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REVIEW ARTICLE

Review of Pharmacological Effects of *Glycyrrhiza* sp. and its Bioactive Compounds

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The roots and rhizomes of licorice (*Glycyrrhiza*) species have long been used worldwide as a herbal medicine and natural sweetener. Licorice root is a traditional medicine used mainly for the treatment of peptic ulcer, hepatitis C, and pulmonary and skin diseases, although clinical and experimental studies suggest that it has several other useful pharmacological properties such as antiinflammatory, antiviral, antimicrobial, antioxidative, anticancer activities, immunomodulatory, hepatoprotective and cardioprotective effects. A large number of components have been isolated from licorice, including triterpene saponins, flavonoids, isoflavonoids and chalcones, with glycyrrhizic acid normally being considered to be the main biologically active component. This review summarizes the phytochemical, pharmacological and pharmacokinetics data, together with the clinical and adverse effects of licorice and its bioactive components. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: licorice; *Glycyrrhiza glabra*; glycyrrhizin; glabridin; glycyrrhitinic acid; isoliquiritigenin.

INTRODUCTION

Licorice species are perennial herbs native to the Mediterranean region, central to southern Russia, and Asia Minor to Iran, now widely cultivated throughout Europe, the Middle East and Asia (Blumenthal *et al.*, 2000). They have been used medically since at least 500 BC and licorice has been described as 'the grandfather of herbs' (Ody, 2000). The genus *Glycyrrhiza* (Leguminosae) consists of about 30 species including *G. glabra*, *G. uralensis*, *G. inflata*, *G. aspera*, *G. korshinskyi* and *G. eurycarpa*, *G. glabra* also includes three varieties: Persian and Turkish licorices are assigned to *G. glabra* var. *violacea*, Russian licorice is *G. glabra* var *gladulifera*, and Spanish and Italian licorices are *G. glabra* var. *typica* (Nomura *et al.*, 2002). It is also known as liquorice, kanzoh, gancao, sweet root and yasti-madhu (Blumenthal *et al.*, 2000; Nomura *et al.*, 2002).

ACTIVE CONSTITUENTS

Saponins

Licorice root contains triterpenoid saponins (4–20%), mostly glycyrrhizin, a mixture of potassium and calcium salts of glycyrrhizic acid (also known as glycyrrhizic or glycyrrhizinic acid, and a glycoside of glycyrrhetinic acid) which is 50 times as sweet as sugar (Blumenthal *et al.*, 2000). Other triterpenes present are liquiritic acid, glycyrretol, glabrolide, isoglaborlide and licorice acid (Williamson, 2003). Recently, it was shown that high concentration glycyrrhizin production is possible within a very short production period under controlled environments (Afreen *et al.*, 2005).

Flavonoids

Other constituents include flavonoids and chalcones (which are responsible for the yellow color of licorice) such as liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin, chalcones isoliquiritin, isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide and licoflavonol (Williamson, 2003). Recently 5,8-dihydroxy-flavone-7-O-beta-D-glucuronide, glychionide A, and 5-hydroxy-8-methoxyl-flavone-7-O-beta-D-glucuronide, glychionide B were isolated from the roots of *G. glabra* (Li *et al.*, 2005). The retrochalcones, licochalcone A, B, C, D and echinatin, were recently isolated from the roots of *G. inflata* (Haraguchi, 2001) (Fig. 1), and the minor flavonoids, isotrifoliol and glisoflavanone, from the underground part of *G. uralensis* (Hatano *et al.*, 2000a).

Isoflavones

Isoflavonoid derivatives present in licorice include glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, kumatakenin (Williamson, 2003). More recently, hispaglabridin A, hispaglabridin B, 4′-O-methylglabridin and 3′-hydroxy-4′-O-methylglabridin (De Simone *et al.*, 2001; Haraguchi, 2001) and glabroisoflavanone A and B glabroiso-flavanone B (Kinoshita *et al.*, 2005) have been found.

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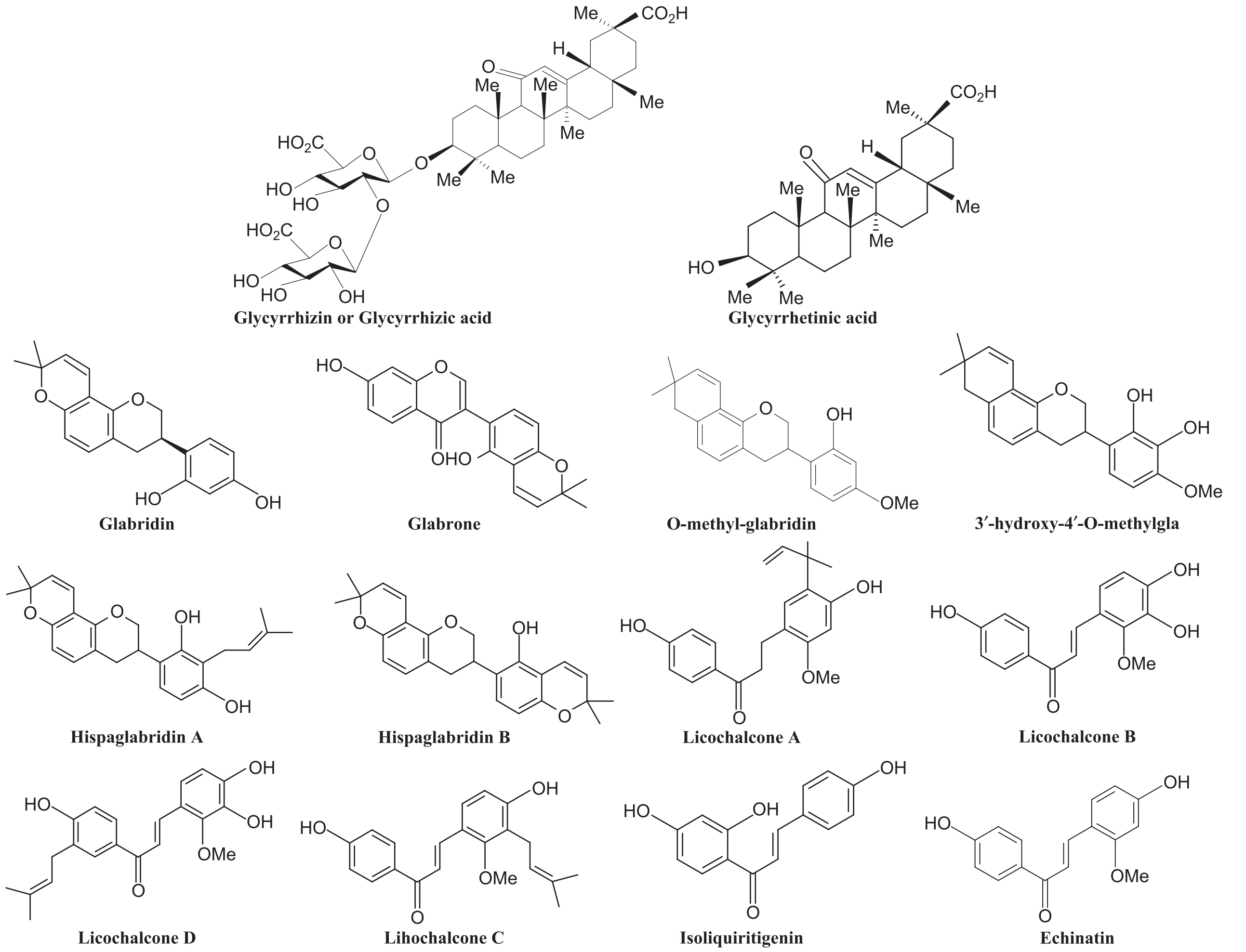

Figure 1. Chemical structure of some active components of Licochalcone C.

