabrone, demonstrated that they have PPARγ ligand-binding activity (Kuroda *et al*., 2010). The effectiveness of licorice extract and glycyrrhizin against the diabetogenic effects of streptozocin has also been established in rats (Kataya *et al*., 2011; Sen *et al*., 2011).

Both derivatives of isoliquiritigenin and liquiritigenin produce antidiabetic effects and could control blood glucose levels in streptozocin-induced diabetic mice (Gaur *et al*., 2014). Additionally, a derivative of licochalcone A has been shown to have inhibitory effects on protein tyrosine phosphatase 1B (PTP1B), an enzyme with an important role in the negative regulation of insulin and the leptin signaling pathway (Yoon *et al*., 2009). Glycybenzofuran and glisoflavone, two flavonoids of *G. uralensis*, significantly inhibit

Table 2. Effects of *Glycyrrhiza* sp. and its active components in some inflammatory models

Component	Model	Study	Mechanism
Glycyrrhiza glabra (glabridin, isoliquiritigenin)	LPS	J774A.1 murine macrophages	Inhibited production of NO, IL-1β, and IL-6 (Thiyagarajan *et al*., 2011)
Glycyrrhiza radix	LPS	Mouse peritoneal macrophages	Regulated activation of NF-κB and caspase-1 (Kim *et al*., 2014)
Glycyrrhiza uralensis	LPS	RAW 264.7 cells	Activated Nrf2 that inhibited NF-κB-mediated inflammatory pathways (Wu *et al*., 2011)
Glycyrrhizin	CpG-DNA stimulation, LPS	RAW 264.7 cells	Suppressed inflammatory responses, impaired internalization of TLR4, activated NF-κB, and MAPKs (Schröfelbauer *et al*., 2009)
	LPS	RAW 264.7 cells	Suppressed NO production and iNOS expression (Uto *et al*., 2012)
Glycyrrhizic acid, 18β-glycyrrhetinic acid	LPS	RAW 264.7 cells	Inhibited the production of NO, PGE_2, TNF-α, IL-6, IL-1β, and ROS, reduced the expression of iNOS and COX-2 genes, blocked activation of transcription factors such as NF-kB and PI3K p110δ and p110γ (Wang *et al*., 2011)
18β-glycyrrhetinic acid	LPS	RAW 264.7 cells	Inhibited RANKL-stimulated osteoclastogenesis and phosphorylation of NF-κB p105, inhibited cytokine production (Sasaki *et al*., 2010)
	Periodontitis by oral infection	IL-10-deficient mice	Inhibited the induction and progression of infection-induced alveolar bone loss (Sasaki *et al*., 2010)
Licorice, roasted licorice	TPA and collagen-induced arthritis	Mice	Reduced clinical arthritis score, paw swelling, and histopathological changes (Kim *et al*., 2010a)

COX, cyclooxygenase; IL, interleukin; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; MAPKs, mitogen-activated protein kinases; Nrf2, nuclear erythroid-related factor 2; RANKL, receptor activator for NF-κB ligand; TNF-α, tumor necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; TLRs, Toll-like receptors; ROS, reactive oxygen species; NO, nitric oxide; iNOS, nitric oxide synthase; PI3K, phosphoinositide-3-kinase; PGE_2, prostaglandin E2.

Table 3. The antibacterial, antiviral, antifungal and antiprotozoal effects of *Glycyrrhiza* sp. and its components

Compound	Microorganism
Antibacterial effects	
Glycyrrhiza sp.	MRSA (Lee *et al.*, 2009a); *Escherichia coli*, *Bacillus subtilis*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis* (Badr *et al.*, 2011)
Glycyrrhiza glabra	*Helicobacter pylori* (Wittschier *et al.*, 2009; Asha *et al.*, 2013)
Leaves	*S. aureus* (Irani *et al.*, 2010)
Roots	*S. aureus* (Snowden *et al.*, 2014); *Campylobacter jejuni* (Bensch *et al.*, 2011)
Glycyrrhizin	*E. coli* (Chen *et al.*, 2009b)
18β-Glycyrrhetinic acid	MRSA (Long *et al.*, 2013)
Deglycyrrhizinated licorice	*Streptococcus mutans* UA159 (Ahn *et al.*, 2012)
Antiviral effects	
Glycyrrhiza uralensis	Enterovirus type 71 (Kuo *et al.*, 2009); rotavirus (Alfajaro *et al.*, 2012)
Glycyrrhiza	Varicella zoster virus (Shebl *et al.*, 2012); rotavirus (Kwon *et al.*, 2010); human respiratory syncytial virus (Feng *et al.*, 2013b); Newcastle disease virus (Omer *et al.*, 2014)
Glycyrrhizin	Influenza A virus (Wolkerstorfer *et al.*, 2009)
Glycyrrhizic acid	HSV1 (Laconi *et al.*, 2014); Coxsackievirus A16 and enterovirus 71 (Wang *et al.*, 2013)
Glycyrrhetinic acid	HIV (Song *et al.*, 2014)
18*β*-Glycyrrhetinic acid	Rotavirus (Hendricks *et al.*, 2012)
Diammonium glycyrrhizin	PrV (Sui *et al.*, 2010)
Antifungal effects	
G. glabra	*Candida albicans* (Irani *et al.*, 2010)
Glycyrrhizic acid	*C. albicans* (Messier and Grenier *et al.*, 2011)
18β-Glycyrrhetinic acid	*C. albicans* (Pellati *et al.*, 2009; Kim *et al.*, 2013b)
Antiprotozoal effects	
G. glabra	
Aerial parts	*Plasmodium falciparum* (Esmaeili *et al.*, 2009)
Roots	*P. falciparum* (Sangian *et al.*, 2013)
Glycyrrhetinic acid	Filaria (Kalani *et al.*, 2013b)
18β-Glycyrrhetinic acid	*P. falciparum* (Kalani *et al.*, 2013a); *Leishmania donovani* (Ukil *et al.*, 2011)

HSV, Herpes simplex virus; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PrV, pseudorabies virus.

PTP1B activity; hence, they could be targets for treatment of type 2 diabetes mellitus and obesity (Li *et al.*, 2010b). Similarly, glycybenzofuran was recently reported as a potent competitive inhibitor of PTP1B (Li *et al.*, 2013a).

In one study, glabrol noncompetitively inhibited rat liver microsomal acyl-coenzyme A : diacylglycerol acyltransferase activity with an IC_{50} of 8 μM (Choi *et al.*, 2010a). This enzyme catalyzes triglyceride synthesis in the glycerol phosphate pathway, and its inhibition may be a critical target for treatment of type 2 diabetes mellitus and obesity.

In conditions of chronic glucose stress, glabridin was shown to upregulate the expression of antioxidant enzymes and antiatherogenic factors such as superoxide dismutase, catalase, and paraoxonase 2 (Yehuda *et al.*, 2011). The enhancement of intracellular antioxidant defense mechanisms by glabridin suggests that it should be investigated as an antiatherogenic agent in diabetes.

