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 anti-inflammatory, 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. korschinskyi 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-madhhu (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 glycyrrhetic 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, glycyretol, glabrolide, isoglabrolide 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, isoflavanone, isoflavanone, from the underground part of G. uralensis (Hatano et al., 2000a).

Isoflavones

Isoflavonoid derivatives present in licorice include glabridin, galbrene, galbroene, shipterocarpin, licoglisoflavones 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 glabroisoflavanone B (Kinoshita et al., 2005) have been found.

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Coumarins

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

Stilbenoids

Four new dihydrostilbenes, dihydro-3,5,5'-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 (C2–C16) and phenols (phenol, guaiacol), together with common saturated linear γ-lactones (C6–C14). 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, dihydrostigmastanol) 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 herb 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.
**Antinflammatory activities**

β-glycyrrhitinic acid has shown antinflammatory properties in different animal models (Capasso et al., 1983; Amagaya et al., 1984; Inoue et al., 1989). β-Glycyrrhitinic acid is the major metabolite of glycyrrhizin (Gumpricht et al., 1989).

Two mechanisms have been suggested for the antinflammatory effects of β-glycyrrhitinic acid: First, it inhibits glucocorticoid metabolism and potentiates their effects. This potentiation was reported in skin and lung after coadministration of them with β-glycyrrhitinic acid (Teelucksingh et al., 1990; Schleimer, 1991). Since, β-glycyrrhitinic acid is a potent inhibitor of 11β-hydroxysteroid dehydrogenase (Walker and Edwards, 1991), it causes an accumulation of glucocorticoids with antinflammatory properties. Oral administration of β-glycyrrhitinic 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 antinflammatory 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).

**Experimental studies**

**Antinflammatory activities**

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G. glabra and glyderine, a derivative of glycyrrhizinic acid, showed an antinflammatory 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 lichochoalcone A have shown an antinflammatory effect in in vivo studies (Furuhashi et al., 2005; Jong et al., 2005).

Glycyrrhetic acid did not inhibit either cyclooxygenase 1 or 2 catalysed prostaglandin biosynthesis with an IC₅₀ 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 glycyrrhetic acid are known to inhibit phospholipase A₂ (Kase et al., 1998). Recently, some derivatives of glycyrrhetic acid have shown their inhibitory activity against interleukin-1β (IL-1β)-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 (Sahabi 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 lichochoalcone 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. uralsensis* 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 lico-pyranocoumarin, 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 lichochoalcone A had anti-HIV activity (Hatano et al., 1988).
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 isoflavon 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<sup>−</sup>) 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 glycyrrhetinic acid is a better hepatoprotective drug than glycyrrhizin in *in vitro* study (Nose et al., 1994). This observation is in keeping with the selective effects of glycyrrhetinic acid against the carbon tetrachloride-induced hepatotoxicity and retorsine-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 glycyrrhetinic acid is a potent inhibitor of bile acid-induced apoptosis and necrosis (Gumprecht et al., 2005). Some hepatoprotective effects of glycyrrhizin have been summarized in Table 3.

### 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             | Cinati et al., 2003              |
| Varicella zoster virus (VZV)  | Baba and Shigeta, 1987           |

### Antiprotzoa 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<sub>50</sub> 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., 1994; Chen, 1994a). It was found that chalcones, such as lichochnalcone 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).

### 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 choroidal neovascular 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...
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 A, 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 Shama, 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 glycyrrhetic 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 licochalcone A and some analogues which showed immunomodulatory effects (Barford 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 3. Cytoprotective effects of glycyrrhizin in the liver**

| Study          | Method                                      | Mechanism                                                                 |
|----------------|---------------------------------------------|--------------------------------------------------------------------------|
| **In vitro**   |                                             |                                                                          |
| Rat hepatocytes| Incubation with anti-liver cell membrane     | Decreased release of AST and inhibition PLA₂ (Shiki et al., 1992)         |
|                | antibody + complement                        | Decreased LDH and glutamic oxaloacetic transaminase (Nakamura et al., 1985) |
|                | CCl₄-induced hepatotoxicity                  |                                                                          |
| Rat hepatocytes| Acetaminophen or α-D-glucosamine-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., 1981) |
| Rat liver      | Retrorsine-induced liver damage              | Normalized serum levels of transaminase                                  |
| Rat liver      | Thioacetamide-induced liver damage          | Normalized serum aminotransferases, alkaline phosphatase and bilirubin (Asgary et al., 2005) |

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), phospholipase A₂ (PLA₂), carbon tetrachloride (CCl₄).

