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# A Study on Pharmacokinetics and Therapeutic Efficacy of *Glycyrrhiza glabra*: A Miracle Medicinal Herb

[1]J.B. Vibha, [2]K. Choudhary, [3]Mangal Singh, [1]M.S. Rathore and [1]N.S. Shekhawat

[1]Department of Botany, Biotechnology Unit, JNV University, Jodhpur (Rajasthan-342005), India
[2] Department of Biotechnology, Lachoo Memorial College of Science and Technology, Jodhpur (Rajasthan-342003), India
[3] Biotechnology Laboratory, FASC, MITS Deemed University, Lakshmangarh, Sikar (Rajasthan-332311), India

**Abstract:** Man has been using mulathi (licorice) from the dawn of the historic era. This plant is distributed in the subtropical and warm temperate regions of the world, chiefly in the Mediterranean countries. The action of Liquorice is demulcent, moderately pectoral and emollient. It is a popular and well-known remedy for coughs, consumption and chest complaints generally most notably bronchitis and is an ingredients in almost all popular cough medicines on account of its valuable soothing properties. The root contains glycrrhizin, 50 times sweeter than sucrose, which encourages the production of hormones such as hydrocortisone. This helps to explain its anti-inflammatory action and also its role in stimulating the adrenal cortex after steroid therapy. The root can help heal gastric ulceration. The plant also possesses antibacterial, antiviral and powerful antispasmolytic activities. Recently, licorice has been attributed with anticancer properties.

**Key words:** Antioxidant · Anti-inflammatory · Demulcent · Expectorant · Mulathi

## INTRODUCTION

Licorice *(Glycyrrhiza glabra)* is one of the commercially important perennial plant grassy or semi-bushy type species from the leguminoceae (Fabaceae) plant family, sub-family papilionaceae. The genus name is driven from the Greek words, *glycy* (or *glulus)* meaning sweet and *rhiza* meaning root [1]. Licorice roots, runners and rhizomes are the commercially desired parts of the plant that contain a number of important chemical compounds. Glycyrrhizin is one of these compounds which shown to be 50 times or more sweeter than sugar and demands high prices in the world market [2, 3]. These compounds are used in medicine for its non-nutritive sweetness and anti-allergic and anti-inflammatory effects as treatment of bronchial asthma, allergic, dermatis and eczema. They are also used as food in the confectionery industry such as sweets, alcohol free drinks etc. and in the tobacco industry [4].

Licorice extracts have been used for more than 60 years in Japan to treat chronic hepatitis and also have therapeutic benefit against other viruses, including human immunodeficiency virus (HIV), cytomegalovirus (CMV) and Herpes simplex. Deglycyrrhizinated licorice (DGL) preparations are useful in treating various types of ulcers, while topical licorice preparations have been used to sooth and heal skin eruptions, such as psoriasis and herpetic lesions (Table 1).

**Botanical Description:** The genus of *Glycyrrhiza* consist of about 30 species, of which *Glycyrrhiza glabra*, *Glycyrrhiza uralensis, Glycyrrhiza inflata, Glycyrrhiza eurycarpa* are generally recognized as licorice for their sweet taste. It is known as mulathi in Hindi, Kanzoh in Japanese and Gancao in Chinese. *Glycyrrhiza glabra* can be classified into two groups with the constituents of isoprenoids-substitued flavonoids. Type1 is Spanish and Russian licorices and type 2 is the Chinese and Kyrghiz. This plant is distributed in the subtropical and warm temperate regions of the world, chiefly in the Mediterranean countries. In India it is reported to be cultivated in Jammu and Kashmir, U.P., Delhi, Gujarat and

**Corresponding Author**: Dr. J.B. Vibha, Department of Botany, Biotechnology Unit, JNV University, Jodhpur, Rajasthan-342005, India

