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Research and application of *Radix Glycyrrhizae*

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Abstract *Radix Glycyrrhizae* is the rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L. They are widely distributed in the northeast and northwest of China. The pharmacological activities of licorice are mainly represented by the main triterpene saponins, glycyrrhizin, glycyrrhizic acid, 18-β-glycyrrhetic acid, glycyrrhizinic acid and its aglycone, glycyrrhetinic acid. Licorice root possesses wide broad pharmacological actions. According to literature reports, its pharmacological activities include the following aspects: effects on central nerve system; cardiovascular system and endronic system; liver, renal and pancreas functions, anti-ulcer action, anticancer action, anti-allergic and anti-iflammatory effects, anti-virus and antibacteria activities, and effect on immune function and so on. Pharmacokinetics of the active principles of Radix Glycyrhizae was studied in rats. After intravenos injection at doses of 20, 50 and 100 $mg.kg^{-1}$ of glycyrrhizin, as shown in Table 1, the half-life was 1.78, 3.72 and 4.68 h, respectively. The result indicated non-linear kinetic nature. The pharmacokinetics of 18-α- and 18-β-glycyrrhetic acid was studied in rabbits following intravenous injection at dose 20 $mg.kg^{-1}$. The half-life was 1.22 and 2.85 h, respectively. It is used as a tonic, antiphlogistic, mucolytic, expectorant, anagesic for the treatment of gastroinstinal and respiratory diseases, and also used to alleviate the toxicity of some drugs.

Key Words Radix Glycyrrhizae; Glycyrrhiza uralensis; Ethnopharmacology; Chemistry; Pharmacological actions; Clinical application

Introduction

Chinese materia medica is an important part of traditional Chinese medicine and Chinese civilization. In the history, Chinese traditional medicine arose from mythical medicine to a system of Chinese drugs and herbal medicine. The first book on materia medica "*Shen-nong Bencao Jing*" known as "the canon of materia medica" was compased in the second century BC by the folk under the pseudonym of Shennong, the Holy Farmer. Chinese medicinal plants are today playing an outstanding role within the framework of official health services. China is endowed with an abundant resource of medicinal plants, more than five thousand plants have been identified as medicinal plants. The 2005 edition of The Chinese Pharmacopoeia recorded about 700 items of Chinese drugs originating from medicinal plants.

In Chinese traditional medicine, licorice is one of herbs that tonify vital energy ("Qi") is used for deficient "Qi" syndrome. It is employed the most frequently as a component of various prescriptions of Chinese medicine. Licorice root is not only used in Chinese traditional medicine and pharmaceutics, but also used in cosmetic, food, ink and cigarette industries. In 2001, we collected some information and published a review paper about basic research and application, and introduce to the ethnopharmacology, chemistry, pharmacological actions and clinical application of licorice root[1]. Based on above review, we finished this review paper.

Plant Origin

Radix Glycyrrhizae is the rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata*

Bat. or *Glycyrrhiza glabra* L. They are widely distributed in the northeast and northwest of China. The original plants of licorice are also distributed in the dry regions on the northern hemisphere from Spain in the West to Mongolia in the East. Russian licorice is originating from *Glycyrrhiza glabra* var. *glandulifuera*, Siberia licorice and Mongonia licorice mainly from *Glycyrrhiza ulalensis* Fisch.. Iranian licorice from *Glycyrrhiza glabra* var. *b-violacea*, Iraqui licorice and Spaish licorice from *Glycyrrhiza glabra* var. *typica*.

Ethnopharmacological actions

Licorice root (*Radix Glycyrrhizae*), is well-known herb in the East and West, and has been used since ancient times as a useful drug in traditional and folk medicine. It constsis of the dried rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L (*Leguminosae*). *Radix Glycyrrhizae* was earliestly recorded in Shengnong Materia Medica (*Shennong Bencao Jing*).

Fig 1. *Glycyrrhiza uralensis* Fisch.

Fig 2. *Glycyrrhiza glabra*

Fig 3. *Radix Glycyrrhizae*

It is a sweet and mild drug. It enters the heart, lung, spleen and stomach meridians. The functions are to tonify the spleen and replenish vital energy, to moderate the lungs and stop coughs, to relax spasms and stop pain, to moderate the action of herbs and to reduce fire and release toxins. It is used to invigorate the functions of the heart and spleen for the treatment of sympotoms due to deficiency of vital energy of these viscera; as a spasmolytic and antitussive for peptic ulcers and cough; as an anti-phlogistic for sore throat, boils and carbuncles; and as an antitoxicant to drug poisoning.[2,3]

Chemical Constituents

The pharmacological activities of licorice are mainly, if not all, represented by the main triterpene saponins, glycyrrhizin, glycyrrhizic acid, 18-β-glycyrrhetic acid, glycyrrhizinic acid and its aglycone, glycyrrhetinic acid in the root of *Glycyrrhiza uralensis*. Addition to glycyrrhizic acid and glycyrrhetic acid, other main chemical constituents are galbrolide, 18-α-hydroxy-glycyrrhetic acid, 23-hydroxy- glycyrrhetic acid, 24-hydroxyglabrolide, uralsaponin A and B, liquiritigenin, isoliquiritigenin, isoliquiritin neoliquitin, neoliquiritin, licoricidin, licoricone, formononetin, licuraside, uralenolide, licroricesaponin A3, B2, C2, D3, E2, F3, G2, H2, J2,and K2, 5-O-methyllicoricidin, liquiritigenin-4'-apyrosyl(1-2)glucoside, liquiritigenin- 7,4'-digluco-side, uralwnol, neouralenol, uralenin, uralenol-3-methylether, uralene, uralenneoside, glycycoumarin, glycyrol, isoglycyrol, neoglycyrol, 5,6,7,8-tetrahydro-4-methylquinoline, 5,6,7,8-tetra-hydro-2,4-dimethylquinoline.Besides the tripene compounds, a number of flavone, isoflavone, chalcone and related compunds were isolated from licorice plant. About 30 non-glycosidic flavonoid compounds have been isolated from licorice. These compounds involve flavones, flavanones chalcones, isoflavones, isoflavanones, isoflavn, isoflavene, pterocarpan, coumestan and 3-arylcoumarin.

RP-HPLC method was developed to analyze the chromatographic profiles of natural components in all combinations. Areas (corrected by weighting amounts) of chromatographic peaks were collected as chemical data. The pharmacological and chemical data were correlated by chemical statistical methods, and then the therapeutic material basis (thirteen chemical constituents with sedative and hypnotic effects among forty-eight chromatographic peaks) of Suanzaoren decoction were elucidated. Spinosin from *Semen Ziziphi Spinosae*, ferulic acid from Rhizoma Chuanxiong, mangiferin from *Rhizoma Anemarrhenae* and glycyrrhizic acid from *Radix Glycyrrhizae* were selected as quality control indices. This paper

provided a new methodology for elucidating the therapeutic material basis and quality control indices for TCM. It is instructive for modernization of Chinese herbs and its compound preparations.[4]

A simple capillary-zone electrophoresis (CZE) method for the analysis of plant specimens, *Glycyrrhiza glabra* L., *G. uralensis* Fisch. and *G. inflata* Bat. (*Leguminosae*) as well as commercial licorices from Europe and China was developed. Contents of glycyrrhizin (GL), glycyrrhetic acid (GA), glabridin (GLAB), liquiritin (LQ) and licochalcone A (LC_A) in ethanolic extracts were investigated. Optimum separation was achieved with sodium tetraborate buffer (pH 9.22; 70 mM); voltage, 25 kV. Recovery rate for GL was found to be 101.90±2.54%. Adequate correlation was observed between GL contents measured by CZE and HPLC (r=0.977). Advantages over conventional HPLC analysis of Glycyrrhiza species are short analysis time (<15 min), simple running buffer preparation and the none-use of organic solvents. Using the present CZE method, it was demonstrated that (1) G. glabra was distinguished from *G. uralensis* especially by phenolic compounds GLAB (*G. glabra*: 0.19±0.11%; n=53) and LQ (*G. uralensis*, 1.34±0.34%, n=10); (2) on average, GL contents were higher in Chinese commercial licorices; (3) relatively high LC_A contents were especially detected in a Chinese commercial licorice (origin estimated as *G. inflata*); (4) *Glycyrrhiza* species were also distinguished by applying PCA on the basis of CZE peak area data of GL, GLAB, GA, LQ and LC_A; and (5) liquiritin apioside was found in all samples.[5]

The HPLC fingerprint including glycyrrhizin (GL) of the cultivated roots was similar to that of medicinal Glycyrrhiza, but different from that of non-medicinal Xinjiang-Gancao (Shinkyo Kanzo in Japanese). Similarity between the cultivated roots and two medicinal Glycyrrhiza cultivated in eastern Nei-Meng-Gu was confirmed quantitatively by hierarchical cluster analysis on the basis of HPLC-7-peak-area data. Moreover, the 4-year-old adventitious roots conformed to the five standards described in the Japanese Pharmacopoeia XIV (JP XIV). The 4-year-old adventitious roots had similar pharmaceutical properties to those of medicinal Dongbei Glycyrrhiza (Tohoku Kanzo in Japanese) as determined by examining IgE-mediated triphasic skin reaction in mice and pharmacokinetic profile of glycyrrhetic acid, an anti-allergic metabolite of GL. The present pharmaceutical study suggests that the 4-year-old adventitious roots of G. uralensis cultivated in eastern Nei-Meng-Gu of China are comparable to medicinal Glycyrrhiza conforming to the JP XIV, and may be a potential medicinal source to compensate for the insufficiency of wild Glycyrrhiza plants caused by collection restriction in China.[6]

Pharmacological Activities

Licorice root possesses wide broad pharmacological actions. According to literature reports, its pharmacological activities include the following aspects: effects on central nerve system; cardiovascular system and endronic system; liver, renal and pancreas functions, anti-ulcer action, anticancer action, anti-allergic and anti-iflammatory effects, anti-virus and antibacteria activities, and effect on immune function and so on.