The antiapoptosis and antiinflammation activity of glycyrrhizic acid against advanced glycation end product-induced damage in human umbilical vein endothelial cells has recently been demonstrated and occurs via inhibition of the receptor for advanced glycation end product/NF-κB pathway (Feng *et al.*, 2013a). These effects may be relevant for the prevention and treatment of diabetic vascular complications.

Lee *et al.* (2010a) demonstrated that semilicoisoflavone B, a flavonoid of *G. uralensis*, noncompetitively inhibits human recombinant aldose reductase and rat lens aldose reductase, as well as inhibiting sorbitol formation of rat lens aldose reductase incubated with a high concentration of glucose. In another study, roasted licorice extract, which had high levels of glycyrrhetic acid, inhibited mesangial cell proliferation and matrix accumulation induced by high glucose (Li *et al.*, 2010a). The glycyrrhetic acid in the extract is a non-polar component that could impede high-glucose-stimulated mesangial matrix deposition by reducing the expression of connective tissue growth factor via Akt activation and transforming growth factor β/Smad signaling. Similar effects have been reported for isoangustone A in high glucose condition (Li *et al.*, 2011).

Table 4. Hepatoprotective effects of *Glycyrrhiza* sp. and its active components *in vivo* and *in vitro*

Study	Method	Mechanism
	In vitro	
Glycyrrhizic acid		
Rat hepatocytes	t-BHP-induced oxidative injury	Reduced ROS formation, prevent depletion of intracellular GSH, inhibited mitochondrial membrane depolarization (Tripathi *et al.*, 2009)
Glycyrrhetinic acid		
HepG2, rat hepatocytes	TNF-α-induced inflammation	Showed antiinflammatory effect by inactivating NF-κB (Chen *et al.*, 2014c)
Glycyrrhiza glabra		
Carp primary hepatocytes	CCl4-induced hepatotoxicity	Decreased serum aminotransferases, increased GSH-Px (Yin *et al.*, 2011)
	In vivo	
Licorice extract		
Rat liver	CCl4-induced liver injury	Inhibited the elevation of serum, aminotransaminases, alkaline phosphatase, and inflammatory cytokine, increased antioxidant enzymes (Huo *et al.*, 2011)
Glycyrrhizic acid		
Rat liver	$NTiO_2$-induced liver injury	Decreased ALT and AST, attenuated morphological damage and oxidative stress (Orazizadeh *et al.*, 2014)
		Increased LPL expression in the quadriceps femoris and prevented visceral obesity, improved dyslipidemia and slowed insulin resistances associated with tissue steatosis (Lim *et al.*, 2009)
Rat liver	High-fat diet	Increased LPL expression, improved insulin sensitivity and dyslipidemia (Eu *et al.*, 2010)
18β-glycyrrhetinic acid		
Mice liver	*Propionibacterium acnes*-induced liver injury	Reduced expression of MIP-1α in Kupffer cells (Xiao *et al.*, 2010)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CCl4, carbon tetrachloride; GSH-Px, glutathione peroxidase; LPL, lipoprotein lipase; MIP-1α, macrophage inflammatory protein 1α; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species; t-BHP, tert-butyl hydroperoxide; TNF-α, tumor necrosis factor-α; $NTiO_2$, titanium dioxide nanoparticles.

Antitumor activity

Anticancer effects of *Glycyrrhiza* spp. extracts and its active ingredients that have been identified in the extracts were summarized (for additional details, see Table 5). It was shown that roasted licorice extract has protective effects against breast cancer-induced bone destruction (Lee *et al.*, 2013). It reduced the viability of breast cancer cells and blocked cancer cell-mediated expression of receptor activator of NF-κB ligand (RANKL) in

Table 5. Anticancer effects of licorice extracts and its active ingredients that have been identified in the extracts in experimental models

Compound	Cancer	Reference
Glycyrrhiza glabra	Prostate	Yo *et al.*, 2009
	Breast	Chu *et al.*, 2014
Glycyrrhiza uralensis	Liver	Popovich *et al.*, 2011
Glycyrrhiza polysaccharide	Liver	He *et al.*, 2011; Chen *et al.*, 2013
Roasted licorice	Skin	Park *et al.*, 2014
	Prostate	
Licorice flavonoid oil	Liver	Nakagawa *et al.*, 2010
Isoliquiritigenin	Breast	Li *et al.*, 2013b
Licochalcone A	Prostate	Park *et al.*, 2014
	Oral	Cho *et al.*, 2014
Isoangustone A[a]	Prostate	Seon *et al.*, 2010
Licoricidin[a]	Prostate	Park *et al.*, 2010

[a]Active component of *G. uralensis*.

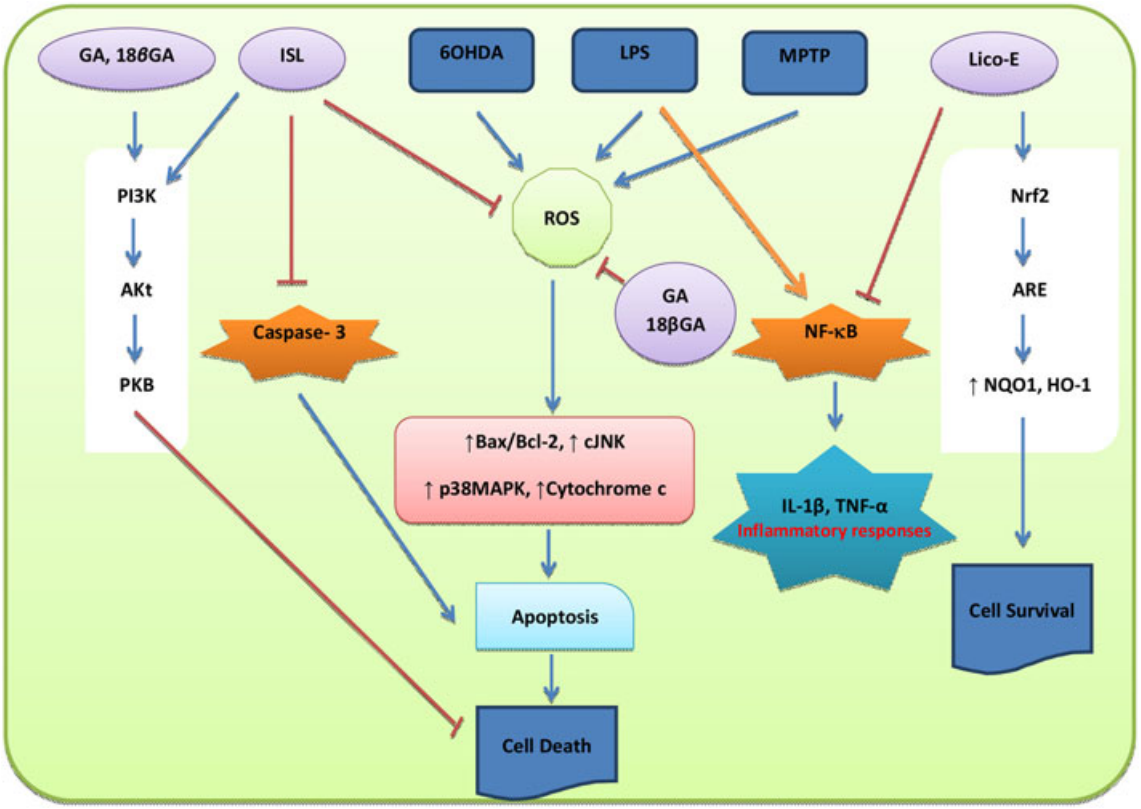

Figure 2. The neuroprotective activity of glycyrrhizic acid, 18β-glycyrrhetinic acid, isoliquiritigenin, and licochalcone E against various models of cell death related to dopaminergic neurons. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