Coumarins

Coumarins present in *G. glabra* include liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycyrin (Williamson, 2003), glycocoumarin, licofuranocoumarin, licopyranocoumarin (De Simone *et al.*, 2001; Haraguchi, 2001) and glabrocoumarin (Kinoshita *et al.*, 2005).

Stilbenoids

Four new dihydrostilbenes, dihydro-3,5-dihydroxy-4′-acetoxy-5′-isopentenylstilbene, dihydro-3,3′,4′-trihydroxy-5-O-isopentenyl-6-isopentenylstilbene, dihydro-3,5,3′-trihydroxy-4′-methoxystilbene and dihydro-3,3′-dihydroxy-5beta-d-O-glucopyranosyloxy-4′-methoxystilbene were isolated from the leaves of *G. glabra* grown in Sicily (Biondi *et al.*, 2005).

Miscellaneous compounds

G. glabra extract also contains fatty acids (C_2–C_{16}) and phenols (phenol, guaiacol), together with common saturated linear γ-lactones (C_6–C_{14}). A series of new 4-methyl-γ-lactones and 4-ethyl-γ-lactones in trace amounts has also been found (Näf and Jaquier, 2006). Asparagines, glucose, sucrose, starch, polysaccharides (arabinogalactants), sterols (β-sitosterol, dihydrostigmasterol) are also present (Hayashi *et al.*, 1998; Blumenthal *et al.*, 2000).

TRADITIONAL USES

Licorice has a long history of medicinal use in Europe and Asia. It is felt to be effective in the treatment of peptic ulcer disease, constipation, cough and other diseases which have been summarized in Table 1. As the table shows, it seems different parts of this herbs may be useful to treat some diseases.

PHARMACOLOGICAL EFFECTS

This part of review will deal with the pharmacological effects of the licorice and its bioactive components and their effects in treatment of diseases in different models of *in vivo* and *in vitro* studies. The pharmacology effects were divided into experimental and clinical studies in this review.

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Table 1. Traditional use of different part of *G. glabra*

Extract	Traditional use
Fresh leaf (external)	Used for wounds (Dafni *et al.*, 1984)
Rhizome + root (infusion, oral)	Used to treat cystitis (Yarnell, 1997)
Root (oral)	Used to treat diabetes (Gray and Flatt, 1997)
Root (decoction, oral)	Used for cough, stomachache (Fujita *et al.*, 1995)
Aqueous extract of stem (oral)	Used for tuberculosis (Arseculeratne *et al.*, 1985)
Stem (oral)	Used for diabetes and as a diuretic (Rajurkar and Pardeshi, 1997)
Root (decoction, oral)	Used for kidney stones, lung ailment, ulcers (Dafni *et al.*, 1984)
Aqueous extract (oral)	Use in Addison's disease, gastric ulcers (Varshney *et al.*, 1983)
Aqueous extract (oral)	Used as anabolic and to improve the voice (Sircar, 1984)
Aqueous extract of root (oral)	Mild laxative (Armanini *et al.*, 2002)
Aqueous extract of rhizome (oral)	Contraceptive (Lee *et al.*, 1977)
Aqueous extract of rhizome + roots (oral)	Improve male sexual function (Nisteswar and Murthy, 1989)

EXPERIMENTAL STUDIES

Antiinflammatory activities

β-glycyhrritinic acid has shown antiinflammatory properties in different animal models (Capasso *et al.*, 1983; Amagaya *et al.*, 1984; Inoue *et al.*, 1989). β-Glycyhrritinic acid is the major metabolite of glycyrrhizin (Gumpricht *et al.*, 2005).

Two mechanisms have been suggested for the antiinflammatory effects of β-glycyhrritinic acid: First, it inhibits glucocorticoid metabolism and potentiates their effects. This potentiation was reported in skin and lung after coadministration of them with β-glycyhrritinic acid (Teelucksingh *et al.*, 1990; Schleimer, 1991). Since, β-glycyhrritinic acid is a potent inhibitor of 11β-hydroxysteroid hydroxygenase (Walker and Edwards, 1991), it causes an accumulation of glucocorticoids with antiinflammatory properties. Oral administration of β-glycyhrritinic acid or glycyrrhizin confirmed this result (MacKenzie *et al.*, 1990). Second, it inhibits classical complement pathway activation and its activity is dependent on its conformation (Kroes *et al.*, 1997). Thus, it is suggested that co-medication of it with hydrocortisone in the treatment of inflammatory lung disease will be useful (Schleimer, 1991).

Glycyrrhizin inhibited reactive oxygen species (ROS) generation by neutrophils which are the potent mediator of tissue inflammation in the *in vitro* study. It was thought that one of its antiinflammatory effect was due to this inhibitory effect (Akamatsu *et al.*, 1991; Wang and Nixon, 2001). Also, the generation of reactive oxygen species was also suppressed by glabridin treatment in RAW 264.7 cells (Jong *et al.*, 2005).

G. glabra and glyderinine, a derivative of glycyrrhizic acid, showed an antiinflammatory effect (Azimov *et al.*, 1988; Tokiwa *et al.*, 2004). It also reduced myocardial inflammatory edema in experimental myocardial damage (Zakirov *et al.*, 1999). In addition, glabridin and lichochalocone A have shown an antiinflammatory effect in *in vivo* studies (Furuhashi *et al.*, 2005; Jong *et al.*, 2005).

Glycyrrhetinic acid did not inhibit either cyclooxygenase 1 or 2 catalysed prostaglandin biosynthesis with an IC_{50} value of 425 μM in an *in vitro* study (Perera *et al.*, 2001). However, in another study *G. radix* was believed to be involved in COX-2 inhibition (Kase *et al.*, 1998). Furthermore, in this paper *G. radix* increased corticosterone levels in rats. Also, glycyrrhizin and glycyrrhetinic acid are known to inhibit phospholipase A_2 (Kase *et al.*, 1998). Recently, some derivatives of glycyrrhetinic acid have shown their inhibitory activity against interleukin-1b (IL-1b)-induced prostaglandin E2 (PGE2) production in normal human dermal fibroblasts (NHDF) (Tsukahara *et al.*, 2005).