Effect on central nerve system

In neuropharmacological screening test found that a licorice mixture including three Chinese herbs lengthened the hexobarbital sleeping time, showed a marked prolonation of time to death in pentylenetetrazole-induced convulsoions, and locomotor activity was inhibited by the mixture. The results suggested that licorice had a sedative effect on the nervous system[7,8]. This herb had anxiolytic and psychomotor effect, It found that the drug decreased the accompanying sympathetic systems and improved psychomotor performance[9].

Glycyrrhetinic acid and derivatives of glycyrrhetinic acid were examined the antinoceptive activity on writhing and vascular permeability induced by acetic acid and antitype-IV allergic effects in mice[1-,11]. A mixture including licorice root showed marked effects on insomnia, infantile convulsions and emotional irritability. It showed an inhibition of sodium, calcium and potassium currents in snail neurons. It also showed an inhibitory effect on pentyenetetrazole-induced bursting activity and local anesthetic action on form nerve fibers. These results suggest that the drug produces inhibition on hyperexcitability or the neuronal membrane and the main cause of the sedative effect[8]. In writhing test induced by 0.7% of acetate acid in mice, glycyrrhitinic acid exhibited the antionciceptive activity[12]. FM-100, an extract of licorice roots, had

been shown to have significant analgesic and anticonvulsant actions.[13]

Glycyrrhizic acid increased Na+, K+-ATPase and Mg++-ATPase and LDH activities, and the outcome of CNS function in dog reperfusion in canine cerebral tissue.[14]

Ginseng Radix, Atractylodis Macrocephalae Rhizoma, Poria, Glycyrrhizae Radix, Angelicae Gigantis Radix, Ligusticum Rhizoma, Rehmanniae Radix, Paeoniae Radix, Acori Graminei Rhizoma, and *Polygalae Radix* have been widely used as herbal medicine against ischemia. In order to test the neuroprotective effect of a novel prescription, Yun et al study examined the effects of Palmul-Chongmyeong-Tang (PMCMT) consisting of these 10 herbs on learning and memory in the Morris water maze task and the central cholinergic system of rats with cerebral ischemia-induced neuronal and cognitive impairments. After middle cerebral artery occlusion (MCAO) for 2 h, rats were administered with saline or PMCMT (200 $mg.kg^{-1}$, p.o.) daily for 2 weeks, followed by their training to the tasks. In the water maze test, the animals were trained to find a platform in a fixed position during 6 d and then received a 60 s probe trial on the 7th day following removal of the platform from the pool. Rats with ischemic insults showed impaired learning and memory of the tasks and treatment with PMCMT produced a significant improvement in escape latency to find the platform in the Morris water maze. Consistent with behavioral data, treatment with PMCMT also reduced the loss of cholinergic immunoreactivity in the hippocampus induced by cerebral ischemia. These results demonstrated that PMCMT has a protective effect against ischemia-induced neuronal and cognitive impairments. The present study suggested that PMCMT might be useful in the treatment of vascular dementia.[15]

Misellaneous actions

Subcutaneous injection of glycyrrhitinic cholate at the dose of 1 $mg.kg^{-1}$ suppressed 80% of the incidence of cough elicited by ammonia water aspiration in guines pigs. significant hypolipidemic activity was obtained in experimental hypertipidemic rabbits after im injection of glycyrrhizic acid at the doese of 10 $mg.kg^{-1}$ once daly for 5 days. Glycyrrhitic acid and its derivative 3-oxy-18-glycyrrhetinic aicd (18-GT) 80 $mg.kg^{-1}$, once daily, inhibited the growth tansplanted oberling-guerin myeloma in rats [13].

Anticarcinogen and antituomr actions

Glycyrrhetinic acid on the metabolic cooperation between 6-thioguanine-resistant (6TGR) and 6-thioguanine-sistigated (6TGS) Chinese hamster V79 H3 cells was studied. Because Glycyrrhetinic acid has been to inhibit tumor formation in mouse skin induced by carcinogens in the presence of tumor promoters, it was expected that glycyrrhetinic acid might rector the metabolic cooperation inhibited by tumor promoters[16]. Glycyrrhetinic acid inhibited tumor promoting stage in two-stage carcinogenesis. Some related compounds were found to be more potent activity than glycyrrhtinic acid in inhibiting tumor promoter-induced phenominon in vitro[17]. Glycyrrhizin inhibited 12-O-tetradecanony-phorbol-13-acetate (TPA) -induced inflammation and markedly suppressed the promoting effect of TPA on skin tumor formation in mice initiated with 7,12-dimethylben anthracene[18]. When BALB/c mice immunized with EL-4 tumor cells were treated with a 20 $mg.kg^{-1}$ i. p. dose of glycyrrhizin 1, 3, 5, 7 and 9 days after immunization, no suppressor cell activity was detected in their spleens. In irraadited these mice injected with normal mice splenic mononuclear cells the growth of inoculated solid tumors increased significantly[19]. 18-GT also has anti-leukemic activity in mice. This is probably due to an adrenocoticominetic action. glycyrrhizic acid and liquiritin were able to elecit morphological changes on tumor cells in ascetic carcinoma of the rat liver and Ehrtich ascites carcinoma in mice. Glycyrrhizic acid was also found to inhibit the subcutaneously transplanted Jitan sarcoma, prevent the development of polyoxybenzidine-induced liver carcinoma in mice as well as the liver carcinoma induced by 0.05% methylaminoazobenzene.[20]

Sodium glycyrrhetinate showed antitumor activity in animal transplanted tumors. The inhibition rate of this compound at dose of 10 $mg.kg^{-1}$ per day for 10 days were 47-53% for S180 and 40-45% for hepatoma in mice. Whereas, EAC was less sensitive. The inhibition rate of mitotic indices of hepatoma cells were moderately increased after ip administration of this compound with 37% for 1 h and 43% after 24 h. The mitochondrince of hepatoma cells showed swelling, dissolution and disapperance of cristae, vacuolations were found inside the cytoplasm of tumor cells. The mitrovilli of cell membrane were diminished. The antitumor mechanism of this compound seemed to be in close

relation to these morphlogical findings.[20]

The popularity of traditional herbal medicine (THM) being used as complementary medicines or alternative medicines is increasing. On the other hand, the development of multidrug resistance (MDR) remains a major hurdle to successful cancer chemotherapy. Some THMs capable of reversing MDR may contribute to the improvement of clinical outcomes in cancer chemotherapy. Herein, 19 kinds of herb were chosen from the ingredients of major THMs, and their effects on the sensitivity to anticancer drugs of tumor cells were investigated using the human cervical carcinoma HeLa cells. Focusing on the major mechanism for MDR, i.e., MDR1/P-glycoprotein, the effects of herbal extracts on its transport function were also examined using a MDR1 substrate Rhodamine123. Glycyrrhizae Radix, Rhei Rhizoma, Scutellariae Radix, Poria, Zizyphi Fructus, Zingiberis Rhizoma (dry), Coptidis Rhizoma, Ephedrae Herba and Asiasari Radix significantly enhanced the sensitivity to a MDR1 substrate paclitaxel, whereas none of the herbal extracts used had any effect on the sensitivity to 5-fluorouracil, which is not a substrate for MDR1. Rhodamine123 uptake was significantly increased by Rhei Rhizoma, Poria or Ephedrae Herba among nine herbal extracts sensitized to paclitaxel. This suggests that the increase in paclitaxel sensitivity by Glycyrrhizae Radix, Rhei Rhizoma, Poria or Ephedrae Herba was caused, in part, by the inhibition of MDR1 function, and the change in paclitaxel sensitivity by the other herbal extracts was not always dependent on this. Collectively, these findings indicate that the combination of anticancer drugs with some herbal extracts contributes to the enhancement of clinical outcomes in cancer chemotherapy.[21]

Niwa et al have previously reported on the inhibitory effect of Glycyrrhizae radix (Gl radix) on mouse endometrial carcinogenesis. Their present study was performed to clarify the effects of Gl radix and glycyrrhizin (GL), the main part of Gl radix, on estradiol (E2)-related endometrial carcinogenesis. Both Gl radix and GL exerted a significant decrease in the COX-2, IL-1 α and TNF-α mRNA expressions. GL generated a significant decrease in the incidence of endometrial adenocarcinoma. Accordingly, the preventive effects of Gl radix may be attributable to GL, thus being related with the suppression of COX-2, IL-1α and TNF-α. Gl radix and GL could therefore be a promising formula for the chemoprevention of human endometrial cancer.[22]

Kim et al study showed that liquiritigenin (LQ), an aglycone of liquiritin in G. radix, exerts cytoprotective effects against heavy metal-induced toxicity in vitro. This study investigated in vivo protective effects of LQ against acute liver injuries induced by acetaminophen (APAP) or APAP plus buthionine sulfoximine (BSO). Liver injuries were assessed by blood biochemistry and histopathology in rats administered with LQ purified from the acid hydrolyates of liquiritin singly (p.o. or i.v., 2-4 days) or in combination with dimethyl-4,4'-dimethoxy-5,6,5',6'-dimethylene dioxybiphenyl-2,2'-dicarboxylate (DDB), a synthetic derivative of Schisandrin C in *Fructus shizandrae,* and exposed to APAP or APAP and BSO. LQ treatments (oral) effectively decreased liver injuries induced by a single dose of APAP, as evidenced by decreases in hepatic necrosis and inflammation as well as plasma alanine aminotransferase and lactate dehydrogenase activities. LQ, when intravenously applied, enhanced hepatoprotective effect with a greater potency. APAP and BSO led to severe liver injuries, resulting in lethality. LQ pretreatments significantly reduced the potentiated liver necrosis, decreasing mortality. In spite of the improvement in blood biochemistry, DDB failed to protect the liver from injuries induced by APAP or APAP + BSO. Combined treatments of rats with LQ and DDB showed some additive protective effect. The present study demonstrates that LQ efficaciously protects the liver from acute injuries induced by APAP or from APAP-induced severe injuries during GSH deficiency, indicating that LQ is one of the principal cytoprotective components comprised in G. radix.[23]