Abbreviation: Antioxidant response element (ARE), c-Jun N-terminal kinase (c-JNK), 6-OH dopamine (6-OHDA), glycyrrhizic acid (GA) and 18β-glycyrrhetinic acid (18βGA), heme oxygenase-1 (HO-1), isoliquiritigenin (ISL), licochalcone E (Lico E), NAD (P)H: quinone oxidoreductase 1 (NQO1), mitogen-activated protein kinase (MAPK), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), neuclear factor- kB (NF-kB), nuclear factor E2-related factor-2 (Nrf2), phosphatidylinositol 3-kinase (PI3K), protein kinase B(PKB), reactive oxygen species (ROS)

osteoblasts, as well as inhibiting RANKL-induced osteoclastogenesis in bone marrow-derived macrophages (Lee *et al.*, 2013).

Effects on the central nervous system

Glabridin has been shown to ameliorate staurosporine-induced damage in cultured cortical neurons from rats, and this neuroprotective effect occurred through modulation of multiple pathways associated with apoptosis (Yu *et al.*, 2008). Glycyrrhizin at doses of 10 and 20 mg/kg per day promoted sciatic nerve regeneration and functional repair (Jia *et al.*, 2014). This observed effect was apparently associated with downregulation of p75 neurotrophin receptor, a protein with an important role in neuronal survival, apoptosis, and axonal growth in the peripheral and central nervous systems. As a component of Yokukansan, *Glycyrrhiza* has also shown antagonistic activity against α_{2A} adrenoceptor (with an IC_{50} of ~151 μg/mL) and inhibited signs of morphine withdrawal in mice (Nakagawa *et al.*, 2012). This inhibitory effect on physical dependence may be related to the prevention of decreased membrane expression of α_{2A} adrenoceptor in the brainstem. Additionally, the chemical constituents of *Glycyrrhiza*, including isoliquiritin, isoliquiritigenin, and 18β-glycyrrhetinic acid, also showed similar antagonistic activity, with IC_{50} values of approximately 56, 47, and 75 μg/mL, respectively (Nakagawa *et al.*, 2012).

Glycyrrhiza inflata, ammonium glycyrrhizinate, and licochalcone A could activate proliferator-activated receptor γ coactivator 1α, as well as signaling of the nuclear factor erythroid 2-related factor 2 antioxidant response elements pathway, and thereby decrease oxidative stress, increase mitochondrial biogenesis, and reduce aggregate formation in the spinocerebellar ataxia type 3 cellular model in both 293 and SH-SY5Y ATXN3/Q75 cells (Chen *et al.*, 2014a). Given the relatively high IC_{50} cytotoxicity/ED_{50} ratios of *G. inflata*, ammonium glycyrrhizinate, and licochalcone A ($5000^{-3} \times 10^5$), these compounds apparently have very low toxicity with high efficacy for aggregation inhibition.

After administration of Yokukansan, 18β-glycyrrhetinic acid was detected in the plasma, cerebrospinal fluid, and brain of rats (Tabuchi *et al.*, 2012). In both *in vivo* and *in vitro* experiments in this study, 18β-glycyrrhetinic acid reached the brain through the blood–brain barrier. These findings provide evidence that the psychotropic effects of Yokukansan may be related to 18β-glycyrrhetinic acid.

Effects on the GABAergic system

The ethanolic extract of *G. glabra* and glabrol (as an active flavonoid) have been shown to induce sleep in rats in a dose-dependent manner; both compounds were considered to have a positive effect on allosteric modulation of $GABA_A$-benzodiazepines receptors

(Cho *et al*., 2012). In addition, glabridin at both high and low concentrations (10^{-12} and 3×10^{-6} M, respectively) can enhance $GABA_A$ receptor function in the dorsal raphe neurons (Jin *et al*., 2013).

Effect on the dopaminergic system

Jeon *et al*. (2008) demonstrated that isoliquiritigenin could suppress cocaine-induced hyperlocomotion in rats by reducing levels of dopamine in the brain and showed that 56 proteins were differentially expressed in response to isoliquiritigenin. Exposure to cocaine causes molecular changes in individual neurons and alters the function of the neural system. Therefore, isoliquiritigenin-responsive proteins may play an essential role in neuroprotection from cocaine (Jeon *et al*., 2008). In another study, Peony–*Glycyrrhiza* Decoction (PGD) suppressed prolactin synthesis and secretion in both *in vitro* and *in vivo* models of hyperprolactinemia, and it caused decreased serum progesterone to return to control levels (Wang *et al*., 2012). Therefore, PGD could not only modulate the dopaminergic system but also normalize the dysfunction of other sex hormones. *G. glabra* and *G. uralensis* reportedly have the strongest capacity for inhibition of the enzyme monoamine oxidase B, with IC_{50} values of <0.07 mg/mL (Mazzio *et al*., 2013).

Fig. 2 summarizes the neuroprotective activity of glycyrrhizic acid, 18β-glycyrrhetinic acid, isoliquiritigenin, and licochalcone E against various models of cell death related to dopaminergic neurons (Kao *et al*., 2009; Kim *et al*., 2012c; Hwang and Chun, 2012).

Effects on the glutamatergic system

In a previous study, glycyrrhizic acid selectively inhibited *N*-methyl-D-aspartate (NMDA) receptor-mediated Ca^{+2} influx and NF-κB in primary neuronal cultures; therefore, a correlation between the neuroprotective effects of glycyrrhizic acid and inhibitory effects on NF-κB activation were assumed (Cherng *et al*., 2006).

Chepkova *et al*. (2008) showed that carbenoxolone ($IC_{50} = 104$), a glycyrrhetinic acid derivative, inhibited NMDA-evoked currents in a dose-dependent manner and suggested that the compound was an antagonist of NMDA receptors that impaired the induction of long-term potentiation. Carbenoxolone also had anticonvulsant activity in mice (Hosseinzadeh and Nassiri Asl, 2003); however, it impaired the learning performance of rats in a Morris water maze test (Hosseinzadeh *et al*., 2005b).

Glycyrrhizic acid and liquiritin can protect the differentiated PC12 rat pheochromocytoma cell line against the toxicity of glutamate, as evidenced by increased cell viability. Both compounds are known to attenuate glutamate-induced apoptotic alterations, including mitochondrial function and the expression of apoptosis-related proteins (Teng *et al*., 2014b; Wang *et al*., 2014). Moreover, although liquiritin could also activate Akt and glycogen synthase kinase 3β, both compounds apparently exhibit neuroprotective effects via activation of the extracellular signal-regulated kinase pathway (Teng *et al*., 2014b).