Table 1: Chemical profile and documented properties of Licorice plant

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|---|---|
| Documented Properties: | Anodyne, Antioxidant, Antispasmodic, Anti-inflammatory, Demulcent, Depurative, Diuretic, Emollient, Estrogenic, Expectorant, Pectoral |
| Plant Chemicals Include: | Acetic-acid, Acetoin,Acetol, Acetophenone, Alphaterpineol Aluminum, Anethole, Apigenin, Ascorbic-acid, Asparagine, Benzaldehyde, Benzoic-acid, Benzyl-alcohol, Beta-sitosterol, Butan-1-ol-2-one, Butan-1-ol-3-one, Butane-2,3-diol, Butanoic-acid, Butylphthalate, Butyricanhydride, Calcium, Camphor, Caproic-acid, Carvacrol, Choline, Chromium, Cobalt, Cumic-alcohol, Decane, Decanoic-acid, Difurfuryl-ether, Dihydro-5,5-dimethyl-2(3h)-furanone, Dimethyl-phenylethyl-alcohol, Docosane, Dodecane, Dodecanoic-acid, Eicosane, EO, Estragole, Estriol, Ethyl-linoleate, Ethyl-linolenate, Ethyl-palmitate, Ethyl-phenol,Ethyl-phenylacetate, Eugenol, Fenchone Formononetin, Fructose, Furfural, Furfuryl-acetate, Furfuryl-alcohol, Furfuryl-butyrate, Furfuryl-formate, Furfuryl-propionate, Furyl-methyl-ketone, Gammabutyrolactone, Gamma-heptalactone, Gamma-hexalactone, Gamma-nonalactone, Gamma-octalactone, Geraniol, Glabrene, Glabric-acid, Glabridin, Glabrol, Glabrolide, Glabrone, Glucose, Glycocoumarin, Glycyrin, Glycyrol, Glycyrram, Glycyrrhetic-acid, Glycyrrhetinic-acid, Glycyrrhetol,G lycyrrhisoflavanone, lycyrrhisoflavone, Glycyrrhizic-acid, Glycyrrhizin, Glyzaglabrin, Glyzarin, Guaiaco, Hederasaponin-c, Henicosane, Heptadecane,Heptane-1,2-diol, Heptanoic-acid, Heranol, Herniarin, Hextrans-3-en-ol, Hexadecane, Hexadecanoic-acid, Hexadecyl-acetate, Hexan-1-ol, Hexanoic-acid, Hexanol, Hexyl-formate, Hispaglabridin-a,Hispaglabridin-b, Indole, Iron, Isobutyladipate, Isoglabrolide, soglycyrol, Isoliquiritin, Isomucronulatol, Isoneoliquiritin, Isoschaftoside, Isoviolanthin, Kumatakenin, Lavandolol, Licochalcone-a, Licochalcone-b, Licoflavonol, Licoisoflavanone, Licoisoflavones, Licoric-acid, Licuraside, Licuroside, Lignin, Linalool, Linalool-oxides, Liqcoumarin, Liquirazide, Liquiritic-acid, Liquiritigenin, Liquoric-acid, Magnesium, Maltose, Manganese, Methyl-ethyl-ketone, Methyl-hexadecanoate, Methyl-hexanoate, Myrtenal, N-methyl-2-pyrrolidone, N-nonacosane, N-tetradecane, Neoliquiritin, Neosoliquiritin, Nonadecane, Nonanoic-acid, O-acetylsalicylic-acid, O-cresol, O-methoxy-phenol, O-tolunitrile, Octacosan-1-ol, Octadecane, Octanoic-acid, P-cymenol, P-methoxy-phenol, Palmitic-acid, Pentadecane, Pentadecanoic-acid Pentan-1-ol, Pentanoic-acid, Phaseollinisoflavan, Phenethyl-alcohol, Phenol, Phenylacetaldehyde, Phenylpropionic-acid, Phosphorus, Propionic-acid, Pyrazole, Rhamnoisoliquiritin, Rhamnoliquiritin, Salicylic-acid, Schaftoside, Silicon, Stigmasterol, Sucrose, Sugar, Terpin-1-en-4-ol, Tetracosan-1-ol, Tetracosane, Tetradecanoic-acid, Tetramethyl-pyrazine, Thiamin, Thujone, Thymol, Tiglaldehyde, Tin, Tricosane, Tridecane, Tridecanoic-acid, Trimethyl-pyrazine, Umbelliferone, Undecane, Undecanoic-acid, Zinc |