The effects of herbal medicines that constitute Gam-du-tang and Gung-gui-tang on cytokine-induced cytotoxicity and thyroid major histocompatibility complex (MHC) class II antigen expression in FRTL rat thyrocytes were investigated. No effect on cell growth was found with interferon IFN-γ. However, tumor necrosis factor TNF-α was cytotoxic, and this was increased by preincubation with IFN-gamma. Ethanol extract of *Glycyrrhizae Radix*, black beans, Angelicae Radix, and Cnidii Rhizoma (0.3-15 mg/ml) in both regimens significantly inhibited IFN-γ and TNF-α-mediated cytotoxicity of rat thyroid cells ($p<0.05$, $p<0.01$). In addition, IFN-γ (1-100 $U.ml^{-1}$) treatment induced class II antigen expression in up to

60% of FRTL cells, as detected by a murine monoclonal antibody to rat MHC class II antigen (FITC-OX6). Aberrant thyroid cell MHC class II antigen expression induced by IFN-γ is suppressed by the extract of herbal medicines. These results indicate that herbal medicines inhibit cytokine-induced thyroid cell destruction, therefore, may have therapeutic potential in the treatment of autoimmune thyroid disease.[24]

Glycyrrhizae radix has been popularly used as one of the oldest and most frequently employed botanicals in herbal medicine in Asian countries, and currently occupies an important place in food products. Cadmium (Cd) induces both apoptotic and non-apoptotic cell death, in which alterations in cellular sulfhydryls participate. In the present study, we determined the effects of G. radix extract (GRE) and its representative active components on cell death induced by Cd and explored the mechanistic basis of cytoprotective effects of *G. radix*. Incubation of H4IIE cells with GRE inhibited cell death induced by 10 microM Cd. Also, GRE effectively blocked Cd (1 microM)-induced cell death potentiated by buthionine sulfoximine (BSO) without restoration of cellular GSH. GRE prevented both apoptotic and non-apoptotic cell injury induced by Cd (10 μMol) or Cd (0.3-1μMol) + BSO. Inhibition of Cd-induced cell injury by pretreatment of cells with GRE suggested that the cytoprotective effect result from alterations in the levels of the protein(s) responsible for cell viability. GRE inhibited mitochondrial Bad translocation by Cd or CD+BSO, and caused restoration of mitochondrial Bcl(xL) and cytochrome c levels. Cd-induced poly(ADP-ribose) polymerase cleavage in control cells or in cells deprived of sulfhydryls was prevented by GRE treatment. Among the major components present in GRE, liquiritigenin, but not liquiritin, isoliquiritigenin or glycyrrhizin, exerted cytoprotective effect. These results demonstrated that GRE blocked Cd-induced cell death by inhibiting the apoptotic processes involving translocation of Bad into mitochondria, decreases in mitochondrial Bcl(xL) and cytochrome c, and poly(ADP-ribose)polymerase cleavage.[25]

To develop safe and effective anti-RSV new medicine from Radix Glycyrrhizae. The anti-RSV effect of Radix Glycyrrhizae in Hela cell culture was observed by means of the inhibition of cytopathic effect. In Hela cell culture, Radix Glycyrrhizae was found to be a inhibitor of RSV in a concentration-dependent manner. The median toxic concentration (TC_{50}) of Radix Glycyrrhizae was 3.43 g/L, the median effective concentration (EC_{50}) of Radix glycyrrhizae against replication of the Long strain of RSV in Hela cells were 0.2535 g/L, the selectivity index (TI = TC50/EC50) is 13.53. In time of addition experiment, Radix Glycyrrhizae inhibited the effect of RSV in Hela cells when it was added at 0 h, 2 h, 4 h, 6 h, 8 h after virus infection. In Hela cell culture, *Radix Glycyrrhizae* was found to be a inhibitor of RSV, there are many ways in the mechanisms.[26]

Anti-inflammatory effect

Inflammation was induced by subcutanous injection of carrageenan into the palm of the hind paw of rats. The extract of radix Glycyrrhezae equivalent to 100, 200 or 500 $mg.kg^{-1}$ of glycyrrhizin, or the same doses of glycyrrhizin and glycyrrhetinic acid were used to treat the ucler. It was found that carraheen induced edema was not affeted by 100 $mg.kg^{-1}$, attenuated by 200 $mg.kg^{-1}$, and potentated by 500 $mg.kg^{-1}$ of these the tested drug.[27] Glycyrrhhizin inhibited to some extent prostaglandin E2 biosynthesis by the activated rat peritoneal macrophage, whereas in the cell-free experiment glycyrrhizin and glycyrrhetinic acid showed little effect on the inhibition of cyclooxygenase. Deoxoglycyrrhetol and its devatives have been demonstrated to inhibit significantly the activities of lipoxygenase and cyclooxygenase.[28]

The anti-inflammatory action of the resembles that butazone or hydrocortisone. The anti-inflammatory principles were found to be glycyrrhizic acid and glycyrrhitic acid. Cotton pledgel-induced granulema, formaldehyde-induced rat paw swelling and subcutaneous granulomalcus inflammation in albino rats were inhibited by glycyrrhitic acid, its anti-inflammatory potency was about one-tenth that of cortixsone or hydrocortisone. In agari-induced paw swelling of albino rats, if the effeicacy of hydrocortisone was rated as one then, that of glycyrrhizic acid and glycyrrhitic acid would be 0.14 and 0.13, respectively[13]. Glycyrrhizic acid 25 or 50 mg.kg-1 given by iv injection to mice inhibited passive cultaneous anaphytazoxis response. Glycyrrhizic acid antagonized the contractionof isolated rabbit illum and guinea pig trachea induced by histamine acetylcholine or slow reacting substance of anaphytaxis in a concentration dependent fashion[29]. The anti-inflammatory effects of glycyrrhetinic acid and its derivatives on

TPA-induced mouse ear edema were studied. Glycyrrhetinic acid derivatives examined strongly inhibited ear edema.[30] The mechanism of the anti-inflammatory effect was to a certain degree related to the adrenal cortex, suppression of vascular permeability and antagonism to inflammation as well[20]. Sodium glycyrrhinic acid (SGA) inhibited significantly paw edema of rats with ajuvant arthritis (AA), reduced proliferation of synovial cells and pannus formation, and eleminated the destruction of articular cartilage in inflammed joints of AA rat. T-lymphocyte ratio was increased in normal mice and decreased in rats with ajuvant arthris by SGA. The result showed that SGA possesses two-way regulating activity for immune functions.[31]

CML-1 is a purified extract from a mixture of 13 oriental herbs (*Achyranthis Radix, Angelicae Gigantis Radix, Cinnamomi Cortex Spissus, Eucommiae Cortex, Glycyrrhizae Radix, Hoelen, Lycii Fructus, Paeoniae Radix, Rehmanniae Radix Preparata and Atractylodis Rhizoma, Zingiberis Rhizoma, Zizyphi Semen, Acori Graminei Rhizoma*) that have been widely used for the treatment of inflammatory diseases in Asia. The previous study has been shown to have the anti-inflammatory activity of CML-1 in vivo and the upregulation of adhesion molecules in response to numerous inducing factors is associated with inflammation, Mo et al study examined the effect of CML-1 on the expression of adhesion molecules induced by TNF-alpha in cultured human umbilical vein endothelial cells (HUVECs). Preincubation of HUVECs for 20h with CML-1 (1-100μ.ml^{-1}) dose-dependently inhibited TNF-α (10 ng.ml^{-1})-induced adhesion of THP-1 monocytic cells, as well as mRNA and protein expression of E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). CML-1 was also shown to inhibit NK-kB activation induced by TNF-α. Furthermore, CML-1 inhibited TNF-α-induced IkB kinase activation, subsequent degradation of IkBα, and nuclear translocation of NK-kB. Evidence presented in this report demonstrated that CML-1 inhibited the adhesive capacity of HUVEC and the TNF-α-mediated induction of E-selectin, ICAM-1 and VCAM-1 in HUVEC by inhibiting the IkB/NF-kB signaling pathway at the level of IkB kinase, which may explain the ability of CML-1 to suppress inflammation and modulate the immune response. [32]

CML-1 is a purified extract from a mixture of 13 Oriental herbs (*Achyranthis Radix, Angelicae Gigantis Radix, Cinnamomi Cortex Spissus, Eucommiae Cortex, Glycyrrhizae Radix, Hoelen, Lycii Fructus, Paeoniae Radix, Rehmanniae Radix Preparata and Atractylodis Rhizoma, Zingiberis Rhizoma, Zizyphi Semen, Acori Graminei Rhizoma*) that have been widely used for the treatment of inflammatory diseases in Asia. The aim of this study was to investigate the anti-inflammatory and analgesic potential of CML-1. The animals used in this study were administered either vehicle or CML-1 (30, 100, 300 and 600 mg.kg^{-1}) orally. The vascular permeability induced by acetic acid was significantly reduced by CML-1 in all doses. The swelling of the rat's hind paw induced by carrageenan was significantly inhibited by CML-1 in doses of 100, 300 and 600 mg·kg^{-1}. In the case of rheumatoid arthritis induced by complete Freund's adjuvant in rats, the treatment with CML-1 at a dose level of 300 mg·kg^{-1} inhibited edema. CML-1 at a dose level of 600 mg·kg^{-1} inhibited acetic acid-induced writhing syndrome, however it did not have any anti-nociceptive action in the Randall-Selitto assay or the hot plate test. Our findings suggest that CML-1 has a potent anti-inflammatory activity.[33]