Four active components of *Glycyrrhiza* root, namely, glycycoumarin, isoliquiritigenin, liquiritin, and 18β-glycyrrhetinic acid, exhibit higher potency for neuroprotection against glutamate-induced neural death at concentrations of 10 μM, with isoliquiritigenin also shown to be an NMDA receptor antagonist that inhibits the glutamate-induced increase in Ca^{2+} influx (Kawakami *et al*., 2011). Similarly, isoliquiritigenin at 10 μM can reverse glutamate-induced changes in Bcl-2 and Bax protein levels in HT22 hippocampal neuronal cells and suppress the release of an apoptosis-inducing factor from the mitochondria into the cytosol (Yang *et al*., 2012). Consequently, isoliquiritigenin is considered to have a protective effect against mitochondrial dysfunction resulting from glutamate-induced oxidative stress.

Dehydroglyasperin C, as an active component of *G. uralensis*, can produce neuroprotective effects against glutamate-induced oxidative stress in mouse hippocampal HT22 cells by inducing heme oxygenase (HO)-1 expression; NF (erythroid-derived 2)-like 2 and the phosphoinositide-3-kinase/AKT signaling pathway may be involved in activation of HO-1 (Kim *et al*., 2012a).

Kawakami *et al*. (2010) reported that glycyrrhizin and 18β-glycyrrhetinic acid (10^{-7}–10^{-4} M) ameliorate thiamine deficiency-induced dysfunction of glutamate uptake in astrocytes and that the two compounds could inhibit protein kinase C activity. However, given the same dose, 18β-glycyrrhetinic acid was more potent than glycyrrhizin (Kawakami *et al*., 2010). Glycyrrhizin (10 mg/kg, intraperitoneal) has also been shown to have neuroprotective effects in mice administered kainic acid (KA); it decreased neuronal death in the hippocampus and inhibited astrocyte and microglia activation in the mouse brain. In addition, it suppressed the induction of inflammatory markers such as cyclooxygenase 2, inducible nitric oxide synthase, and tumor necrosis factor-α (TNF-α). Furthermore, glycyrrhizin inhibited NMDA-induced, KA-induced, or glutamate-induced neural death and showed antiexcitotoxic effects in primary cortical cultures. However, the efficacy of glycyrrhizin's neuroprotective effects was different depending on treatment (Luo *et al*., 2013). Furthermore, glycyrrhizin has been shown to suppress both acute and delayed induction of high-mobility group box 1, which has an important role in stimulating inflammatory responses in the hippocampus and its accumulation in serum in KA-induced seizure animal model (Luo *et al*., 2014). Some of the effects of *Glycyrrhiza*, its active components, and carbenoxolone that are exhibited in experimental models of the central nervous system are summarized in Table 6.

Effects on beta-amyloid formation and beta-amyloid-induced apoptosis

The active compound of *G. glabra*, 2, 2′,4′-trihydroxychalcone (TDC), is reportedly a specific non-competitive inhibitor against beta-site amyloid precursor protein (APP)-cleaving enzyme 1, which is an enzyme considered an attractive target for anti-Alzheimer drug discovery. TDC, a flavonoid belonging to the chalcone family, has been shown to significantly reduce the insoluble beta-amyloid (Aβ) peptides in the hippocampus and inhibit β-cleavage of APP and production of Aβ in APPswe human embryo kidney cells (Zhu *et al*., 2010). As a component of Yokukansan, *G. uralensis* exhibited protective effects against Aβ oligomer-induced apoptosis in cultured neurons at concentrations of 6–600 μg/mL,

Table 6. The effects of *Glycyrrhiza* sp. and its active component in some central nervous system experimental models

Treatment	Method	Effect
Convulsion		
Glycyrrhiza glabra		
Root	PTZ	Anticonvulsant activity (Chowdhury *et al*., 2013; Nassiri-Asl *et al*., 2007)
Leaf	PTZ	Anticonvulsant activity (Yazdi *et al*., 2011)
Memory		
G. glabra		
Leaf	Elevated plus maze	Enhancing effects (Chakravarthi and Avadhani, 2013)
	Hebb–William maze and Morris water maze tests	Stimulated neuronal dentritic growth (Chakravarthi and Avadhani, 2014)
	Passive avoidance paradigms	Reversed scopolamine-induced amnesia by augmenting cortical, hippocampal, and striatal NA, DA, and 5-HT levels (Michel *et al*., 2013)
TDC	Morris water maze test	Ameliorated memory impairment in APP-PS1 Tg mice (Zhu *et al*., 2010)
Glabridin	Passive avoidance learning	Reversed STZ-induced learning and memory deficits (Hasanein, 2011)
Ischemia		
CBX	4VO	Decreased MDA in the brain (Hosseinzadeh *et al*., 2005a)
Glabridin	MCAO	Decreased MDA level in the brain, increased levels of SOD and GSH (Yu *et al*., 2008)
SNMC	MCAO	Suppressed infarct formation, improved motor impairment, and neurological deficits (Kim *et al*., 2011)
Glycyrrhizic acid	MCAO	Suppressed infarct formation, improved motor impairment and neurological deficits (Kim *et al*., 2012d)
Liquiritin	MCAO	Decreased neurological deficits, infarct volume, and the levels of MDA, upregulated the activity of SOD, CAT, and GSH-Px, inhibited apoptosis by decreasing 8-OHdG and TUNEL-positive cells (Sun *et al*., 2010)
Parkinson's disease		
Glycyrrhizic acid	MPP^+-induced neurotoxicity	Inhibited overload of [Ca + ^{2}], improved function of mitochondria, and increased the expression and migration of p-ERK in DPC12 cells (Teng *et al*., 2014a)
Glycyrurol, licopyranocoumarin	MPP^+-induced cell death	Inhibited ROS production, limited activation of JNK, and caused decreasing in($\Delta\Psi_{mit}$) in PC12D (Fujimaki *et al*., 2014)

APP-PS1 Tg mice, B6C3-Tg (APPswe/PSEN1dE9) double-transgenic mice; JNK, c-Jun N-terminal kinase; CAT, catalase; DA, dopamine; DPC12, differentiated PC12 cells; GSH-Px, glutathione peroxidase; 4VO, four-vessel occlusion; MDA, malondialdehyde; MCAO, middle cerebral artery occlusion; NA, noradrenaline; MPP^+, 1-methyl-4-phenylpyridinium; p-ERK, phosphorylated extracellular signal-regulated kinase; PTZ, pentylenetetrazole; 5-HT, serotonin; SNMC, Stronger Neo-Minophagen; STZ, streptozotocin; SOD, superoxide dismutase; TDC, 2′,4′-trihydroxychalcone.

and it reduced Aβ oligomer-induced activation of caspases 3/7 (Kanno *et al*., 2013). Lee *et al*. (2012) showed that *Glycyrrhiza radix* and isoliquiritigenin inhibit neuronal apoptotic death induced by Aβ (25–35), elevation of [Ca^{2+}], and generation of (ROS). Both compounds also reduced expression of caspase 3 and Bax and increased expression of the antiapoptotic protein Bcl-2 (Lee *et al*., 2012).