Antimicrobial and antiviral activities

The methanol extract of aerial parts of *G. glabra* showed antibacterial activity against several kinds of bacteria (Sabahi *et al.*, 1987). Several flavonoids with C5 aliphatic residues were isolated as the effective constituents of licorice against methicillin-resistant *Staphylococcus aureus* (MRSA) and restored the effects of oxacillin and β-lactam antibiotic against MRSA (Hatano *et al.*, 2000b, 2005). Glabridin, glabrene and licochalcone A exhibited antimicrobial activity against *Helicobacter pylori in vitro* (Fukai *et al.*, 2002a, 2002b). The ether–water extracts of *G. glabra* were found to have effective antibacterial activity against all the five bacteria, *E. coli*, *B. subtilis*, *E. aerogenes*, *K. pneumoniae* and *S. aureus* (Onkarappa *et al.*, 2005). Glycyrrhizol A and 6, 8-diisoprenyl-5, 7, 4′-trihydroxyisoflavone from the root of *G. uralensis* exhibited potent antibacterial activity against *Streptococcus mutans* with minimum inhibitory concentrations of 1 and 2 μg/mL, respectively (He *et al.*, 2006).

Glycyrrhizic acid inhibits the replication of several viruses *in vitro* (Table 2) and some mechanisms have been found for the antiviral effects of glycyrrhizin (Van Rossum *et al.*, 1998; Cohen, 2005). In another study glycyrrhizic acid induced apoptosis of primary effusion lymphoma (PEL) cells that were transformed by Kaposi sarcoma-associated herpesvirus (KSHV) and terminated latent infection in B lymphocytes (Curreli *et al.*, 2005).

Two coumarins of *G. glabra*, glycocoumarin and licopyranocoumarin, were able to inhibit giant cell formation in HIV-infected cell cultures without any cytotoxicity (Hatano *et al.*, 1988; De Simone *et al.*, 2001) (Fig. 2). Also, Hatano *et al.* (1988) showed that lichochalcone A had anti-HIV activity (Hatano *et al.*, 1988).

Table 2. Antiviral effects of glycyrrhizin in *in vitro* study

Virus	Reference
Epstein-Barr virus (EBV)	Lin, 2003
Herpes simplex virus	Pompei *et al.*, 1979
Hepatitis A virus (HAV)	Crance *et al.*, 1990
Hepatitis B virus (HBV)	Takahara *et al.*, 1994; Sato *et al.*,1996
Hepatitis C virus (HCV)	Van Rossum *et al.*, 1998
Human cytomegalovirus (CMV)	Numazaki *et al.*, 1994
Human immunodeficiency virus (HIV)	Ito *et al.*, 1988
Influenza virus	Utsunomiya *et al.*, 1997
SARS coronavirus	Cinatl *et al.*, 2003
Varicella zoster virus (VZV)	Baba and Shigeta, 1987

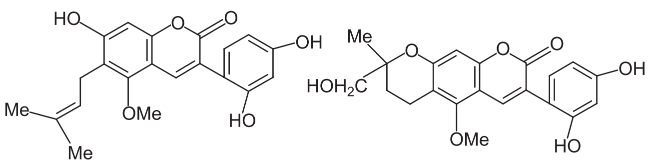

Figure 2. Anti-HIV coumarins isolated from *G. glabra.*

Antiprotozoal activities

Chinese licorice roots which can be obtained from the three species of *Glycyrrhiza* genus, *G. glabra*, *G. uralensis* or *G. inflata*, were found to potentially inhibit the growth of *Plasmodium. falciparum* and *Leishmania donovani* in *in vitro* studies (Christensen *et al.*, 1994; Christensen and Kharazmi, 2001). Chalcones such as licochalcone A from Chinese licorice roots are known to possess antiplasmodial activity with IC_{50} values between 4.5 and 0.6 mg/mL (Chen *et al.*, 1994b; Jenett-Siems *et al.*, 1999). Also, chalcones have a potent antileishmanial activity and might be developed into a new class of antileishmanial drugs (Chen *et al.*, 1993; Chen, 1994a). It was found that chalcones, such as lichochalcone A, alter the ultrastructure of the parasite mitochondria and inhibit their function by selectively inhibiting fumarate reductase (FRD) in the respiratory chain of the parasite (Zhai *et al.*, 1995; Chen *et al.*, 2001).

Antioxidative activities

The constituents of *G. inflata*, licochalcone A, B, C, D and echinatin, were effective in preventing microsomal lipid peroxidation induced by Fe (III)-ADP/NADPH and licochalcone B, D showed potent antioxidative and superoxide scavenging activities (Haraguchi *et al.*, 1998). Furthermore, the isoflavone derivatives of *G. glabra* such as glabridin inhibited lipid peroxidation in rat liver microsomes and protected mitochondrial functions from oxidative stresses (Haraguchi *et al.*, 2000). Hispaglabridin A, especially, showed a potent antioxidative activity against peroxidation induced by Fe-ascorbate (Haraguchi, 2001).

Moreover, glabridin, an isoflavan of *G. glabra*, was a potent antioxidant toward LDL oxidation in *in vitro* and *in vivo* studies (Fuhrman *et al.*, 1997; Vaya *et al.*, 1997; Belinky *et al.*, 1998a). The consumption of licorice or glabridin by atherosclerotic apolipoprotein E-deficient (E^0) mice caused a significant reduction not only in their LDL oxidation but also in the development of atherosclerotic lesions (Fuhrman *et al.*, 1997; Rosenblat *et al.*, 1999). It seems that glabridin may possess this property by two mechanisms: first it binds to the LDL and substantially protects its oxidation (Fuhrman *et al.*, 1997; Belinky *et al.*, 1998a). The hydroxyl groups on the B ring of glabridin were found to be most important for its antioxidative properties (Belinky *et al.*, 1998b). Second it accumulates in cells such as macrophages, causing a reduction of cellular oxidative stress by reducing NADPH oxidase activation and increasing cellular glutathione (GSH) (Rosenblat *et al.*, 1999, 2002). In addition, other constituents of *G. glabra* such as isoflavones hispaglabridin A, hispaglabridin B and 4′-O-methylglabridin, the two chalcones, isoprenylchalcone derivative and isoliquiritigenin were antioxidants against LDL oxidation (Vaya *et al.*, 1997).

Hepatoprotective studies

In an *in vitro* study, glycyrrhizin was hepatoprotective, probably by preventing changes in cell membrane permeability (Nakamura *et al.*, 1985). Nevertheless, it was suggested that glycyrrheitinic acid is a better hepatoprotective drug than glycyrrhizin in *in vitro* study (Nose *et al.*, 1994). This observation is in keeping with the protective effects of glycyrrhetinic acid against the carbon tetrachloride-induced hepatotoxicity and retrorsine-induced liver damage, respectively, in mice and rats (Lin *et al.*, 1999; Jeong *et al.*, 2002). Furthermore, in a hepatocyte model of cholestatic liver injury, glycyrrhizin exhibited pro-apoptotic properties, whereas glycyrrheitinic acid is a potent inhibitor of bile acid-induced apoptosis and necrosis (Gumpricht *et al.*, 2005). Some hepatoprotective effects of glycyrrhizin have been summarized in Table 3.