Anti-ulcer effect

In cases of acetic acid-induced chronic gastric ulcer in rats, oral administration of glycyrrhizic acid afforded a cure rate of 97.7%, glycyrrhizic acid not only decreased gastric acidity but also promoted healing of ulcers. glycyrrhrtic aicd given ig at the dose of 300 mg·kg^{-1} to rats did not affect adenyl cyclase activity of the gastric mucous but inhibited phosphodiesterase activity, thereby, increasing cAMP level of the mucous of the pylorus and cardisa, and suppressng gastric acid secretion. The pylorus of rats was completely inhibited by ip injection of total flavones of licorice (FM-100) at dose of 100 mg·kg^{-1}, the total flavone minus glycyrrhizinic acid infected ip injection at the dose of 100 mg.kg^{-1} to rats with ligated pylorus completely inhibited ulcer formation. Gastric acid serection induced by ig administration of actylcholine or im injection of histamine was also significantly inhibited FM-100 at the concentration of 200μg.ml^{-1} exerted spasmolytic action on the isolated intestinal tract of the guinea pig. Inhibition of the concentration of isolated intestinal tract of the animals was achieved with FM-100 and isoquiritigenin at the concentration of 10 μg.ml^{-1}, by

agents were also found to relieve intestinal spasms elicited by acetycholine, barium chloride, and histamine. But, no inhibitory action on the smooth muscles was detected for glycyrrhizic acid and glycyrrhetic acid. To obtain a better therapeutic effect and reduced side effect, glycyrrhizic acid may be removed from the Kan-Tsao preparations or use the isolated flavonids clinically.[13]

Glyccyrrhiza root extract showed significant therapeutic effect against chronic gastric ulcer induced by acetic acid in rats treated at doses of 200-400 $mg.kg^{-1}$. But pure glycyrrhizin showed no effect on the ulcer.[34, 35]

Glycyrrhizin or glycyrrhetinic acid, which is the main pharmacological activite principle of licorice, is a lead compound having therapeutical applicabilities. The anti-stress ulcerogenic activity of deoxoglycy-rrhhetol, a reducted compound of glycyrrhetinic acid, was studied by the experiment of restraint water immersion using mice and rats. This compound was administered orally to the animals. It was effective to inhibit stress-induced ulcer in mice at 200 $mg.kg^{-1}$. It was noted that the molecular modified compounds brought a remarkable enhancement of therapeutic effect.[28]

The origins of gastric hyperacidity, gastric and duodenal ulcer appearance includes genetic predisposition, incorrect diet and unbalanced lifestyle, e.g. increased stress level, cigarette smoking. Herbal drugs have been proved to be very effective in treatment of hyperacidity, gastric and duodenal ulcer. They can be applied as drugs supplementing or enhancing the activity of synthetic medicines. Moreover, herbal drugs have been successfully applied inprophylactic of hyperacidity, gastric and duodenal ulcer. Herbal therapeutic preparations are administered as infusions from individual herbs, from mixtures of herbs, tinctures, herbal preparations. The most often used herbs include mucus: *Lini semen, Psylli semen, Foenugraeci semen, Althaeae radix/folium, Sinapis albae semen; antiphlogistic volatile-oils: Chamomillae anthodium, Millefolii herba, moreover Glycyrrhizae radix, Aloe gel*.[36]

Anti-allergic action

Glycyrrhizin showed an anti-allergic activity. It inhibited the passive cultaneous anaphylaxis response in rats. It inhibited the contraction of rabbit ileum and guinea pig trached induced by histamine, acetylcholine or slow-reacting substances of anaphylaxis[10, 23]. Glycyrrhizin has clinically been employed as an anti-allergic agent. Thus it can be as a lead compound, and modified its molecule to study the anti-allergic actions of the modified compunds on Type I, II and IV allergy in experimental animals. The effect of deoxoglycyrrhetol and its devatives against the type IV allergy in mice was studied in the passive cutaneous anaphyaxis test. The preventing effective dose of 25-200 $mg.kg^{-1}$.[15]

Anti-virus and antibiotica activities

Glycyrrhizin achieved a dose-dependent inhibition of the replication of human immunomoduficiency virus type 1 (HIV-1) in mot-4 cells within the concentration range of 0.075 to 0.6 mmol. Within this concentration range, glycyrrhizin also effected a dose-dependent reduction in the protein kinase D activity of Mot-4 cells. Glycyrtrhizin sulfate completely inhibited HIV-induced plaque formation in mot-4 cells at a concentration of 1 $mg.ml^{-1}$, the 50% inhibitory dose was 0.055 $mg.ml^{-1}$. Glycyrrhizin was foud to be an effectient inhibitor for reverse transcriptase. The effect of glycyrrhizin sulfate was 4 times stronger than that of glycyrrhizin in molar terms[37]. When human embryonic fibroblast (HEF) cells were treated with glycyrrhizin after inoculation of virus, the average 50% inhibitory dose for fire varicella-zoster virus (VZV) stains was 0.71 mMol, and the selectivity index was 30. Glycyrrhizin was also effectve against VZV replication when HEF cells were treated 24 h before the inoculation[38].

The increase of glycyrrhizin (GL) and beta-glucuronidase paralleled the growth of the Eubacterium stain in pure culture. The increase in GL beta-glucuronidase activity in the presence of GL was observed during the cultivation of human intestinal flora in a general anaerobic medium. During mixed cultivation of the Eubacterium stain with Streptococcus faecalis, which does not increased by GL, but not by glycyrrhetic acid. It is suggested that GL stimulates the growth of stain GLH even in the mixed culture[39]. The effect of the glycosaminoglycan (GAG) layer on the adherence of Escherichia coli to the bladder urothelium of rats has been studied. The study was performed by destroying , the GAG layer and the changes were observed using the electron microscope. Bacterial adherence to the badder with a destroyed GAG layer was much higher than to the normal bladder. Following the destruction of the GAG layer, the instillation of sodium pentosanpolysulphate significantly reduced the adhesion of bacteria. Prophylactic intramuscular administration of

carben-oxolone increased the speed of regeneration of the destroyed GAG layer[40]. 18-β-glycyrrhzic acid had antibiotical activity, The MIC were 1.6×10^{-4}, 6.3×10^{-4}, 6.3×10^{-4}, 1.6×10^{-4} and 4×10^{-5} mmol.L^{-1} to aurococcus, α-streptococcus, β-streptococcus and acidici lactici bactericem, respectiviely[41].

By using lambda-lysogen as a model, the inhibitory effects of anti-severe acute respiratory syndrome (SARS) traditional Chinese medicines (TCMs) prescription I on the UV irradiation were investigated in this present study. It was found that the prescription I possessed obvious inhibitory effects on the UV induction of lambda-lysogen, the inhibitory rate reaching 83.87%. Among five medicinal herbs prescribed in that formula, Herba Patriniae, Radix Astragali and Radix Glycyrrhizae played important roles. When these three herbs were eliminated from the recipe separately, the inhibitory effects were prominently decreased. If only one of these five medicinal herbs was added into the medium of lambda-lysogen, the inhibitory rates ranged from 27.0% approximately 45.0%. By electron spin resonance (ESR) detection, we found that the prescription I, Herba Patriniae and other main herbs in that recipe, could quench effectively the free radicals generated in the process of lambda-lysogenic cells by UV. These results provide a novel idea for further studying the pharmacology of TCM and exploring the mechanism of SARS virus infection.[42]

Effect on cardiovascular system

Carbenoxolone (43, 3 mg.kg^{-1}) and oleanoc acid sodium hydrogen succinate (66, 6 mg.kg^{-1}) were orally given to rats twice daily for 4 weeks. The systolic blood pressure was elevated already after the first week of treatment. The hypertension was accompanied by bradycardia, which increased with the time of treatment. In the blood an increase in the creatinine level, a decrease in the urea level, and a sight elevation in sodium concentration during the treatment period remained unchanged. Although the principlal aldosterone-like effects of carbenoxolone were attributed to the oxygen presence in position 11 of the glycyrrhetinic acid ring, the absence of an oxygen at that position on oleanoic acid sodium hydrogen succnate did not cause the loss of the adverse circulatory effect.[43]

The hypolipidemic effects of Glycyrrhiza root and isolated glycyrram, glycyrrhizic acid monoammonium salt and glycyrrhethinate sodium, were tested in rats with hyperlipemia induced by ip tween-80 or hypervitaminosis D2. All agents had stronger hypolipidemic effects than polysaponin[44]. In rabbits maintained on an atherogenic diet, blood activity of superoxide dismutase did not change during early stages of hyperholesterolemia development, but then increased as a result of an adaptive process directed at increased free radical activity, but 3-amino-3-deoxy-glycyrrhetic acid markedly stimulated it.[45]

Total flavones of licorice at doses of 25-50 mg.kg^{-1} was effective against oubain-induced tachyarrhythmias in genuia pigs and at doses of 50-100 mg.kg^{-1} was effective against aconitine- or chloroform-induced arrhythmias in mice.[46]

Glycyrrhiza decoction 100g.L^{-1} and glycyrrhinic acid 2.5 mmol.L^{-1} can reduce the transmural potential of recerted mouse *in vivo* test[47]. SGA 0.1, 0.2 and 0.4 mmol.L^{-1} reduced the release of lactate dehydrogenase (LDH) from myocardial cells injured by deprivation of oxygen and glucose at 6 or 9 h. The chloropromazine-demaged and xathine-xanthin-codase injured myocardial cells could be protected by treating with 1, 0.2 and 0.4 mmol.L^{-1} at 6 or 9 h.[34] Glycyrrhiza saponins had significant protective effect on the reduction of Na^+, K^+-ATPase activity induced by oxygen free radicals, the activity increased by 27.9% at 0.2 mg.L^{-1} and 46.6% at 0.8 mg.L^{-1}.[48]