Cardiovascular studies

In one study, licochalcone A inhibited proliferation of rat vascular smooth muscle cell (rVSMC) and platelet-derived growth factor-induced rVSMC proliferation (Park *et al*., 2008). In another study, the hexane/ethanol extract of *G. uralensis* lacking glycyrrhizin protected cardiac myoblasts against doxorubicin-induced apoptosis by inhibiting activation of p53 in H9c2 cells (Choi *et al*., 2008).

Traditionally, licorice has been used for treatment of cardiovascular disorders. To investigate the mechanism of its action, the effects of glycyrrhetinic acid on the peak and late components of sodium currents (I_{Na}) was evaluated in *Xenopus* oocytes. Their results showed that glycyrrhetinic acid reduced peak I_{Na} (33% at 90 μM) and especially late I_{Na} (72% at 90 μM), which have an important role in generation of arrhythmias and ventricular dysfunction (Du *et al*., 2009). In another study, Ojha *et al*. (2013) used biochemical and histopathological techniques to establish the cardioprotective effects of *G. glabra* (400 mg/kg) against oxidative stress in myocardial ischemia–reperfusion injury in rats (Ojha *et al*., 2013).

Glycyrrhetinic acid (50 and 100 μM/L) has been shown to inhibit expression of intercellular adhesion molecule 1 in TNF-α-activated endothelial cells by interrupting the c-Jun N-terminal kinase/c-Jun and IκB/NF-κB signaling pathways; thus, this compound may be useful for the treatment of inflammatory vascular diseases (Chang *et al*., 2010). Several studies have reported that licochalcone A (Kim *et al*., 2010b), isolicoflavonol (Han *et al*., 2012), and isoliquiritigenin (Cao *et al*., 2010; Han *et al*., 2012; Jhanji *et al*., 2011) have antiangiogenic activity in different models of angiogenesis. Additionally, DGC has been shown to have significant cardiovascular protection effects in experimental models; for example, it suppressed cell migration and the dissociation of actin filaments by platelet-derived growth factor in human aortic smooth muscle cells and in a rat vascular balloon injury model, and it inhibited excessive reduction of luminal diameters and neointimal formation (Kim *et al*., 2013a).

Immunological studies

For pigs, licorice as a dietary supplement enhances immune function and potentially increases mucosal immunity and antiinflammation effects in the peripheral tissues (Katayama *et al*., 2011). Glycyrrhetinic acid could induce the expression of toll-like receptor 4 and its downstream signaling molecules, which has an important role in modulating innate immune responses against pathogens (Peng *et al*., 2011).

By inhibiting Kv1.3 channels, 18β-glycyrrhetinic acid has antiinflammatory effects in human Jurkat T cells (Fu *et al*., 2013). Glycyrrhizin has been shown to increase activity of dendritic cells, enhance proliferation of allogenic T cells along with production of interferon (IFN)-γ and interleukin (IL)-10 cytokines, and reduce IL-4 production (Bordbar *et al*., 2012). In contrast, Kim *et al*. (2013c) showed that 18β-glycyrrhetinic acid impaired the capacity of dendritic cells to proliferate and initiate the T helper 1 response in lipopolysaccharide (LPS)-stimulated mature dendritic cells. This compound also suppressed the expression of surface molecules CD80, CD86, and major histocompatibility complex classes I and II and reduced levels of IL-12 production (Kim *et al*., 2013c).

Respiratory studies

Antitussive effects. In one study, *G. radix* produced a persistent antitussive effect in guinea pigs, leading to suggestions that liquiritin apioside, as the main antitussive component, plays an important role in the earlier phase, whereas liquiritigenin and liquiritin play an important role in the late phase (Kamei *et al*., 2005). This result is in keeping with the previous antitussive effects of licorice. Nosalova *et al*. (2013) showed that an oral extract of polysaccharide from *G. glabra* [50 mg/kg, per os (p.o.)] suppressed coughing in a citric acid model in guinea pigs; application of this extract produced the strongest antitussive effect (81%) compared with other herbs (Nosalova *et al*., 2013). In another study (Saha *et al*., 2011), an aqueous extraction of polymeric fraction isolated from *G. glabra* (50 mg/kg, p.o.) showed similar effects and decreased the number of coughs produced by guinea pigs.

Asthma and chronic obstructive pulmonary disease. Flavonoids of *G. uralensis* including liquiritigenin, isoliquiritigenin, and 7,4′-dihydroxyflavone (DHF) have been shown to inhibit secretion of eotaxin-1, a key chemokine involved in eosinophil migration into the lung in asthma, by human fetal lung fibroblasts; thus, with their antiinflammatory effects, these flavonoids apparently have potential applications in the treatment of asthma (Jayaprakasam *et al*., 2009). In addition, the licorice flavonoids liquiritin, liquiritin apioside, and liquiritigenin (at 3, 10, and 30 mg/kg, respectively) significantly reduced LPS-induced pulmonary inflammation by inhibiting the infiltration of inflammatory cells, oxidative stress, and proinflammatory mediator expression in the lungs (Xie *et al*., 2009). Furthermore, *G. uralensis* is known to suppress activation of NF-κB, phosphorylation of IκB, and expression of intercellular adhesion molecule 1 by LPS in cultured human lung cells (Lee *et al*., 2009b).

Glycyrrhizin (10 mg/kg, 7 days, p.o.) has beneficial effects on long-term histopathological changes to the respiratory airway in a mouse model of chronic ovalbumin (OVA)-induced asthma (Hocaoglu *et al*., 2011). In addition, Ma *et al*. (2013) demonstrated that glycyrrhizic acid could suppress IL-4, IL-5, IL-13, and IFN-γ and inhibit both the recruitment of eosinophils and mucus overproduction in mice treated with OVA (Ma *et al*., 2013). They showed that the compound reduced inflammation and hyperactivity of the airway and increased $CD4^+$, $CD25^+$, and $Foxp3^+$ regulatory T cells. Similarly, in another study, licochalcone A suppressed IL-4, IL-5, and IL-13 in OVA-treated mice, as well as reducing levels of specific IgE and IgG in OVA (Chu *et al*., 2013).

Anti-asthma Herbal Medicine Intervention (ASHMI™) formula contains *G. uralensis* with the three flavonoids isoliquiritigenin, 7,4′-DHF, and liquiritigenin. The flavonoid 7,4′-DHF is the most potent compound; it has been shown to inhibit memory Th2 cells in lung cell cultures and to reduce production of IL-4 and IL-5, as well as cell proliferation, without altering cell viability. Furthermore, 7,4′-DHF reduced some antigen-induced Th2 responses and airway inflammation in mice (Yang *et al*., 2013).