Antitumor activities

The aqueous extract of *G. glabra* inhibits the *in vivo* and *in vitro* proliferation of Ehrlich ascites tumor cells and inhibits angiogenesis in *in vivo* assay, peritoneal and chorioallantoic membrane assays (Sheela *et al.*, 2006). Also, the ethanol extract of *G. uralensis* root induced apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells (Jo *et al.*, 2005). On the other hand, there are many studies about the anticancer effects of several derivatives of its components both

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Table 3. Cytoprotective effects of glycyrrhizin in the liver

Study	Method	Mechanism
In vitro		
Rat hepatocytes	Incubation with anti-liver cell membrane antibody + complement	Deceased release of AST and inhibition PLA_2 (Shiki *et al.*, 1992)
Rat hepatocytes	CCl_4-induced hepatotoxicity	Deceased LDH and glutamic oxaloacetic transaminase (Nakamura *et al.*, 1985)
Rat hepatocytes	Acetaminophen or D-galactosamine induced liver injury	Increased survival rate of the hepatocyte culture (Nacagiri *et al.*, 2003)
In vivo		
Rat liver	Ischemia-reperfusion damage	Suppressed the elevation lipid peroxides, AST, ALT, LDH and decreased morphological damage (Nagai *et al.*, 1991)
Rat liver	Retrorsine-induced liver damage	Normalized serum levels of transaminase Lin *et al.*, 1999)
Rat liver	Thioacethamide-induced liver damage	Normalized serum aminotransferases, alkaline phosphatase and bilirubin (Asgary *et al.*, 2005)

Aspartate aminotransferase (AST), alanine aminotrasferase (ALT), lactate dehydrogenase (LDH), phospholipase A_2 (PLA_2), carbon tetrachloride (CCl_4).

in *in vivo* and *in vitro* studies. For more detail see Table 4.

Glycyrrhetinic acid could also trigger the pro-apoptotic pathway by inducing mitochondrial permeability transition and this property may be useful for inducing apoptosis of tumor cells (Salvi *et al.*, 2003; Fiore *et al.*, 2004). Recently, licochalcone E, a new retrochalcone from the roots of *G. inflata*, exhibited the most potent cytotoxic effect compared with the known antitumor agents, licochalcone A and isoliquiritigenin (Yoon *et al.*, 2005).

Central nervous system studies

Glabridin inhibited serotonin reuptake (Ofir *et al.*, 2003). In addition, recently, the aqueous extract of *G. glabra* L. showed antidepressant activity in both the forced swim test (FST) and tail suspension test (TST) in mice (Dhingra and Sharma, 2005). The ethanol extract of *G. glabra* had an anticonvulsant effect in PTZ and lithium-pilocarpine-induced convulsion models (Ambawade *et al.*, 2002). Also, the aqueous extract of *G. glabra* showed memory enhancing effects in the plus-maze and passive avoidance paradigm (Dhingra *et al.*, 2004). Moreover, chronic administration of the extract of *G. glabra* in both low and high doses induced correction of the passive avoidance performance in ovariectomized female rats (Fedotova *et al.*, 2005). Combined treatment with licorice root and vibration resulted in increased succinate dehydrogenase (SDH) activity in different parts of the brain, improved brain energy supply and ameliorated the effect of vibration (Oganisyan *et al.*, 2005). In addition, isoliquiritigenin showed protective effects in cerebral ischemia-reperfusion injury in rats (Zhan and Yang, 2006).

Carbenoxolone has shown anticonvulsant, sedative and muscle relaxant activities in mice and in genetically epilepsy prone rats (GEPRs) (Hosseinzadeh and Nassiri Asl, 2003; Gareri *et al.*, 2004). Also, it was able to suppress the generation of superoxide anions and hydrogen peroxide in macrophages and it also showed protective effects in the skeletal muscle and hippocampus against acute ischemic-reperfusion effects in rats (Suzuki *et al.*, 1983; Hosseinzadeh *et al.*, 2005a). In addition it could decrease the learning performances of rats in a spatial memory task (Hosseinzadeh *et al.*, 2005b).

Cardiovascular studies

Licorice showed an antiplatelet aggregation effect (Tawata *et al.*, 1992; Yu *et al.*, 2005). In other experiments, glycyrrhizin has been identified as a thrombin inhibitor in *in vitro* and *in vivo* studies and it was believed that glycyrrhizin might be used as a model for searching new antithrombotic drugs (Francischetti *et al.*, 1997; Mendes-Silva *et al.*, 2003). Also, *G. glabra* accelerated the metabolism of cells in the bone marrow erythroid stem and increased the animal's resistance to stress (Adamyan *et al.*, 2005).

Isoliquiritigenin, an active component of licorice, is reported to have a vasorelaxant effect (Yu and Kuo, 1995). It could also able to decrease tube formation in vascular endothelial cells. Thus, the anti-angiogenic effect of licorice extract depended on the anti-tube formation effect of isoliquiritin (Kobayashi *et al.*, 1995). On the other hand, as for the estrogen-like activities of glabridin in *in vivo* and *in vitro* studies, it was demonstrated that it could modulate vascular injury and atherogenesis. Therefore, it is suggested for the prevention of cardiovascular diseases in post-menopausal women (Somjen *et al.*, 2004b).

Immunological studies

Several immunomodulatory activities have been attributed to glycyrrhizin and glycyrrhetinic acid (Ohuchi *et al.*, 1981; Kobayashi *et al.*, 1993; Zhang *et al.*, 1993; Kondo and Takano, 1994; Raphael and Kuttan, 2003). The same results were seen with lichochalchone A and some analogues which showed immunomodulatory effects (Barfod *et al.*, 2002).

On the other hand, glycyrrhizin selectively activated extrathymic T cells in the liver and in human T cell

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Table 4. Anticancer effects of some active component of licorice