Effect on endocrine system

Glycyrrhizin and paeoniflorin exhibited similar steroid-binding behaviors in rabbits. They bound minimally to estrogen and androgen receptors, but not to the progesterone receptor in uterine cytysol and exhibited a moderate binding activity to glucocorticoid receptors in liver cytosol, and exhibited weak binding activity to both cortico-steroid-binding globulin and sex-hormone-binding globulin.[39]

Oral administration of baicalin and licorice dramatically reduced sorbitol levels in red blood cells without affecting blood glucose levels. The sorbitol level was restored to its original levels one week after discontinuing the treatment. It was deminstrated that the effectiveness of baicalin and licorice in reducing sorbitol levels in red blood cells of diabetic rats. The mechanism is presumably through inhibition of aldose reductase.[50]

Carbenoxolone significantly decreased the glucose uptake and the oncorporation of glucose into triglycerides and CO_2 in rats. The effect produced by insulin on these metabolic pathways was reduced when adipose tissue was incubated with insulin in the presence of carbenoxolone.[51] Nasal absorption

of lnsulin in rats was enhanced by addition of sodium glycyrrhetinate, dipotassium glycyrrhizinate and carbenoxolone (glycyrrhetinic acid hydrogen succinate) disodium salt. The latter agent was effective. It suggested that the latter agent is an useful promoter which does not irritate the nasal mucosal membrane or degrade insulin.[52]

Aluminum glycyrrhizinate inhibited PEGα and PEG2 α formation by mouse lung and kidney in vivo and in vitro. It suggests that glycyrrhizin has an inhibitory action on PG-cyclo-oxyenase.[53] Glycyrrhizin inhibited zymosan-stimulated PEG2 production by rat macophages and decreased cAMP levels in macrophages stimulated glycyrrhizin may be mediated through effects on PEG2 formation and effects on the macrophage response to various factors. Glycyrrhizin also slightly enhanced phagecytosis, but had no effect on lymphocyte proliferation.[54]

Oxidative stress plays a key role in the pathophysiologic process of acute and chronic renal diseases. Intracellular component such as lipids, proteins and nucleic acids are easily and rapidly oxidized by excessive reactive oxygen species (ROS), and such reactions lead to increased levels of lipid peroxide. Rhyu et al study examined the antioxidant effects of Wen-Pi-Tang and its component crude drugs on 2,2'-azobis(2-amidino- propane) dihydrochloride (AAPH)- or 2,2'-azobis(2,4-dimethyl-valeronitrile) (AMVN)-induced ROS generation and lipid peroxidation of linoleic acid. As a result, Wen-Pi-Tang significantly decreased AAPH or AMVN-induced ROS in renal mitochondrial particles. For the components in Wen-Pi-Tang's prescription, Rhei Rhizoma and Glycyrrhizae Radix extracts strongly inhibited peroxide levels, but Ginseng Radix, Aconiti Tuber and Zingiberis Rhizoma extracts were comparably low. Rhei Rhizoma extract showed the strongest inhibitory activity on oxidative injury, and two of its tannin compounds, (-)-epicatechin 3-O-gallate and procyanidin B-2 3,3'-di-O-gallate, inhibited AAPH or AMVN-induced ROS significantly. The data suggest that Wen-Pi-Tang and its component crude drugs effectively prevent biological toxicity on oxidative stress through potent antioxidant and anti-lipid peroxidation activities.[55] Glycyrrhizae radix is used to treat abdominal pain as a component of Shaoyao-gancao-tang (SGT), a traditional Chinese medicine formulation. Previously, Sato et al have reported the isolation of glycycoumarin as a potent antispasmodic with an IC_{50} value of 2.93±0.94 mM for carbamylcholine (CCh)-induced contraction of mouse jejunum from an aqueous extract of Glycyrrhizae radix (licorice), and clarified that its mechanism of action involves inhibition of phosphodiesterase 3. The purpose of the present study was to examine an antispasmodic principle of licorice other than glycycoumarin. Isoliquiritigenin was isolated from an aqueous extract of licorice as a potent relaxant, which inhibited the contraction induced by various types of stimulants, such as CCh, KCl, and $BaCl_2$ with IC50 values of 4.96±1.97 mMol, 4.03±1.34 mMol and 3.70±0.58 mMol, respectively, which are close to those of papaverine. However, the amount of isoliquiritigenin in the aqueous extract of licorice was very small. When the aqueous licorice extract was treated with naringinase, the amounts of glycosides such as isoliquiritin, which were abundant but had much less potent relaxant activity, were decreased while isoliquiritigenin was increased. At the time, the relaxant activity of the treated sample was increased significantly, shifting the IC_{50} from 358±104 to 150±38 $\mu g.ml^{-1}$ for CCh-induced contraction. Isoliquiritigenin also showed the most potent inhibition of mouse rectal contraction induced by CCh with an IC_{50} value of 1.70±0.07 mMol. These results suggest that isoliquiritigenin acts as a potent relaxant in the lower part of the intestine by transformation from its glycosides.[56] Paeoniflorin (PF), an active glycoside of SGT, is metabolized into the antispasmodic agent paeonimetabolin-I (PM-I) by intestinal bacteria after oral administration. The objective of the present study was to investigate whether the co-administered laxative (sodium picosulfate) influences the metabolism of PF to PM-I by intestinal bacteria. We found that the PF-metabolizing activity of intestinal bacteria in rat feces was significantly reduced to approximately 34% of initial levels by a single sodium picosulfate pretreatment and took approximately 6 days to recover. Repeated administration of SGT after the sodium picosulfate pretreatment significantly shortened the recovery period to around 2 days. Similar results were also observed for plasma PM-I concentration. Since PM-I has muscle relaxant activity, the present results suggest that repetitive administration of SGT after sodium picosulfate pretreatment might be useful to relieve the pain associated with colonoscopy.[57]

Effects on liver, renal and pancreas functions

Glycyrrhizic acid and glycyrrhitic acid were shown to prevent the development of experimental cirrhesis. In carbon tetrachloride intoxicated rats, the elevation of SGPT was impeded significantly by glycyrrhizic acid but not by glycyrrhitic acid. Glycyrrhizic acid was found to be able to decrease the accumulation of triglycerde in the liver. histopathological investigation revealed that lessions of the liver of glycyrrhizic acid and glycyrrhitic acid treated rats were esssevere than those of carbon tetrachloride controls. Histochemical observation indicated that the liver glycogen in the glycyrrhizic acid treated rats was increased significantly. The number of AFP positive rats of glycyrrhizic acid treated groups was also higher than that of the control group. They did not exert any effect on collagenolytic activity and collagen resorption[58]. Liver cell damage is induced when isolated liver cells coated with specific antibody against the liver cell membrane are cultured with peripheral blood mononuclear cells. These cell injuries caused by either ADCC or macrophage culture supernatants were significantly reduced by pretreatment of the isolated liver cells with glycyrrhizin before the addition of the cytotoxic culture supernatants. These results suggest that glycyrrhizin may protect liver cells from immunological injuries[59]. The patients with chronic liver disease were treated with the immunoprotector, interferon, glycyrrhizin and adenine arabinoside, the HBeAg became negiative, natural killer activity elevated during the treatment.[60]

After oral administration of glycyrrhizic acid to rats, 11-β-dehydrogenase inhibition, and not intrinsic mineralocorticoid activity, is the primary mechanism of licorice induced pseudoaldosteronism. Glycyrrhizic acid inhbited renal 11-β-dehydrogenase. The antimineralo-corticoid effects of dexamethasone in licorice excess states are not mediated through a derect effect on 11-betadehydrogenase activity. The effects of licorice on corticosteroid metabolism in the kidney are based on its inhibition of 11-β-dehydrogenase [61]. Glycyrrhetinic acid inhibited the activity of the Na-pump enzyme dose-dependently, but had no effect on that of the Ca-pump enzyme of kidney. Glycyrrhizin also inhibited the Na-pump enzyme activity but had lest effect. The effects of these compunds were due to competitive inhibition with ATP binding to the enzyme and so were different from that of ouabain. The direct effect of glycyrrhetinic acid on the membrane may be important role in the multiple actions of licorice.[62]

Intraduodenal administration of licorice extract in 3 doses, 0.5, 1 and 2g, to dogs resulted in significant increases of both plasma secretion concentrations and pancreatic bicarbonate secretion in a dose-related manner. Intragastric administration of licorice extract at dose of 2 g resulted in significant increases of both plasma secretion and pancreatic bicarbonate output. The study indicates that the endogenous release of secretion is involved in a mechanism off an increase in exocrine pancreatic secretion induced by this licorice extract[63].