Oral administration of glycyrrhizic acid (50 and 100 mg/kg) has been shown to protect lung epithelium against benzo(a)pyrene toxicity in exposed rats. This protection was confirmed by histopathological, biochemical, and molecular studies. By enhancing the activity of two intracellular enzymes, namely, soluble epoxide hydrolase and thioredoxin reductase, it appears that glycyrrhizic acid could reverse suppression of NF-κ B (Qamar *et al*., 2012).

In a mouse model of chronic obstructive pulmonary disease, liquiritin exerts antiinflammatory activity. Liquiritin (3, 10, and 30 mg/kg) inhibited cigarette smoke extract-induced cytotoxicity in a dose-dependent manner by decreasing transforming growth factor β and TNF-α mRNA expression, enhancing levels of glutathione, and preventing apoptosis in a human type II alveolar epithelial cell line (A549) (Guan *et al*., 2012). Additionally, Lee *et al*. (2011) found that prunetin, a flavonoid of *G. glabra*, inhibited mucin secretion, production, and gene expression from airway epithelial cells in an *in vitro* study (Lee *et al*., 2011). They suggested that

prunetin could be considered a mucoregulator in pulmonary disease that is worthy of further investigation.

Other respiratory diseases. Licorisoflavan A (10 μg/mL) was effective for reducing volatile sulfur compound levels produced by *Porphyromonas gingivalis* by 50% (Tanabe *et al*., 2012). This effect might be useful for the treatment of halitosis.

Gastrointestinal studies

A combination therapy using both famotidine (0.57 mg/kg) and licorice (100 mg/kg) produced higher antiulcer activity than either of the compounds alone in indomethacin-induced gastric ulcer rats (Aly *et al*., 2005).

The aqueous extract of *G. glabra* (1 mg/mL) could inhibit the adhesion of *Helicobacter pylori* to human stomach tissue. It seems that both aqueous extracts and polysaccharides from the roots of the plant are strong antiadhesives and show cytoprotective effects (Wittschier *et al*., 2009). GutGard®, a flavonoid-rich extract of *G. glabra*, exhibited anti-*H. pylori* activity in an *in vitro* study (Asha *et al*., 2013). This compound also produced antiulcer effects in different animal models of gastric mucosal injury in rats; its antioxidative activity may be involved in these protective effects (Mukherjee *et al*., 2010).

Isoliquiritigenin has shown a dual role in regulating gastrointestinal motility *in vitro*, both spasmogenic and spasmolytic. Its spasmogenic effect may be due to the activation of muscarinic receptors, as shown in isolated rat stomach fundus. However, its spasmolytic effect may be due to the blockade of calcium channels, as shown in isolated guinea pig ileum and rabbit jejunum. Additionally, isoliquiritigenin has a dual dose-related effect on the charcoal meal travel in mice: inhibitory effects at low doses and prokinetic effects at high doses (Chen *et al*., 2009a).

Ammonium glycyrrhizinate, prepared from glycyrrhizin, could protect gastric epithelial cells from H_2O_2-induced damage because it blocked the expression of genes related to apoptotic cell death (*GDF15*, *ATF3*, *TNFRSF10A*, and *NALP1*) or oxidative stress pathways (*HMOX1*) during damage induced by exposure to H_2O_2 (Oh *et al*., 2009).

Endocrinological studies

Glycyrrhiza glabra has been shown to inhibit 11β-hydroxysteroid dehydrogenase-2 (Kratschmar *et al*., 2011; Makino *et al*., 2012) and has antiandrogenic activity in male rats (Zamansoltani *et al*., 2009). Glabrene-rich fractions of *G. glabra* have an agonistic action on estrogen receptor subtype α (ERα), whereas glabridin (6×10^{-6} M) has antagonistic action on ERα (Simons *et al*., 2011). Saunier *et al*. (2011) found that, when compared with estradiol, an extract of *G. uralensis* root could reverse weight gain and fat accumulation in ovariectomized obese mice fed on a high-fat diet; however, it did not induce proliferative effects on the mammary glands and uterus (Saunier *et al*., 2011). Therefore, the extract of *G. uralensis* apparently bound to ERα and induced estradiol-like regulation of genes in abdominal fat but not in the mammary glands and uterus. Recently, the estrogenic effects of *Glycyrrhiza* spp. were compared and found to follow the order *G. uralensis* > *G. inflata* > *G. glabra* in MCF-7 and T47D cells (Hajirahimkhan *et al*., 2013). In this study, liquiritigenin also selectively activated ERβ. Similarly, liquiritigenin has an accelerating effect on the growth and differentiation of osteoblasts in osteoblastic MC3T3-E1 cells (Choi, 2012). Moreover, isoliquiritigenin can suppress RANKL-induced osteoclastogenesis *in vitro* and prevent inflammatory bone destruction *in vivo* (Zhu *et al*., 2012). Therefore, further studies are required to investigate the effects of these novel licorice compounds when applied as potential treatments for lytic bone diseases.

Dermatological studies

Afnan *et al*. (2012) demonstrated that glycyrrhizic acid could scavenge ultraviolet B-induced cellular ROS and inhibit NF-κB activation; thus, it may be effective as a therapeutic agent against photoaging (Afnan *et al*., 2012). Additionally, *G. glabra* extracts were shown to have good antioxidant and free radical scavenging activity in topical formulations (Di Mambro and Fonseca, 2005). At concentrations of 50 μg/mL, the methanolic extract of *G. glabra* produces 78.9% mushroom tyrosinase inhibitory activity (Adhikari *et al*., 2008).

Aydemir *et al*. (2011) found that the aqueous extracts of both the leaf and flower of *Glycyrrhiza flavescens* (subspecies *antalyensis*) (62.5 μg/mL) induced apoptosis in melanoma cells by altering amounts of caspase-3, TNF-α, and IFN-c and demonstrated that both extracts were not toxic to normal 293T cells (Aydemir *et al*., 2011).

CLINICAL STUDIES

Dental caries

Hu *et al*. (2011) evaluated the efficacy of herbal lollipops containing glycyrrhizol A for their ability to kill cavity-causing bacteria in human oral cavities in two pilot studies conducted at (1) UCLA Children's Dental Clinic (20 subjects) and (2) two Los Angeles nursing homes (six subjects). Results showed that a brief application of the lollipops (twice a day for 10 days) led to a marked reduction of cavity-causing bacteria in the oral cavity of most of the human subjects. However, the study contained no control group. The concentration of glycyrrhizol A was the same in all batches of licorice that were added to the lollipops.