Compound	Method	Effects
Lichochalcone A	MCF-7 breast, HL-60 leukemia and PC-3 prostate cancer cell lines	Antitumor activity, induced apoptosis by modulating bcl-2 protein expression (Rafi *et al.*, 2000, 2002; Fu *et al.*, 2004)
	DMBA-initiated and TPA-promoted skin papilloma in mice	Antitumor promoting activity by preventing TPA to bind to the membrane receptors (Kitagawa *et al.*, 1986; Shibata *et al.*, 1991)
	TPA-promoted $^{32}P_i$-incorporation into phospholipids of HeLa cells	Inhibitory effect (Shibata *et al.*, 1991)
Glycyrrhetinic acid (GA)	Tumor promoted by TPA *in vivo* study	Antitumor-promoting activity (Kitagawa *et al.*, 1986)
Glycyrrhizic acid (aqueous extract of licorice root)	AFB1-induced cytotoxicity in human HepG2 cells	Protective effect and prevent chemical-induced carcinogenicity by inhibition the activation of hepatotoxic metabolites (Chan *et al.*, 2003)
Isoliquiritigenin (ILG)	AOM-treated ddY mice	Inhibited induction of ACF and colon carcinoma development (Baba *et al.*, 2002; Takahashi *et al.*, 2004)
	DMBA-induced skin carcinogenesis in mice	Inhibited epidermal ODC and suppressed DMBA effects (Yamamoto *et al.*, 1991)
	B16 melanoma 4A5 cells	Induced cell death and promotion of Bax expression (Iwashita, *et al.*, 2000)
	MGC-803 gastric cancer cells	Antiproliferative activity (Ma *et al.*, 2001)
	MCF-7 breast cancer cells	Antiproliferative activity (Maggiolini *et al.*, 2002)
	DU 145 and LNCaP prostate cancer cells	Antiproliferative activity (Kanazawa *et al.*, 2003)
	MLL(rat) and DU145 (human) prostate cancer cells	Inhibited cell growth and decreased cell number, induced apoptosis (Jung *et al.*, 2006)
	A549 lung cancer cells	Antiproliferative activity, enhanced expression of $p21^{CIP1/WAF1}$ expression (Hsu *et al.*, 2004; li *et al.*, 2004)
	Pulmonary metastasis model of murine renal cell carcinoma cell line (Renca)	Reduced pulmonary metastasis (Yamazaki *et al.*, 2002)
	Hep G2	Induced apoptotic cell death by inhibiting the NF-kappaB survival-signaling pathway (Hsu *et al.*, 2005)
Glabridin	In the human breast cell line	Antiproliferative effects (Tamir *et al.*, 2000)
Dibenzoylmethane (DBM)	DMBA-induced mammary tumor in Sencar mice	Inhibited formation, proliferation of total DMBA-DNA adducts in mammary gland (Lin *et al.*, 2001)
	LNCaP, DU145, and PC-3 prostate carcinoma cell lines	Cytostatic effect with deregulation cell cycle (Jackson *et al.*, 2002)

Dimethylbenz [*a*] anthracene (DMBA), 12-O-tetradecanoylphorbol 13-acetate (TPA), aflatoxin B1 (AFB1), hepatoma cell line (HepG2), azoxymethane (AOM), aberrant crypt foci (ACF), ornithine decarboxylase (ODC), MAT-LyLu (MLL), 7,12-dimethylbenz[a]anthracene (DMBA).

lines and glycyrrhizic acid enhanced Fas-mediated apoptosis without alteration of caspase-3-like activity (Kimura *et al.*, 1992; Ishiwata *et al.*, 1999). Glycyrrhizin also improved the impaired resistance of thermally injured mice to herpes virus infection (Utsunomiya *et al.*, 1995). Moreover, glycyrrhetinic acid was an inducer of type 2 antagonistic CD41 T cells in *in vivo* and *in vitro* studies (Kobayashi *et al.*, 1993; Utsunomiya *et al.*, 1995; Nakajima *et al.*, 1996). It improved the resistance of mice infected with LP-BM5 murine leukemia virus (MAIDS) mice to *Candida albicans* infection (Utsunomiya *et al.*, 2000). Also, it stimulated macrophage-derived NO production, and was able to up-regulate iNOS expression through nuclear factor *k*B (NF- *k*B) transactivation in murine macrophages (Jeong and Kim, 2002). Both of them could induce interferon activity and augment natural killer cell activity and in this study glycyrrhizin was superior to glycyrrhetinic acid in inducing interferon (Abe *et al.*, 1982). It also has inhibitory effects on TNF-alpha-induced IL-8 production in intestinal epithelial cells (Kang *et al.*, 2005).

In addition, there are some studies on the immunomodulatory effects of polysaccharide fractions obtained from shoots of *G. glabra* and hairy roots of *G. uralensis in vitro* (Nose *et al.*, 1998). GR-2IIa and GR-2IIb, two isolated acidic polysaccharides of *G. uralensis*, have shown anticomplementary activity. Also, GR-2IIc had both anticomplementary activity and mitogenic activity (Zhao *et al.*, 1991; Yamada *et al.*, 1992; Kiyohara *et al.*, 1996). Recently, the haemolytic activities of *G. uralensis* saponins (GLS) and its adjuvant potentials against ovalbumin (OVA) were established in mice (Sun and Pan, 2006).

Renal studies

Glabridin showed an antinephritis effect in the mouse glomerular disease model (Fukai *et al.* 2003). Also, glycyrrhizin could ameliorate renal defects in gentamicin-induced acute renal failure in rats (Sohn *et al.*, 2003). Also, the extract of *G. radix* could protect the kidneys against peroxynitrite ($ONOO^-$)-induced oxidative stress *in vivo* through scavenging $ONOO^-$ and/or its precursor NO (Yokozawa *et al.*, 2005).

Cytotoxic activities

Sixty nine compounds of *Glycyrrhiza* phenols showed an inhibitory activity on the growth of *Bacillus subtilis* H17 and M45 and some of them, such as isoliquiritigenin, were positive in the rec-assay (Fukai *et al.*, 1998).

Respiratory studies

Recently in one study, *G. radix* produced a persistent antitussive effect in the guinea-pig, suggesting that liquiritin apioside, a main antitussive component, plays an important role in the earlier phase, while liquiritigenin and liquiritin play an important role in the late phase (Kamei *et al.*, 2005). This result is keeping with the previous antitussive effects of licorice.

Effects on gap junction channels

Glycyrrhitinic acid and its derivatives were shown to inhibit gap junction channels (Davidson and Baumgarten, 1988). The inhibitory effects of 18β-glycyrrhetinic acid on gap junction channels of arteriolar smooth muscle, endothelial cells, renal pelvis, ureter and mesenteric small arteries were studied (Yamamoto *et al.*, 1998; Santicioli and Maggi, 2000; Matchkov *et al.*, 2004).

Endocrinological studies

Some effects of licorice on the endocrine system in *in vitro* and *in vivo* studies are summarized in Table 5. It seems that this herb acts on the metabolism of steroids with different mechanisms.

Other studies

In endocrinological studies, glabridin increased the growth of mouse osteoblastic (MC3T3-E1) and human cell lines (Somjen *et al.*, 2004a; Choi, 2005). The alcohol extract of licorice reduced the glucose levels of genetically diabetic KK-A^y mice (Kuroda *et al.*, 2003).

Table 5. The effects of licorice on the function of different enzymes

Enzyme	Effects
11β-HSD Type 1	Inhibition (Jellinck *et al.*, 1993; Hult *et al.*, 1998;
11β-HSD Type 2	Inhibition (Monder *et al.*, 1989; Ferrari *et al.*, 2001; Palmero *et al.*, 2004)
3HSD	Inhibition (Latif *et al.*, 1990)
17HSD	Inhibition (Armanini *et al.*, 2003)
17-20 lyase	Inhibition (Armanini *et al.*, 2003)
Aromatase	Increase (Sakamoto and Wakabayashi, 1988)
5α-Reductase	Increase (Latif *et al.*, 1990; Fugh-Berman and Ernst, 2001)

In addition, dermatological studies showed that three flavonoids of licorice, licuraside, isoliquiritin and licochalcone A, have high potential for studying depigmenting agents by inhibiting tyrosinase (Fu *et al.*, 2005). The same results were reported for glycyrrhisoflavone and glyasperin C (Kim *et al.*, 2005).