Yokozawa *et al* investigated the protective effects of Glycyrrhizae Radix extract against peroxynitrite (ONOO-)-induced oxidative stress under *in vivo* as well as *in vitro* conditions. The extract showed strong ONOO- and nitric oxide (NO) scavenging effects under in vitro system, in particular higher activity against ONOO-. Furthermore, elevations of plasma 3-nitrotyrosine levels, indicative of *in vivo* ONOO- generation and NO production, were shown using a rat in vivo ONOO(-)-generation model of lipopolysaccharide injection plus ischemia-reperfusion. The administration of Glycyrrhizae Radix extract at doses of 30 and 60 mg/kg body weight/day for 30 days significantly reduced the concentrations of 3-nitrotyrosine and NO and decreased inducible NO synthase activity. In addition, the nitrated tyrosine protein level and myeloperoxidase activity in the kidney were significantly lower in rats given Glycyrrhizae Radix extract than in control rats. However, the administration of Glycyrrhizae Radix extract did not result in either significant elevation of glutathione levels or reduction of lipid peroxidation in renal mitochondria. Moreover, the in vivo ONOO- generation system resulted in renal functional impairment, reflected by increased plasma levels of urea nitrogen and creatinine, whereas the administration of Glycyrrhizae Radix extract reduced these levels significantly, implying that the renal dysfunction induced by ONOO- was ameliorated. The present study suggests that Glycyrrhizae Radix extract could protect the kidneys against ONOO- through scavenging $ONOO^-$ and/or its precursor NO, inhibiting protein nitration and improving renal dysfunction caused by $ONOO^-$.[64]

Immunopharmacological activity

Immune effects have been observed in some compounds of licorice. glycyrrhizin inhibited to some extent prostaglandin E_2 bio-synthesis by the activated rat peritoneal macrophage, whereas in the cell-free

experiment glycyrrhizin and glycyrrhetinic acid showed little effect on the inhibition of cyclo-oxygenase.[20,21]

The *in vitro* immunomodulatory activities of a number of saponins and glycyrrhizic acids are described. Addition of these saponin preparations to mouse spleen cell cultures resulted in significant cell proliferation. B-cells were inducedto proliferate in the presence of the saponin. On the other hand, glycyrrhizic acid stimulated both T- and B-lymphocytes esually. The selective proliferation of subtypes of lymphocytes correlated with restimulation responses by polyclonal mitogens. In comparison, similar exposure of lymphocytes to glycyrrhizic acid prodiced markedly increased responses to PHA, Con A, PWM and LPS. Imcubation of lymphocytes in the presence of saponins caused effector cell generation as determined in a one-way mixed lymphocyte reaction. In the case of lymphocytes cultured in the presence of saponins or glycyrrhizic acid, the supernatants contained active soluble factors. It was demonstrated by the observation that glycyrrhizic acid has the most profound immunomodulatory activity *in vitro*. [65]

Biochemical pharmacological studies

Glycyrrhizic amide is a derivative of glycyrrhizin. The influence of glycyrrhizic amide on immunoregulation and PGE_2 and cAMP levels of the spleen of mice was investigated. This compound significantly increased spleen weight of mice, tissue $mg \cdot g^{-1}$ body weight was to be from 4.3 to 5.50; phagocytotic index of phagocytosis carbon particle was to be from 1.23 to 4.4; and the number of leucocytes in peripheral circulation was to be from 5.87 to 10.1. It also ignificantly increased PGE_2 and cAMP levels of spleen in mice. The PGE_2 levels of spleen was from 17.7 to 31.8 $pg.mg^{-1}$ tissue, and the cAMP levels were from 0.56 to 1.12 $pmol.mg^{-1}$ tissue of spleen. There were no significant differences of PGE_2 levels in peripheral circulation. This compound stimulated PGE secretion and increased spleen lymphocytes, while indomethacin inhibited it. These studies suggest that glycyrrhizic amide has immuno-regulatory function, and the change in PGE_2 and cAMP levels may be its pharmacological mode of action.[66]

Aluminum glycyrrhizinate is the amide of glycyrrhetinic acid which derives from glycyrrhiza. Using ammonium glycyrrhizinate at oral dose of 100 $mg.kg^{-1}$ for 7 days in mice showed inhibiting the biosyntheses of PGE_2 and PGF_2, blocking the release of cAMP whereas stimulate release of cGMP. Prostaglandins and cyclic nucleotides participate in many bodily functions. It is suggested their levels may be of importance as a possible mechanism by which ammonium glycyrrhinate acts in diseases, especially as a prospective therapeutic regimen for the treatment of acquired immune deficiency syndrome.[67]

Radix Glycyrrhizae (RG) is a medicinal herb extensively utilized in numerous Chinese medical formulae for coordinating the actions of various components in the recipes and strengthening the body functions. In this report, we demonstrate that the aqueous extract of *Radix Glycyrrhizae* is capable of stimulating the c-Jun N-terminal kinase and p38 subgroups of mitogen-activated protein kinases (MAPKs), and the nuclear factor-kappaB (NF-κB) in Jurkat T-lymphocytes. The activation magnitudes of MAPKs and NF-κB were dose-dependent (EC_{50} approximately 1 $mg \cdot ml^{-1}$) and time-dependent (maximal around 15-30 minutes). Stimulations of MAPKs and NF-κB were not associated with changes in intracellular Ca^{++} mobilization. Similar activation profiles of MAPK and NF-κB were obtained from THP-1 monocytes treated with the extract. In terms of chemotactic activity, the SDF-induced chemotaxis of Jurkat cells and THP-1 cells were inhibited by RG extract at 1-10 $mg \cdot ml^{-1}$, while a lower RG concentration (0.1-0.3 $mg \cdot ml^{-1}$) potentiated the SDF-induced chemotaxis for the former, but not the latter cell type. Given the fact that MAPKs and NF-κB are important signaling intermediates for lymphocyte activities, our results suggest that Radix Glycyrrhizae may contain active constituents capable of modulating immuno-responses through various intracellular signaling pathways.[68]

The present study investigated whether Jakyak-Gamcho-Tang (JGT, Shaoyao-Gancao-tang) and its constituents have the protective effect against tert-butyl hydroperoxide (t-BHP)-induced cytotoxicity on hippocampal HT22 cell line. JGT consists of two medicinal herbs, Paeoniae Radix (PR) and Glycyrrhizae Radix (GR). In contrast to treating with t-BHP alone, pre-treatment of HT22 cells with JGT, PR and GR (50-400 $\mu g \cdot ml^{-1}$) for 3 hours significantly increased the cell viability in a concentration-dependent manner. In addition, JGT, PR and GR exhibited the scavenging activity in both 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and superoxide anion assays. Among the tested extracts, PR showed the most potent protective and

antioxidative activities. These results suggest that PR acts as an antioxidant and this property may contribute to the neuroprotective activity of JGT extract.[69]

Glycyrrhizae Radix is used to treat abdominal pain as a component of Shakuyaku-kanzo-to, a traditional Chinese medicine formulation. We aim at clarifying the antispasmodic principles of *Glycyrrhizae Radix*, and consequently isolated glycycoumarin as a potent relaxant on the carbamylcholine (CCh)-induced contraction of mouse jejunum. In this paper we investigated the effects and the action mechanism of glycycoumarin on the contraction of mouse jejunum. Glycycoumarin inhibited the contraction induced by various types of stimulants, such as CCh, KCl, $BaCl_2$, and A23187 (calcium ionophore III) with IC_{50} values of 2.93±0.94 micromol/l (1.08±0.35μg·ml^{-1}), 2.59±0.58 μmol·L^{-1} (0.95±0.29μg·ml^{-1}), 4.09±1.82μmol·L^{-1} (1.51±0.67 μg·ml^{-1}) and 7.39±5.19μmol·L^{-1} (2.72±1.91 μg·ml^{-1}), respectively, with a potency similar to that of papaverine (a representative antispasmodic for smooth muscle). Furthermore, pretreatment with glycycoumarin enhanced the relaxation induced by forskolin on CCh-evoked contraction, similar to that by pretreatment with IBMX, a non-specific inhibitor of phosphodiesterases (PDEs). Pretreatment with glycycoumarin also enhanced the relaxation effect of rolipram, a specific inhibitor of PDE isozyme 4, as pretreatment with milrinone, a specific inhibitor of isozyme 3, did. Moreover, the effect of glycycoumarin was associated with dose-dependent accumulation of cAMP, but not cGMP, in mouse jejunum. These results indicate that glycycoumarin has an inhibitory effect on smooth muscle contraction induced by various types of stimulants through the inhibition of PDEs, especially isozyme 3, followed by the accumulation of intracellular cAMP.[70]

Due to the severe damage caused by free hydroxyl radicals (OH.) to cells and tissues, there is much interest in finding and studying effective and non-toxic OH. scavengers, including traditional Chinese herbs. In this paper, the simple and highly-sensitive technique of capillary zone electrophoresis with amperometric detection (CZE-AD) was used to study the OH. scavenging activities of aqueous extracts from some traditional Chinese herbs. Salicylic acid (SAL) was used as an OH. trap, and the content of OH. It could be determined by assaying their products, 2,3-dihydroxybenzoic acid (2,3-DHBA) and 2,5-dihydroxybenzoic acid (2,5-DHBA). The optimum conditions for CZE-AD for the determination of 2,3-DHBA and 2,5-DHBA were explored. The linearity ranges of 2,3-DHBA and 2,5-DHBA were 1.0 x10^{-7} approximately 1.0 x10(-4) mol L^{-1}, and their detection limits were as low as 2 x 10^{-8} mol L^{-1}, which were much better than the CE-UV method often used. The traditional Chinese herbs studied included *Radix angelicae sinensis, Rhizoma coptidis, Ligustrum lucidum, Ligusticum wallichii, Radices glycyrrhizae* and Semen plantaginis. The experiments showed that the aqueous extracts from all of the above traditional Chinese herds had free OH. scavenging activities, although to different degrees.[71]

Antidiabetic effect

Radix Glycyrrhiza was found to exhibit markedly inhibitory effect on aldose reductase. The IC50 was 16.3 μ g.mL-1. .It suggests that this herb used in the control of diabetic complication may act through the pharmacological action of inhibiting aldose reductase. This herb can inhibit aldose reductase in steptozotocin-induced diabetic rats. Licorice markedly reduced sorbitol levels in red blood cells and without affecting blood glucose.[72,73] When the extract of licorice was given orally at dose of 7.5g.kg-1.d-1 for one week in diabetic rats, licorice extract reduced sorbitol levels in WBC without affecting blood glucose level. [72]