Recurrent aphthous stomatitis

The efficacy of bioadhesive patches containing licorice extract (applied four times a day for 5 days) was studied in a placebo-controlled clinical trial containing 15 patients (five women, 10 men, all aged 22–35 years) who suffered from ulcers of the anterior region of the mouth (Moghadamnia *et al*., 2009). The bioadhesive patches significantly reduced

Table 7. Some clinical study of licorice on treatment of gastrointestinal diseases

Treatment	Dose	Study design	Effects	References
GutGard[a] (n = 55) Placebo (n = 52), quadruple therapy: amoxicillin, omeprazole, metronidazole in both groups	150 mg, 60 days	Double-blind placebo-controlled trial	Treatment with GutGard was more effective in reducing *Helicobacter pylori* and gastric load	Puram *et al.*, 2013
Bismuth (n = 20) Licorice (n = 20)	500 mg/3 times/30 days 500 mg/3 times/30 days	Double-blind study	Administration of licorice instead of bismuth subnitrate could effectively heal peptic ulcer and eradicate *H. pylori* pathologically	Rahnama *et al.*, 2013
Licorice root (n = 33) Placebo (n = 33)	2 g/day aqueous extract/2 month 20% glycyrrhizin	Double-blind controlled trial	Licorice root significantly reduced ALT and AST levels in NAFLD patients before and after study compared with placebo	Hajiaghamohammadi *et al.*, 2012
Glavonoid™[b] Placebo 1: n = 22 2: n = 23	300 mg/day/8 weeks	Two separated double blind	No significant changes on anthropometric and biochemical markers health and adiposity	Bell *et al.*, 2011
GutGard (n = 25) Placebo (n = 25)	75 mg/twice/30 days	Double-blind placebo-controlled trial	Significantly decreased score symptom of dyspepsia compared with control	Raveendra *et al.*, 2012
Group A: pentoprazole + Migreal®[c] (n = 29) Group B: Pentoprazole + alginate (n = 29)	Twice/8 weeks	Open-label two-center study	Symptom of NERD was less in group A, better tolerated, and has less adverse effects compared with group B	Di Pierro *et al.*, 2013

NAFLD, non-alcoholic fatty liver disease; NERD, nonerosive reflux disease.
[a]GutGard: Extract of *G. glabra*.
[b]Glavonoid™: Contains 30% licorice glabra polyphenol and 3% glabridin.
[c]Migreal®: A multi-ingredient formulation containing alginate 500 mg + pure glycyrrhetinic acid 25 mg and bilberry anthocyanosides 20 mg.

pain and inflammation in the subjects' mouths, as well as the necrotic zoom diameter of aphthous ulcers.

Postextubation sore throat

In a study by Agarwal *et al.* (2009), 40 adults were randomized into two groups of 20. Five minutes before they were anesthetized, the first group received water, and the second group received 0.5 g licorice in water. Subjects in the licorice group showed decreased symptoms of postoperative sore throat compared with the control group (Agarwal *et al.*, 2009).

In a randomized double-blind study, Ruetzler *et al.* (2013) compared gargling licorice against sugar–water for the prevention of postoperative sore throat and postextubation coughing. Compared with sugar–water (5 g), a 1-min gargle of licorice (0.5 g) 5 min before induction of anesthesia significantly reduced sore throat in patients 30 min, 1.5 h, and 4 h after their arrival in the postanesthesia care unit (Ruetzler *et al.*, 2013).

Gastrointestinal disorders

In some clinical trials, licorice alone or in combination with other drugs was shown to be effective for reducing *H. pylori*, gastric load, and dyspepsia (Puram *et al.*, 2013; Rahnama *et al.*, 2013; Raveendra *et al.*, 2012). In another study, Migreal® with pentoprazole improved the symptoms of nonerosive reflux disease compared with administration of alginate with pantoprazole (Di Pierro *et al.*, 2013). Licorice root also significantly reduced alanine aminotransferase and aspartate aminotransferase levels in non-alcoholic fatty liver disease patients in a double-blind controlled trial (Hajiaghamohammadi *et al.*, 2012). However, licorice flavonoid oils had little effect in overfeeding condition in two double-blind studies. For more details, see Table 7.

Skin disorders

In a prospective, randomized, investigator-blinded, controlled half-side comparison conducted using patients with atopic dermatitis (Angelova-Fischer *et al.,* 2014), the forearms/arms of each volunteer received oil/water formulation containing licochalcone A, decanediol, menthoxypropanediol, and either ω-6-fatty acids or 1% hydrocortisone. After 1 week, both formulations were then discontinued, and another formulation containing licochalcone A and ω-6-fatty acids was applied to both arms for a further 3 weeks. On both arms, patients showed reduced symptoms of dermatitis, and there was no difference between the two groups.

In another randomized clinical study, a new tonic, EUCERIN®-Dermo-Capillaire, containing the active ingredients urea, lactate, polidocanol, and *G. inflata* root extract (which contains licochalcone A) was administrated to 30 subjects with dry and itchy scalp conditions (Schweiger *et al.*, 2013). This was a half-head study, in which the tonic was applied three times per week for 4 weeks on one side of the scalp only. Results showed that the tonic could improve scalp dryness, itching, and microinflammation.

Costa *et al.* (2010) conducted a study using 56 volunteers with melasma, in which patients were divided into two treatment groups; the first group applied cream with emblica, licorice, and belides (7%) twice a day, whereas the second group applied hydroquinone cream (2%) at night, both for 60 consecutive days (Costa *et al.*, 2010). There was no significant difference in the improvement of melasma between the two groups.

Endocrinological effects

The consumption of licorice has been shown to increase salivary dehydroepiandrosterone, deoxycorticosterone, and testosterone levels and inhibit conversion of cortisol to cortisone, in normal volunteers (men and women) (Al-Dujaili *et al.*, 2011). Furthermore, in an investigation of the mechanism, treatment of H295 cells with glycyrrhizic acid showed that these effects may be due to inhibition of steroid conjugation by the adrenal gland (Al-Dujaili *et al.*, 2011).

In a randomized, double-blind clinical trial conducted with postmenopausal women (Menati *et al.*, 2014), each patient was randomly allocated to a licorice or hormone replacement therapy (HRT) group ($n = 26$ in each group). In the licorice group, patients received 1140 mg/day D-Reglis®, containing 650 mg licorice root extract, for 90 days, whereas the HRT patients received conjugated estrogen (0.312 mg/day) and medroxyprogesterone (2.5 mg/day) for 90 days. Results showed that HRT reduced the number and severity of hot flashes more than licorice. However, licorice was apparently more effective than HRT for reducing the duration of the hot flashes.

Side effects and toxicity

Mutations of the *11β-HSD2* gene do not appear to constitute a common cause for licorice-induced hypertension. However, subtle variants of the epithelial sodium channel, including subunits of α, β, and γ, were suggested to have a role in producing licorice-induced side effects (Miettinen *et al.*, 2010). In a case where death was reported, intoxication from eating licorice for several months was suspected; biochemical evidence showed that the patient had died from lethal hyperglycemic coma (Albermann *et al.*, 2010). Several research groups have reported side effects caused by consumption of licorice, and some of the studies are summarized in Table 8.

Pregnancy

Children exposed prenatally to high levels of glycyrrhizin (≥500 mg/week), a potent inhibitor of 11β-HSD2, through maternal consumption of licorice confectionery have been shown to display decrements in verbal and visuospatial abilities and increments in externalizing symptoms, and attention and aggression problems. Furthermore, exposure to glycyrrhizin at these levels also altered diurnal and stress-induced hypothalamic–pituitary–adrenocortical axis function at the age of 8.1 years in a dose-associated manner (Räikkönen *et al.*, 2009, 2010).