CLINICAL STUDIES

Gastrointestinal effects

It was shown that oral licorice in a combination product could heal ulcers as effectively as an H2 blocker (Kassir, 1985; Aly *et al.*, 2005). Glycyrrhizinic acid, a major component of licorice, has antiulcer properties, it seems by raising the local concentration of prostaglandins that promote mucous secretion and cell proliferation in the stomach, leading to healing of ulcers in experimental studies (Van Marle *et al.*, 1981; Baker, 1994).

Carbenoxolone, a hemisuccinate derivative of 18β-glycyrrhetinic acid, and enoxolone are two chemical synthetic derivatives of licorice which have been used in clinical therapies (Fig. 3). Enoxolone, an analogue of carbenoxolone, has been used for the treatment of peptic ulcer disease and other GIT disorders, skin disorders, mouth and throat disorders (Sweetman, 2005). Carbenoxolone has been used for peptic ulcer disease, gastro-oesophageal reflux and also it has been used for the symptomatic management of mouth ulceration as a gel or mouthwash (Sweetman, 2005).

Anticancer effects

Licorice root has been identified by the National Cancer Institute as possessing cancer-preventive properties (Craig, 1999; Wang and Nixon, 2001). It has been used among patients with prostate cancer as an ingredient of PC-SPES, a commercially available combination of eight herbs (DiPaola *et al.*, 1998).

Antioxidative effects

G. glabra extracts showed great antioxidant and free radical scavenging activities in topical formulations and may be used in topical formulations in order to protect the skin against damage caused by free radical and reactive oxygen species (Di Mambro and Fonseca, 2005).

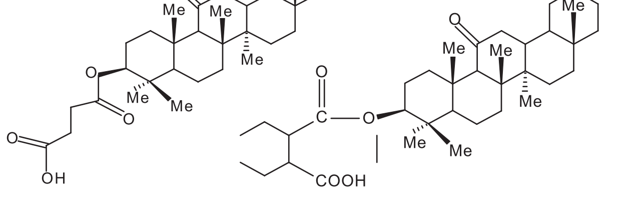

Figure 3. Chemical structures of carbenoxolone and enoxolone.

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Antiviral and hepatoprotective effects

In the world, especially in Asia, glycyrrhizic acid is used intravenously for the treatment of chronic hepatitis B and C and its preparation under the name of Stronger Neo-Minophagen C (SNMC) decreased aminotransferase levels in patients with chronic hepatitis in multiple double-blind studies (Van Rossum *et al.*, 1999; Iino *et al.*, 2001; Zhang and Wang, 2002). It is suggested that glycyrrhizin has a preventive effect on the development of hepatocellular carcinoma (HCC) in patients with HCV-associated chronic hepatitis (Arase *et al.*, 1997; Miyakawa and Iino, 2001).

Licorice has been reported to have a direct hepatoprotective effect (Luper, 1999; Leung *et al.*, 2003). Glycyrrhizin, its major component, is often used to treat patients with chronic liver damage who do not receive or respond to interferon (IFN) therapy (Okuno *et al.*, 2001). Stronger Neo-Minophagen C® (SNMC), containing 2 mg/mL of glycyrrhizin, has been used clinically as an antihepatitis agent (Shibata, 2000).

Dermatological studies

G. glabra L. has been used in herbal medicine for skin eruptions, including dermatitis, eczema, pruritus and cysts (Saeedi *et al.*, 2003). In this section the various studies of licorice on the skin are summarized in Table 6.

Recently glycyrrhizin treatment has showed protective effects against UVB-irradiated human melanoma cells (Rossi *et al.*, 2005). Moreover, licorice extract and its active component, glycyrrhizic acid has been described as effective skin whitening effects (Smith, 1999). The group of Briganti classified liquiritin as a skin turnover accelerator (Briganti *et al.*, 2003). However, it was suggested that liquiritin causes depigmentation by two mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the acceleration of epidermal renewal (Amer and Metwalli, 2000). Concerning the mechanisms of glabridin on melanogenesis and inflammation, it has been shown that it inhibits the tyrosinase activity of melanocytes and as a result, it seems that hydroquinone will be replaced by licorice extract in a new preparation for dermal melasma (Piamphongsant, 1998). However, in a few cases, allergic dermatitis can develop to oil soluble licorice extracts (Nishioka and Seguchi, 1999).

Table 6. Licorice and its components in skin therapies

Compound	Treatment
Licorice (topical gel 2%)	Atopic dermatitis (Saeedi *et al.*, 2003)
GA	Inflammatory dermatoses (Cohen and Heidary, 2004)
Deglycyrrhizinated licorice and carbenoxolone (topical)	Recurrent aphthus stomatitis (RAS) (Scully *et al.*, 2002)
Liquiritin (topical 2%)	Hyperpigmentation (in patient with bilateral and symmetrical idiopathic epidermal melasma) (Amer and Metwalli, 2000)
Glabridin	Melanogenesis, inflammation (Yokota *et al.*, 1998; Petit and Pierard, 2003; Halder and Richards, 2004)

Glycyrrhetinic acid (GA).

Endocrinological effects

Glycyrrhiza root has been shown to decrease circulating levels of testosterone in men and women (Armanini *et al.*, 1999, 2002; Rafi *et al.*, 2002; Armanini *et al.*, 2004). But it was not able to reduce salivary testosterone in men significantly (Josephs *et al.*, 2001). Moreover, it induced regular ovulation and pregnancy in infertile hyperandrogenic patients (Yaginuma *et al.*, 1982).

On the other hand, isoliquiritigenin (ILC), glabrene and glabridin are phytoestrogens. ILC and glabrene can bind to the human estrogen receptor (ER) with higher affinity than glabridin. It was suggested that isoflavenes may serve as natural estrogen agonists in preventing the symptoms and diseases associated with estrogen deficiency (Tamir *et al.*, 2000, 2001). In some traditional Chinese medicine preparations, the root of *G. glabra* is used for treatment menopause-related symptoms. But there are no clinical data regarding its safety or efficacy for treating hot flashes (Santoro *et al.*, 2004).

Moreover, the activity of 11β-HSD-2 potently is blocked *in vivo* and *in vitro* by glycyrrhetinic acid by two mechanisms, direct competitive inhibition and pretranslational inhibition (Ferrari *et al.*, 2001). It seems that this herb acts on the metabolism of steroids with different mechanisms. The consumption of licorice extract and glycyrrhetinic acid could decrease body fat mass in humans and a possible mechanism seems to be by inhibiting 11β-HSD1 at the level of fat cells (Armanini *et al.*, 2005).