Wen-Pi-Tang, an Oriental medical prescription composed of *Rhei Rhizoma, Ginseng Radix, Aconiti Tuber, Zingiberis Rhizoma* and *Glycyrrhizae Radix*, is used clinically as a medicine to treat renal failure. This study was conducted to examine the inhibitory activity of the five crude drug components of Wen-Pi-Tang and several pure compounds isolated from *Rhei Rhizoma* and *Glycyrrhizae Radix* against the protein glycation reaction. Rhei Rhizoma exerted the most potent activity, *Zingiberis Rhizoma* and *Glycyrrhizae Radix* showed relatively moderate activity, whereas *Aconiti Tuber* and *Ginseng Radix* showed weak activity. On the other hand, of 20 compounds obtained from *Rhei Rhizoma* and *Glycyrrhizae Radix*, tannins, especially rhatannin, RG-tannin and procyanidin B-2 3,3'-di-O-gallate, showed significantly strong activities that were more effective than the positive control, aminoguanidine. Some flavones such as licochalcone A and licochalcone B, and anthraquinones such as emodin

and aloe-emodin, also showed inhibitory activity. These findings may help to explain, at least in part, certain pharmacological activities of Wen-Pi-Tang, whose clinical efficacy against renal failure is already recognized.[74]

Detoxifying effect

Experiments on mice revealed that extract of Licorice roots and glycyrrhizic acid have significant detoxifying actions against chloral hydrate, strychning, urethane, cocaine, arsenobenzene and mercurous chloride. They also exhibited detoxicate actions, though at lower potency, against picrotoxin, inactive against atropine, sulfanal, scopolamine, morphine, and antimony. Conversely, they increased the toxicity of ephedrine and epunephedrine, glycyrrhizic acid also detoxified tetrodoxin and snake venom. As a nonhemolytic saponin, glycyrhizic acid prevented the hemolysis of erythrocytes by other saponinis *in vitro.* [13]

Pharmacokinetics

Pharmacokinetics of the active principles of Radix Glycyrhizae was studied in rats. After intravenos injection at doses of 20, 50 and 100 $mg.kg^{-1}$ of glycyrrhizin, as shown in Table 1, the half-life was 1.78, 3.72 and 4.68 h, respectively. The result indicated non-linear kinetic nature. The pharmacokinetics of 18-α- and 18-β-glycyrrhetic acid was studied in rabbits following intravenous injection at dose 20 $mg.kg^{-1}$. The half-life was 1.22 and 2.85 h, respectively[75]. To mice at doses of 25, 50 and 100 $mg.kg^{-1}$ after intravenous injection, the plasma glycyrrizin concentration-time curves were fitted by two-compartment model, and the t1/2αand t1/2βwere 2.58-9.51 and 49.3-55.1 min, respectively; the clearance were 0.0033-0.0047 L.kg-1.min^{-1}, and volume of distribution were 0.1443-0.1954 $L.kg^{-1}$. The plasma protein binding ratio was 92.7-96.0% at the concentrations of 50-300 $mg.L^{-1}$ [76].

Table 1. Pharmacokinetic parameters of glycyrrhizin in rats

Dose($mg.kg^{-1}$)	20	50	100
$t_{1/2}$(h)	1.78	3.72	4.68
Cl (ml..$min^{-1}.kg^{-1}$)	1.98	0.84	0.63
Vd ($L.kg^{-1}$)	0.33	0.27	0.26
AUC ($\mu g.h.ml^{-1}$)	1.78	10.57	2645

In order to investigate the pharmacokinetic behavior of Glycyrrhizin GLY in human after oral administration of GLY or licorice root, a liquid chromatography/tandem mass spectrometry (LC-MS/MS) method was developed and validated for the simultaneous determination of GLY and its major metabolite glycyrrhetic acid (GA) in human plasma. The method involved a solid phase extraction of GLY, GA, and alpha-hederin, the internal standard (IS), from plasma with Waters Oasis MCX solid phase extraction (SPE) cartridges (30 mg) and a detection using a Micromass Quattro LC liquid chromatography/tandem mass spectrometry system with electrospray ionization source in positive ion mode. Separation of the analytes was achieved within 5min on a SepaxHP CN analytical column with a mobile phase of acetonitrile:water (50:50, v:v) containing 0.1% formic acid and 5mM ammonium acetate. Multiple reaction monitoring (MRM) was utilized for the detection monitoring 823→ 453 for GLY, 471→ 177 for GA and 752→ 456 for IS. The LC-MS/MS method was validated for specificity, sensitivity, accuracy, precision, and calibration function. The assay had a calibration range from 10 to 10,000 $ng.mL^{-1}$ and a lower limit of quantification of 10 $ng.mL^{-1}$ for both GLY and GA when 0.2 mL plasma was used for extraction. The percent coefficient of variation for accuracy and precision (inter-run and intra-run) for this method was less than 11.0% with a % Nominal ranging from 87.6 to 106.4% for GLY and 93.7 to 107.8% for GA. Stability of the analytes over sample processing (freeze/thaw, bench-top and long-term storage) and in the extracted samples was also tested and established.[77]

Ichikawa et al reported that the plasma decay in normal rats following an iv dose of 100 $mg.kg^{-1}$ of glycyrrhizin was generally bi-phase. The secondary peaks were observed in all rats in the elimination phase to be 0.5 to 12 h. The bile excretion was 80.6% of the administered dose[78]. Disposition of glycyrrhetic acid in healthy subjects and patients with psecudoaldosteronism was studied by an enzyme immuno-antobody technique. The serum glycyrrhetic acid levels in two cases who presented pseudoaldosteronism by licorice containing formulations were as high as 70-80 $ng.mL^{-1}$, with glycyrrhetic glycoside levels being very low. The utinary excretion of glycyrrhetic acid was about 2% of the total dose of glycyrrhizin administered [79].

Liu et al evaluated the potential of 15 herbal medicines (HMs), commonly used in Korea, to inhibit the catalytic activities of several cytochrome P450 (CYP) isoforms and microsomal NADPH-CYP

reductase. The abilities of 1-1000 μg.mL^{-1} of freeze-dried aqueous extracts of 15 HMs to inhibit phenacetin O-deethylation (CYP1A2), tolbutamide 4-methylhydroxylation (CYP2C9), S-mephenytoin 4'-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), chlorzoxazone 6-hydroxylation (CYP2E1), midazolam 1-hydroxylation (CYP3A4) and NADPH-CYP reductase were tested using human liver microsomes. The HMs Epimedii herba, Glycyrrhizae radix and Leonuri herba inhibited one or more of the CYP isoforms or NADPH-CYP reductase. Of the three HMs, Epimedii herba extracts were the most potent inhibitors of several CYP isoforms (IC_{50}) 67.5μg.mL^{-1} for CYP2C19, 104.8 μg.mL^{-1} for CYP2E1, 110.9 μg.mL^{-1} for CYP2C9, 121.9 microg/mL for CYP3A4, 157.8 μg.mL^{-1} for CYP2D6 and 168.7μg.mL^{-1} for CYP1A2) and NADPH-CYP reductase (IC_{50}) 185.9 μg.mL^{-1}). These results suggest that some of the HMs used in Korea have the potential to inhibit CYP isoforms *in vitro*. Although the plasma concentrations of the active constituents of the HMs were not determined, some herbs could cause clinically significant interactions because the usual doses of those individual herbs are several grams of freeze-dried extracts. Controlled trials to test the significance of these results are necessary. [80]

TJ-8117 (Onpi-to) is a herbal medicine extracted from mixture of five crude drugs (*Rhei Rhizoma, Glycyrrhizae Radix, Ginseng Radix, Zingiberis Rhizoma and Aconiti Tuber*), which has been developed as a drug for chronic renal failure. (-)Epicatechin 3-O-gallate (ECG), one of the active compounds of TJ-8117, was labeled with tritium and spiked to TJ-8117. Effects of food, renal failure and repeated administration to pharmacokinetics of ECG-related radioactivity in the plasma were investigated after oral administration of TJ-8117 containing ^{3}H-ECG (^{3}H-TJ-8117) in male rats. After oral administration of ^{3}H-TJ-8117, the radioactivity in the plasma in non-fasted rats was higher than that in fasted rats. $AUC_{0\text{-}72\ h}$ and *Cmax* in the non-fasted was 123% and 248% of those in the fasted. After oral administration of ^{3}H-TJ-8117, the radioactivity in the plasma in 5/6 nephrectomized rats was higher than that in sham-operated rats. $AUC_{0\text{-}72\ h}$ and *Cmax* in 5/6 nephrectomized was 332% and 236% of those in sham-operated. After repeated administration of TJ-8117 for 6 days, ^{3}H-TJ-8117 was administered on 7th day. Radioactivity in plasma in first day was similar to that in 7th day. The pharmacokinetic parameters were not significantly different between single and repeated administration.[81] Kamei et al examined the pharmacokinetic and pharmacodynamic properties of liquiritin apioside, a main antitussive component of Glycyrrhizae radix (licorice), with regard to its antitussive effect in guinea pigs. The peak plasma concentration of the unchanged compound was observed 15 min after the administration of liquiritin apiosaide. The plasma concentration then gradually decreased and was almost undetectable 4 h after administration. Liquiritigenin, a des-glycoside 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. When the antitussive effects of liquiritin apioside, liquiritin and liquiritigenin, at respective doses of 30 mg/kg, p.o., were examined 1 h after administration, liquiritin apioside and liquiritigenin caused a significant reduction in the number of capsaicin-induced coughs. However, at the same dose, liquiritin had no significant effect on the number of capsaicin-induced coughs. On the other hand, when the antitussive effects of liquiritin apioside, liquiritin and liquiritigenin, at doses of 30 mg.kg^{-1}, p.o., were examined 4 h after administration, each caused a more than 40% reduction in the number of capsaicin-induced coughs. The present results suggest that *G. radix* (licorice) may produce a persistent antitussive effect, and that liquiritin apioside plays an important role in the earlier phase, while liquiritigenin, which is a metabolite of liquiritin apioside and liquiritin, plays an important role in the late phase.[82]