Table 8. Some side effects associated with licorice extract consumption

Side effects	References
Neurologic	
Thunderclap headache	Chatterjee *et al.*, 2010; van Beers *et al.*, 2011
RCVS-PRES	Chatterjee *et al.*, 2010
PERS	Morgan *et al.*, 2011
Carpal tunnel syndrome	Tacconi *et al.*, 2009
Cardiovascular	
Cardiac arrest	Crean *et al.*, 2009; Yorgun *et al.*, 2010
Hypertension	Henderson *et al.*, 2010; Ruiz-Granados *et al.*, 2012
Edema	Johns, 2009; Caubet-Kamar *et al.*, 2010
Endocrine	
Pseudohyperaldosteronism	Pseudohyperaldosteronism (Imtiaz, 2011; Kishimoto *et al.*, 2011; Robles *et al.*, 2013)
Hypokalemia	Henderson *et al.*, 2010; Miyamoto *et al.*, 2010; Chen *et al.*, 2011; Dehours *et al.*, 2013
Myopathy	Lapi *et al.*, 2008
Rhabdomyolysis	Shah *et al.*, 2012
Myoglobinuria	Johns, 2009
Blood	
Thrombocytopenia	Celik *et al.*, 2012

RCVS-PRES, reversible cerebral vasoconstriction syndromes–reversible encephalopathy syndrome.

In a prospective cohort study design, two groups were created with 185 pregnant women who had been treated with licorice (250 mg/day) and 370 pregnant women who had not received any drugs or herbal medicine (Choi *et al.*, 2013). In this study, the consumption of licorice was not associated with adverse fetal and neonatal outcomes; however, preliminary evidence showed that licorice might increase the risk of stillbirth.

Drug interaction

In one study, *G. uralensis* had an induction effect on P450 isozymes both *in vivo* and *in vitro* (Tang *et al.*, 2009). The inhibitory effects of glycyrrhetinic acid on all tested isoforms of uridine 5′-diphospho-glucuronosyltransferases (UGTs), including 1A3 and 2B7, have been reported; thus, the possibility of an herb–drug interaction with

Table 9. Some drug interactions due to consumption of licorice and its bioactive components

Licorice	Drug	Results of interaction
Glycyrrhiza uralensis	Lidocaine	Increased total CL, reduced AUC, decreased elimination $t_{1/2}$ in rats (Tang *et al.*, 2009)
Glycyrrhiza radix	Hypaconitin	Enhanced metabolic rate of hypaconitin in rat liver S9 (Shen *et al.*, 2013)
Glycyrrhizin	Methotrexate	Increased AUC and MRT of MTX in rats (Lin *et al.*, 2009)
Glycyrrhetinic acid	Cortisone, cortisol	Increased AUC, $t_{1/2}\beta$, and Cmax in both cortisone and its metabolite cortisol in rats (Lin *et al.*, 2012)
Licorice	Hydrochlorothiazide	Increased hypokalemia in healthy volunteers (Hukkanen *et al.*, 2009)
	Methotrexate	Increased AUC and MRT of MTX in rats (Lin *et al.*, 2009)
	Cortisone acetate	Increased cortisol level by inhibited renal 11β-HSD-2 in patients with Addison's disease (Methlie *et al.*, 2011)
	Cyclophosphamide	Exacerbated teratogenicity of cyclophosphamide via upregulating CYP2B in fetuses of rat (Park *et al.*, 2011)
	Cyclosporine	Decreased bioavailability of cyclosporine by activating P-gp and CYP3A4 (Hou *et al.*, 2012)
	Valerian or alprazolam	Enhanced anti-anxiety effects of both in mice (Bhatt *et al.*, 2013)
	Verapamil	Decreased verapamil systemic concentration in rabbits (Al-Deeb *et al.*, 2010)
Black licorice	Warfarin	Enhanced anti-coagulant effect of warfarin and risk of bleeding in gastrointestinal (Liu *et al.*, 2010)
MXCT[a]	Theophylline	Speeded up the metabolism of theophylline by inducing CYP1A2 activity in rats (Tang *et al.,* 2012)

CL, clearance; AUC, area under the curve; $t_{1/2}\beta$, half-time; MRT, mean residence time; MTX, methotrexate; Cp, plasma concentration; 11β-HSD-2, 11β-hydroxysteroid dehydrogenase-2; P-gp, P-glycoprotein.

[a]Cough tablet ephedra and licorice.

glycyrrhetinic acid after consumption of licorice should be considered (Huang *et al*., 2013). In contrast, oral administration of 18β-glycyrrhetinic acid in rats enhanced UGT 1A8, which is responsible for detoxifying some toxicants (Lee *et al*., 2013). Recently, the bioactive components of *G. uralensis* were shown to inhibit the expression of CYP2D6 and CYP3A (Chen *et al*., 2014b).

Dehydroglyasperin C from licorice is known as a potent phase 2 enzyme inducer. For example, in different hepatoma cells, it induces NAD(P)H:oxidoquinone reductase and other phase 2 detoxifying/antioxidant enzymes such as glutathione S-transferase, gamma-glutamylcysteine synthase, glutathione reductase, and HO-1. Apparently, by inducing accumulation of NF (erythroid-derived 2)-like 2 in the nucleus, DGC activates expression of these phase 2 detoxifying enzymes (Seo *et al*., 2010). The recently reported drug interactions of licorice that have been reported are summarized in Table 9.

CONCLUSION

Licorice and several of its important constituents are widely used in traditional medicine and for industrial purposes. In recent years, several studies have focused on the experimental effects of different species of licorice and its constituents in order to understand the mechanisms underlying these effects. Indeed, several pharmacological properties of licorice have been reported, including gastroprotective, hepatoprotective, neuroprotective, and cardioprotective effects. The effects of licorice in the treatment of gastrointestinal, skin diseases, and HRT were established in human studies. It seems that the mechanisms of licorice in these clinical studies is similar to animal and *in vitro* studies. On the other hand, it seems that these results might be linked to traditional uses of licorice.

But licorice and active constituents should be used in clinical trials for the other pharmacological properties including antiviral, antimicrobial, antidiabetic, antiasthma, and anticancer activities as well as immunomodulatory, neuroprotective, and cardioprotective effects, and the efficacy of these compounds needs to be evaluated in humans. However, there are several question remaining open about the active constituents of licorice that will be used in clinical trials: Can the findings of the clinical studies be underpinned by preclinical studies? Can we suggest possible mechanisms of action? How do complex herbal extracts compare with pure isolated compounds? Can the results be linked to traditional applications of licorice? The results of *in vitro* and preclinical studies have to be critically evaluated and integrated into the practical applications of licorice. This review brings together the most recent studies in the field of licorice research; therefore, it will help to provide greater accessibility to the established experimental and clinical data and will promote further studies aimed at confirming the observed effects.

Conflict of Interest

The authors have no conflicts of interest related to this manuscript. This research is not under submission, in whole or in part, to other journals. All authors have contributed to the paper.

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