Fig. 1: a) Licorice plant, b) Fruits of licorice plant, c) Roots of licorice plant

Haryana. *Glycyrrhiza* belongs to family Leguminoseae (Fabaceae). It is a perennial herb, which is 3-5 feet in height, smooth rising from thick rhizome (Fig. 1a). Leaves are pinnate with 4-7 pairs of leaflets which are ovate in shape. Flowers are in axillary spikes, papilionaceous and lavender to violet in color. The floral structures and fruits (Fig. 1b) of this family pose the mode of cross-pollination, mainly by insect pollinators [3, 5], resulting in variability of offspring in successive generations. Only the root (rhizome) of the plant is valuable (Fig. 1c) and all the above ground parts are just as fagots.

**Active Constituents:** A number of components have been isolated from licorice, including a water-soluble, biologically active complex that accounts for 40-50 percent of total dry material weight (Table 1). This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts and various other substances [6]. Glycyrrhizin, a triterpenoid compound, accounts for the sweet taste of licorice root (Fig). This compound represents a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2-25 percent range. Among the natural saponins, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid and a hydrophobic fragment, glycyrrhetic acid [6]. The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone) and other compounds [7]. The isoflavones glabridin and hispaglabridins A and B have significant antioxidant activity, [8] and both glabridin and glabrene possess estrogen-like activity [9].

**Pharmacokinetics:** After oral administration of licorice in humans, the main constituent, glycyrrhizic acid, is hydrolyzed to glycyrrhetic acid by intestinal bacteria possessing a specialized ß-glucuronidase [10, 11]. Glycyrrhetic acid is 200-1,000 times more potent an inhibitor of 11-ß-hydroxysteroid dehydrogenase (involved in corticosteroid metabolism) than glycyrrhizic acid; therefore, its pharmacokinetics after oral intake are more relevant. After oral dosing, glycyrrhetic acid is rapidly absorbed and transported via carrier molecules to the liver. In the liver it is metabolized to glucuronide and sulfate conjugates, which are subsequently rehydrolyzed to glycyrrhetic acid. Glycyrrhetic acid is then reabsorbed, resulting in a significant delay in terminal clearance from plasma [12]. After oral administration of 100 mg glycyrrhizin in healthy volunteers, no glycyrrhizin was found in the plasma but glycyrrhetic acid was found at < 200 ng/mL. In the 24-hour period after oral administration, glycyrrhizin was found in the urine, suggesting it is partly absorbed as an intact molecule [7].

**Mechanisms of Action:** The beneficial effects of licorice can be attributed to a number of mechanisms. Glycyrrhizin and glycyrrhizic acid have been shown to inhibit growth and cytopathology of numerous RNA and DNA viruses, including hepatitis A [13] and C [14,15], herpes zoster [16], HIV[17,18], Herpes simplex [19,20] and CMV [21]. Glycyrrhizin and its metabolites inhibit hepatic metabolism of aldosterone and suppress 5-ßreductase, properties responsible for the well-documented pseudoaldosterone syndrome. The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and glucocorticoid activity of glycyrrhizic acid [22].

Licorice constituents also exhibit steroidlike anti-inflammatory activity, similar to the action of hydrocortisone. This is due, in part, to inhibition of phospholipase A2 activity, an enzyme critical to numerous inflammatory processes. 19 *In vitro* research has also demonstrated glycyrrhizic acid inhibits cyclooxygenase activity and prostaglandin formation (specifically prostaglandin E2), as well as indirectly inhibiting platelet aggregation, all factors in the inflammatory process [23,24].