Respiratory diseases

Licorice has been used as a cough-relieving medicinal herb from ancient times. It seems that mucilage present in it or secretion produced under the influence of the active substances covers the oral and throat mucosa soothing its irritability and relieving dry cough (Ody, 2000; Puodziuniene *et al.*, 2005).

Other effects

Ammonium glycyrrhizate (from licorice root) is used in toothpastes, mouth rinses and other products for the control of periodontal disease (Goldie, 2005). The extract of *G. glabra* in combination with other herbs, such as ImmunoGuard®, has been effective for the prophylactic management and treatment of patients with Familial Mediterranean Fever (FMF) (Amaryan *et al.*, 2003).

INDUSTRIAL USES

Commercially, licorice is added to chewing gum, chocolate candy, cigarettes, smoking mixtures, chewing tobacco and snuff as sweetening agents (Tyler *et al.*, 1988; De Klerk *et al.*, 1997) and as a depigmentation

Table 7. Products containing considerable amounts of glycyrrhizinic acid (De Klerk *et al.*, 1997)

Confectionery	Licorice sticks, bricks, cakes, toffee, pipes, bars, balls, tubes, Catherine wheels, pastilles and allsorts
	Sorbits chewing gum
	Stimorol chewing gum
Health products	Licorice flavored diet gum
	Throat pearls
	Licorice flavored cough mixtures
	Herbal cough mixtures
	Licorice tea
All types of licorice root	Russian, Iranian, Chinese, Turkish, Afghan and unknown origin
	Chewing tobacco
	Alcoholic drinks

agent in cosmetics (Nomura *et al.*, 2002). Also, licorice is frequently employed to mask the taste of bitter drugs such as aloe, quinine and others. The surfactant property of the saponins may also facilitate the absorption of poorly absorbed drugs, such as the anthraquinone glycosides (Tyler *et al.*, 1988). Some of the products which have glycyrrhizinic acid are summarized in Table 7 (De Klerk *et al.*, 1997).

Table 8. Some side effects associated with licorice extract treatment

Side effects	Reference
Neurologic	
Headache	De Groot *et al.*, 1988
Paralysis	Van Den Bosch *et al.*, 2005
Transient visual loss	Dobbins and Saul, 2000; Fraunfelder, 2004
Cardiovascular	
Torsades de points tachycardia	Eriiksson *et al.*, 1999
Cardiac arrest	Bannister *et al.*, 1977
Hypertension	Olukoga and Donaldson, 2000
Edema	De Groot *et al.*, 1988; Shibata, 2000
Endocrine	
Hypokalemia	Nielsen and Pedersen, 1984; Olukoga and Davidson, 2000
Reduction testosterone	Armanini *et al.*, 1999
Premature birth	Strandberg *et al.*, 2001
Renal	
Acute renal failure	
Musculoskeletal	
Muscle weakness	Van Den Bosch *et al.*, 2005
Myopathy	Gross *et al.*, 1966; Shintani *et al.*, 1992
Myoglobinuria	Gross *et al.*, 1966
Rhabdomyolysis	Van den Bosch *et al.*, 2005
Other	
Increase body weight	Bernardi *et al.*, 1994

SIDE EFFECTS AND TOXICITY

Large amounts of licorice may result in severe hypertension, hypokalemia and other signs of mineralocorticoid excess. This hypertension is caused by decreased 11β-HSD2 activity. This enzyme is responsible for the renal conversion of cortisol to cortisone. Thus, licorice leads to activation of renal mineralocorticoid receptors by cortisol, resulting in a state of apparent mineralocorticoid excess and suppression of the rennin angiotensin system (Conn *et al.*, 1968, Stewart *et al.*, 1990; Van Uum, 2005). Some side effects due to the consumption of licorice have been reported by different groups and are summarized in Table 8.

Carmines *et al.* (2005) reported that adding licorice extract to cigarette tobacco at levels of ≤5% (about 0.269% glycyrrhizic acid) did not significantly alter the toxicity of smoke. Also, in this paper, it was mentioned that licorice is not a teratogen or genotoxic (Carmines *et al.*, 2005). In another study, the toxicity of licorice extract was shown in the liver of Black molly fish (Radhakrishnan *et al.*, 2005).

PHARMACOKINETICS

After oral administration, glycyrrhizin is metabolized to glycyrrhetinic acid by intestinal bacteria which contain β-D-glucuronidase (Hattori *et al.*, 1985). Furthermore, intravenously administered glycyrrhizin is metabolized in the liver by lysosomal β-D-glucuronidase to 3-mono-glucuronide glycyrrhetinic acid. This metabolite is excreted with bile into the intestine, where it is metabolized by bacteria into glycyrrhetinic acid, which can be reabsorbed (Akao *et al.*, 1991) (Fig. 4).

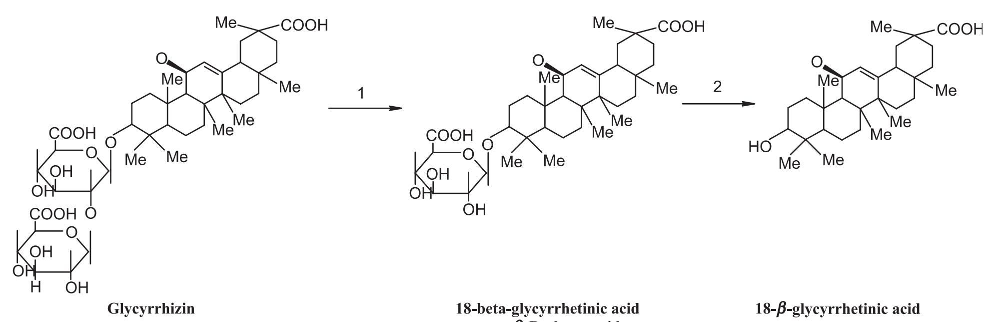

Figure 4. Metabolism of glycyhrrizin in the liver (1) by lysosomal β-D-glucuronidase to 3-mono-glucuronide glycyrrhetinic acid and then in the intestine (2) by bacteria β-D-glucuronidase after intravenous administration (Akao *et al.*, 1991).