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**Table 4.**

| Study          | Method                                      | Mechanism                                                                 |
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lines and glycyrrhizic acid enhanced Fas-mediated apoptosis without alteration of caspase-3-like activity (Kimura et al., 1992; Ishiwhata et al., 1999). Glycyrrhizin also improved the impaired resistance of thermally injured mice to herpes virus infection (Utsunomiya et al., 1995). Moreover, glycyrrhetic acid was an inducer of type 2 antinfective CD4+ T cells 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 kB (NF-κB) 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 glycyrrhetic 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-2Ia and GR-2Ib, two isolated acidic polysaccharides of G. uralensis, have shown anticomplementary activity. Also, GR-2Ic had both anticomplementary activity and mitogenic activity (Zhao et al., 2005). Also, the extract of Glycyrrhiza glabra could protect the kidneys against peroxynitrite (ONOO−)-induced oxidative stress.

### 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 peroxyxinitrite (ONOO−)-induced oxidative stress.

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**Table 4. Anticancer effects of some active component of licorice**

| Compound                     | Method                                                                 | Effects                                                                                     |
|------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Licochalcone 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 32P-i incorporation into phospholipids of HeLa cells       | Inhibitory effect (Shibata et al., 1991)                                                    |
| Glycyrrhetic acid (GA)       | Tumor promoted by TPA in vivo                                          | 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 (Iwasha, 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} (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)                                               |
|                              | 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).
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 in 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). In addition, dermatological studies showed that three flavonoids of licorice, licuraside, isoliquiritin and licoricechalcone 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 antiallerc 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 (DiMambro and Fonseca, 2005).

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**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 | Increase (Sakamoto and Wakabayashi, 1988) |
| Aromatase | Increase (Sakamoto and Wakabayashi, 1988) |
| 5α-Reductase | Increase (Latif et al., 1990; Fugh-Berman and Ernst, 2001) |

---

*Figure 3. Chemical structures of carbenoxolone and enoxolone.*
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 mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second

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   | Recurrent aphthous stomatitis (RAS)         |
| and carbenoxolone (topical)   | (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 glycyrrhetic 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 glycyrrhetic 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...
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).

**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).

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**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 |

**Table 8. Some side effects associated with licorice extract treatment**

| Side effects            | Reference                        |
|-------------------------|----------------------------------|
| Neurologic              | De Groot et al., 1988            |
| Headache                | Van Den Bosch et al., 2005       |
| Paralysis               | Fraunfelder, 2004                |
| Transient visual loss   | Dobbins and Saul, 2000           |
| Cardiovascular          | Erikkson et al., 1999            |
| Hydraulic               | Bannister et al., 1977           |
| Hypertension            | Olukoga and Donaldson, 2000      |
| Throat pearls           | De Groot et al., 1988; Shibata, 2000 |
| Licorice flavored cough mixtures |                    |
| Herbal cough mixtures   |                                  |
| Nicotinic               |                                  |
| Cardiovascular          |                                  |
| Cardiac arrest          |                                  |
| Edema                   |                                  |
| All types of licorice root |                              |
| Russian, Iranian, Chinese, Turkish, Afghan and unknown origin Chewing tobacco Alcoholic drinks |

**Figure 4.** Metabolism of glycyrrhizin 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).
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), Cmax, and Tmax 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 AUCs 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 concentrations 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 (Krahnenhul et al., 1994).

Administration intravenously of G to an animal model of liver disease (n-galactosamine-intoxicated (GAL) rat), significantly decreased the apparent volume of distribution (Vss) and the total body clearance (CLtotal) 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 (Tmax) for G were higher, but the maximum plasma concentration (Cmax) 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 Tmax, Cmax 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 (Tylet 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, glycyrrhishosflavone, glicoricone, licofuranone, licoypyranoconuamarin 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 licoypyranoconuamarin, 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 licochalones 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 (3R)-vestitol, 4-hydroxyguaiacol apio glucoside, 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
Table 9. Some drug interaction due to consumption of licorice and its bioactive components

| Licorice   | Drug               | Results of interaction                                                                 |
|------------|--------------------|----------------------------------------------------------------------------------------|
| Gan Ca o   | Warfarin           | Increase metabolism of warfarin in rats (Mu et al., 2006)                                |
| (G. urale nis) | Acetaminophen      | Increased the excretion of acetaminophen-glucuronide 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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