Shaoyao-Gancao-Tang (SGT), a traditional Chinese formulation composed of Shaoyao (Paeoniae Radix) and Gancao (*Glycyrrhizae Radix*), is frequently used in conjunction with laxatives such as sodium picosulfate in colonoscopy to relieve abdominal pains. We have investigated the alterations of the bioavailability of glycyrrhizin when SGT was co-administered with sodium picosulfate and we tried to identify a regimen that might minimize the alterations. Glycyrrhizin is one of the active glycosides in Gancao and SGT and is hydrolysed into the bioactive metabolite, 18 β-glycyrrhetic acid (GA)

by intestinal bacteria following oral administration. We found that the maximum plasma concentration (*Cmax*) and the area under the mean concentration *vs* time curve from zero to 24 h ($AUC_{0\text{-}24\ h}$) of GA from a single dose of SGT administered 5 h after a single pretreatment with sodium picosulfate were significantly reduced to 15% and 20% of the control level in rats, respectively. These reductions were still significant four days after sodium picosulfate pretreatment, but were restored by repetitive administration of SGT following sodium picosulfate pretreatment. Similar reductions and recovery were observed for the glycyrrhizin-metabolizing activity of intestinal bacteria in rat faeces. The results warrant clinical studies for co-administration of laxatives such as sodium picosulfate and SGT.[83]

Toxicology

The LD_{100} of the extract of Radix Glycyrrhizae in mice by subcutaneous injection was found to be 3.6 $g.kg^{-1}$. The MLD of glycyrrhizic acid in mice by subcutaneous injection was 1 $g.kg^{-1}$. The LD_{50} of glycyrrhitic hemisuccunate in mice was found to be 101 $mg.kg^{-1}$ by ip injection and 430 $mg.kg^{-1}$ by iv injection. The LD_{50} of FM-100 in mice was 760 $mg.kg^{-1}$ by ip injection. .Subcutaneous injection of glycyrrhitic hemisuccunate at the dose of 500 $mg.kg^{-1}$ to cats and 2.5 $mg.kg^{-1}$ to rabbits for 30 days did not result in changes in body weight or caused any mortality. Glycyrrhizic acid at the low doses from 20 to 30 $mg.kg^{-1}$ for more than one week produced edema. At high dose (1250 $mg.kg^{-1}$), glycyrrhitic acid caused respiratory inhibition and weight less in mice [13].

Intragastric administration of extract of licorice root for 6 months in doses of 100 and 250 $mg.kg^{-1}$ per day produce in animal functional changes of the liver and kidneys, which one should take into consideration when prescribing the preoaration to patients suffering from diseases of these organs[84]. Glycyrrhiza extract inhibited the mutagenicity of activated Trp-P-1. It was clear that the inhibitory effect was not due to inhibition of enzyme activity of the S9 fraction[85].

Glycyrhiza extract has been shown to inhibit mutagenic activity of ethyl methanesulfonate (EMS) and 2-(2-furyl)- 3- (5-nitro-2-furyl) acrylamide (FNFA). Glycyrrhi-zinic acid decreased the the mutagenicity of 3-amino-1- methyl- 5H- pyrido-[4,3-β]ondole, 2-acetyl-aminofluorene and glucose pyrolysate. 18α-glycyrrhetinic acid and 18β-glycyrrhetinic acid have been shown to inhibit the mutagenicity of benzopyrene, 2-amino-flurene and aflatoxin B1. Desmutagenic and antimutagenic activities of glycyrrhizic acid were eveluated bymeasuring the inhibition of Salmonella typhimurium TA100 revertants induced by EMS, N-nitro-N-nitrosoguanidine (NNNG) and riboselysine. The concentrations of the mutagens used induce a limited number of revertants/plate. The glycyrrhiza extract, glycyrrhizinic acid and 18α-and 18β-glycyrrhetinic acids showed desmutagenic activity against riboselysine induced mutagents. 18β-glycyrrhetinic acid was the most effective among these substances in inhibiting riboselysine mutagenicity. At a concentration of 100 μg/plate, it resulted in 79% inhibition of mutagenicity. The different activities of the two stereoisomers may be due to the different stereochemical structure of the D/E ring conformation. Glycyrrhiza extract also showed anti-mutagenic activity against riboselysine. These studies suggest that compounds from Glycyrrhiza roots nay be used as effecttive and particle chemo-preventive agents to inhibit or to reduce genotoxic effects, and to reduce cancer frequency in humans[86].

Clinical therapeutics

Licorice root (*Radix Glycyrrhizae*) is officially listed in the Chinese Pharmacopeia. It is used as a tonic, antiphlogistic, mucolytic, expectorant, anagesic for the treatment of gastroinstinal and respiratory diseases, and also used to alleviate the toxicity of some drugs. In traditional Chinese medicine, the herb is one of herbs that tonify spleen and replenish "Qi". The indications and combinations of this herb are the following aspects: (1) Deficient "Qi" of the spleen and stomach manifested as poor appetite, loose stool and lassitude. Licorice root is used with White atractylodes, Poria and Ginsng in the formula Sijunzi decoction; (2) Cough and asthma. licorice root is used with Apricot seed and Ephedra in the formula Sanniu decoction; (3) Carbuncles, furuncles, sore throat and swelling due to toxic heat. Licorice root is used with Platycodon root, Scrophularia and Arctium fruit for sore throat. Licorice root can also be used with Honeysuckle flower and Forsythia fruit for carbuncles, furucles and swellings; (4) Abdominal pain due to spasms of the stomach or intestines, licorice root is used with White peony root; (5) Moderating the action of other drugs. Licorice root with Prepared aconite root and dried ginger can weaken the heating properties and lessen the side

effects of some herbs[87]. It counteracts Peking spurge root, Genkwa flower, Kansui root and Seaweed. Prolonged overdosing of the herb may cause edema.

Ingestionof licorice 100 g daily for 8 weeks caused a rise in 81% in plasma atrial natriuretic peptide concentration in 12 healthy volunteers. The plasma concentrations of antdiuretic hormone, aldosterone and plasma renin activity decreased. All these hormonal effects, reflecting retention of sodium and fluid volume were probably due to the known mineralocorticoid properties of licorice. Blood pressure increased transiently and two subjects developed reversible hypertension. The rise in plasma atriuretic peptide concentration during ingestion of licorice may be considered a physiological response to prevent fluid retention and development of hypertension [88].

In clinical application, licorice extract and its chemical constituents and preparations are used for the treatment of gastric and duodenal ulcers, inflammatory diseases, chronic hepatitis, Addison's disease and other diseases.

The therapeutic efficiency of a new formulation that incorporates 0.2% idoxuridine in glycyrrhizin gel has been tested on patients who suffer from herpes of the lips and nose. The preparation was more effective than a commercial 0.5% idoxuridine oitment. It reduced the healing time and produced an almost intanatnaeous relief from pain. The higher efficacy of the new preparation may be a scribed to the reported anti-inflammatory and antiviral activities of glycyrrhizin together with an enhanced permeation of the idoxuridine through the skin[61]. 60 cases of perpetic keratitis, keratocon-junctivitis, and fascicular keratitis had been treated with eye drops of 5% sodium glycyrrhizinzte, or 8-125 suspension o glycyrrhitic acid, or the 10-30% extract of the herb three to four times daily. 56 of the cases so treated were cured after 2-7 days of treatment [13].

In 10 carriers positive for chronic hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), and DNA polymerase, theefficacy of the combination of therapy consisting of glycyrrhizin with thedrawal and human fibroblast interferon. Glycyrrhizin was given for 4 weeks. Glycyrrhizin appeared to act as an antiviral agent in cases and had cortecolid-like effect in 3 cases. DNA polymerase decreased remarkedly after administration. no side effects were observed inpatients recieving glycyrrhizin. Thus this combination therapy seems safe and effective[89].

Four cases of Addison's disease had been treated with licorice extract 15 ml once daily. The patients strengh was increased, the objective improvement included increase of serum sodium, elevation of blood pressure and decrease of skin pigmentation. Glycyrrhizic acid was found to be useful for this disease. The therapeutic and maintenance doses varied with different individuals. The dosage was gradually reduced after several weeks of continuous administration. As patients developed increased sensitivity to the drug, the maintenance dose prescribed for some cases was reduced to only one-tenth the initial dose.

Glycyrrhiza extract was used to treat 100 cases with gastric and duodenal ulcers. To these patients, the extract was used with 15 ml in 4 times per day for 6 weeks. Good effects wee achieved in 905 of the treated cases. The herb power gave better effects as it contains the complete components. Large doses or long-term injection of low dose doses of the herb produced the following reactions in 20% of patients, edema, weak limbs, spastic numbness, dizziness, headache, hypertension and hypokalemia. The herb should be used with caution in elderly patients and in those with cardiovascular and renal diseases because of their susceptibility to hypertension and congestive heart failure [13]. Glycyrrhizin tablets was officially listed in therapeutic drugs for the treatment of chronic hepatitis in 1992. Hayashi et al reported the results on the combination therapy of glycyrrhizin with dracial and human fibrolast interferon for chronic hepatitis.[90]

Asian Journal of Drug Metabolism and Pharmacokinetics had published in English a series of reviews on the ehtnopharmacology, pharmacology, pharmacokinetics and clinical application of some traditional Chinese medicines and herbs commonly used.[91-98] These literatures will be helpful and valuable to readers and researchers wishing to study and understand traditional Chinese drugs and herbal drugs as well as traditional Chinese medicine. In this paper, the introduced information on *Radix Glycyrrhizae* will also be helpful.

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