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Other components of the extract could affect the pharmacokinetics of glycyrrhizin (G) and glycyrrhetic acid (GA), a main metabolite of G. After administration of aqueous licorice root extract (LE) to rats and humans, G and GA levels were lower compared with G alone and the pharmacokinetic curves showed significant differences in the areas under the plasma-time curve (*AUC*), C_{max}, and T_{max} parameters. Also, the data obtained from urine samples confirmed a reduced bioavailability of G present in LE compared with pure G. Interaction between the G constituent and other components in LE during intestinal absorption was mentioned. Thus, modified bioavailability could explain the various clinical adverse effects resulting from the chronic oral administration of G alone as opposed to LE (Cantelli-Forti *et al.*, 1994). However, it seems that the pharmacokinetics differ in other species. In another study the *AUC*s of G and GA after oral administration of LE were significantly higher than those after pure G in rabbits and the bioavailabilities of G and GA were significantly better from licorice than from pure G in rabbits, but the presystemic metabolism of pure G in the rabbit is rather different from that in rat, pig and human (Hou *et al.*, 2005). It was shown that the pharmacokinetics of G is nonlinear. After bolus intravenous administration at a dose of 20, 50, or 100 mg/kg in rat, the decline in the concentration of G in plasma, was generally biexponential at each dose, but the terminal disposition became much slower as the dose was increased. In addition, the apparent total body clearance decreased significantly with increases in the dose. But the apparent distribution volume after intravenous administration was unaffected by the dose (Tsai *et al.*, 1992). Administration of different oral doses of 18-beta-glycyrrhetinic acid (β-GRA) in healthy volunteers showed a biphasic decay of the plasma concentration-time curve at doses >500 mg. The peak plasma concentration and the *AUC* increased with increasing β-GRA doses. Urinary elimination of β-GRA and its glucuronides over 24 h was less than 1% of the dose administered. The data based on single dose kinetic analysis revealed that after multiple doses of 1.5 g β-GRA/day, 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD) might be constantly inhibited, whereas at daily doses of 500 mg or less, such an inhibition might occur only transiently (Krahenbuhl *et al.*, 1994).

Administration intravenously of G to an animal model of liver disease (D-galactosamine-intoxicated (GAL) rat), significantly decreased the apparent volume of distribution (V_{dss}) and the total body clearance (CL_{total}) than those in normal rats. When G was administered orally, the *AUC*, the mean residence time (*MRT*) and the time to reach the maximum plasma concentration (T_{max}) for G were higher, but the maximum plasma concentration (C_{pmax}) in GAL rats was lower than that in normal rats. But, the bioavailability of G was not significantly changed. Also, the *AUC* for GA, after oral administration of G was higher in GAL rats than in normal rats, although there was no significant difference in *MRT* or T_{max}, C_{pmax} or the bioavailability for GA between GAL and normal rats. However, the changes in the absorption rate and reduction of the hepatic elimination rates in GAL rats could explain these differences (Wang *et al.*, 1996). GA has a large volume of distribution, a long biological half-life, and undergoes substantial enterohepatic circulation (Tyler *et al.*, 1988). Thus, large doses of KCl supplementation for weeks are necessary because of the long half-life of glycyrrhetic acid (Van Den Bosch *et al.*, 2005).

In another study, liquiritin apioside showed a peak plasma concentration 15 min after administration in guinea-pigs, which gradually decreased and was almost undetectable 4 h after administration. Liquiritigenin, an aglycone of liquiritin apioside, appeared in the plasma 2 h after the administration of liquiritin apioside and remained for more than 6 h after administration. The plasma concentration of unchanged liquiritigenin was observed 15 min after administration and then gradually increased for more than 6 h after administration (Kamei *et al.*, 2005).

Glycyrrhizin, genistein, glycyrrhisoflavone, glicoricone, licofuranone, licopyranocoumarin licocoumarone and other licorice constituents were found to inhibit monoamine oxidase (MAO) *in vitro* (Hatano *et al.*, 1991b). However, the clinical significance of this is not known and not all these compounds are found in all species.

Based on the phenolic constituent of licorice sp, they were classified into three types A, B, C:

Type A: roots and rhizomes of *G. uralensis* containing licopyranocoumarin, glycycoumarin and/or licocoumarone, which were not found in *G. glabra* and *G. inflata*. Type B: *G. glabra*, containing glabridin and glabrene, which were not found in the samples of the other two species. Type C: *G. inflata*, containing licochalcones A and B, which were not found in the other two species.

Extracts of some licorice specimens of types A, B, and C inhibited 40–56% of xanthine oxidase activity. Extracts of some licorice specimens of types A and B also showed inhibitory effects on monoamine oxidase (44–64%) (Hatano *et al.*, 1991a).

DRUG INTERACTIONS

The extract of *G. uralensis* showed potent CYP3A4 inhibitory activity (Hu *et al.*, 1999; Budzinski *et al.*, 2000; Tsukamoto *et al.*, 2005). After bioassay purification, other components such as (3*R*)-vestitol, 4-hydroxyguaiacol apioglucoside, liquiritigenin 7, 4′-diglucoside, liquiritin apioside showed potent CYP3A4 inhibitory activities among them (Tsukamoto *et al.*, 2005). Glabridin was also found to inactivate the enzymatic activities of CYP 3A4 and 2B6 and competitively inhibited 2C9 (Kent *et al.*, 2002).

In other hands, prolonged intake of high LE or G doses may result in accelerated metabolism of coadministered drugs. Daily oral doses of LE or G for 1, 4 or 10 consecutive days in mice, were able significantly to induce hepatic CYP3A- and, to a lesser extent, 2B1- and 1A2-dependent activities, as well as 6-beta- (mainly associated to CYP3A), 2-alpha-, 6-alpha- (CYP2A1, 2B1), 7-alpha-, 16-alpha- (CYP2B9) and 16-beta-testosterone hydroxylase (TH) activities. Thus, the induction of cytochrome P450-dependent activities by long-term ingestion of licorice may have clinical consequences for patients taking drugs metabolized by the same CYP enzymes (Paolini *et al.*, 1998). But, high doses of LE and G could cause significant adverse effects. Thus, it seems that routine licorice consumers under CYP3A induction might therefore be predisposed to associated

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

Licorice	Drug	Results of interaction
Gan Cao (*G. uralensis*)	Warfarin	Increase metabolism of warfarin in rats (Mu *et al.*, 2006)
G. glabra	Acetaminophen	Increased the excretion of acetaminophen–glucoronide conjugate in rats (Moon and Kim, 1996)
G. glabra	Prednisolone	Decreased CL, increase AUC and Cp of prednisolone (Chen *et al.*, 1991)
GA	Hydrocortisone	Increase effect of hydrocortisone in mice (Teelucksingh *et al.*, 1990)
GA	Oral contraceptive	Hypertension, edema, hypokalemia, increase sensitivity to glycyrrhizin, sensitivity to adverse effects in women is more than in men (Bernardi *et al.*, 1994; De Klerk *et al.*, 1997)

Clearance (CL), area under curve (AUC), plasma concentration (Cp), glycyrrhetinic acid (GA).

adverse effects. Furthermore, consumption of licorice is contraindicated during pregnancy and for patients with liver disorders, hypokalemia like those who are taking cardiac glycosides. The aldosterone effects of licorice root may counteract antihypertensive action of prescribed medications (Cassileth and Barazzuol, 2001). Recently, a direct interaction of glycyrrhetinic acid absorption with sennosides and its derivatives has been studied in humans (Mizuhara *et al.*, 2005). Some drug interactions of licorice which have been reported are summarized in Table 9.

CONCLUSION

In summary, licorice is used throughout the world as a traditional herbal remedy. As for the properties of licorice and its active constituents, it is suggested that their potential roles are evaluated for their effects in the treatment of different kinds of disease such as cancer, atherosclerosis, immunodeficiency, hormone deficiency endocrine and skin diseases. However, it is necessary to carry out further studies to confirm these effects.

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