Certain licorice constituents possess significant antioxidant and hepatoprotective properties. Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation [25, 26]. *In vitro* studies have demonstrated licorice isoflavones, hispaglabridin A and B, inhibit $Fe^{3+}$-induced mitochondrial lipid peroxidation in rat liver cells [27]. Other research indicates glycyrrhizin lowers lipid peroxide values in animal models of liver injury caused by ischemia reperfusion [28]. Licorice constituents also exhibit hepatoprotective activity by lowering serum liver enzyme levels and improving tissue pathology in hepatitis patients [29].

Glycyrrhizin and other licorice components appear to possess anticarcinogenic properties as well. Although the exact mechanisms are still under investigation, research has demonstrated they inhibit abnormal cell proliferation, as well as tumor formation and growth in breast [30], liver [31] and skin cancer [32, 33].

Deglycyrrhizinated licorice formulations used in the treatment of ulcers do not suppress gastric acid release like other anti-ulcer medications. Rather, they promote healing by increasing mucous production and blood supply to the damaged stomach mucosa, thereby enhancing mucosal healing [34,35].

**Clinical Indications**

**Chronic Hepatitis:** In Japan, glycyrrhizin has been used for more than 60 years as a treatment for chronic hepatitis C. Stronger Neo-Minophagen C (SNMC), a glycyrrhizin preparation, has been extensively used with considerable success [14,15].

**Oral Lichen Planus:** Patients with chronic hepatitis C often experience oral lichen planus, an inflammatory disease characterized by lymphocytic hyperkeratosis of the oral mucosa. It is rarely cured and effective treatments are limited. On treatment using licorice extract it was noted improved clinical symptoms, such as decreased redness, fewer white papules and less erosion of the mucosa. In the non-glycyrrhizin group of eight patients, only one (14.3%) reported any improvement [36].

**Other Viral Illnesses:** It has been reported that licorice inhibits growth and cytopathology of many unrelated DNA and RNA viruses, while not affecting cell activity or cellular replication [19]. Hepatitis A virus (HAV) causes acute hepatitis, a major public health concern in numerous countries. In comparison to ribavirin (an antiviral agent used to treat hepatitis), glycyrrhizin proved to be 10 times more potent at reducing infectivity of HAV, as measured by reduction in viral titres. These results indicate glycyrrhizin may be a potential therapeutic adjunct in fighting HAV infections [13]. Studies show licorice and its constituents, specifically glycyrrhizin, have antiviral activity against Herpes simplex and are capable of irreversibly inactivating the virus [20, 37, 38]. Glycyrrhizin has also been shown to inhibit viral replication and infectivity of HIV[18, 38], herpes zoster [39], Varicella zoster [16] and CMV [21, 40, 41].

Peptic Ulcer Disease: Licorice has been used as a demulcent and emollient for 2,000 years to promote the healing of ulcers by acting on the mucosal layer. Glycyrrhizin (as carbenoxolone sodium) speeds healing of gastric ulcers and protects against aspirin-induced damage to the gastric mucosa. Helicobacter pylori infection is prevalent in individuals with peptic ulcer and is also a known risk factor for gastric cancer [42, 43]. Consequently, an *in vitro* study was performed to investigate the effects of licorice flavonoids on the growth of *Heliobacter pylori*. These flavonoid components showed promising anti-*H. pylori* activity against clarithromycin-and amoxicillin-resistant strains. As the antimicrobial property seems to be attributed to the flavonoid constituents of licorice, DGL preparations may provide therapeutic benefit for H. pylori infection [44]. Other studies have demonstrated DGL's benefit in healing duodenal ulcers [45].

Several animal and *in vitro* studies indicate glycyrrhizin and its constituents possess anticarcinogenic activity against a variety of cancers, warranting further investigation in clinical trials [31-34]. Studies also show licorice constituents to be effective in the treatment of eczema [46], melasma [47], eosinophilic peritonitis [48], postural hypotension [49], erosive gastritis [50] and as anti-malarial [51] and anti-Leishmanial agents [52]. More recently, animal studies indicate aqueous extracts of *G. glabra* may have memory-enhancing activity via reversal of chemically-induced amnesia, as measured by maze and passive avoidance testing in mice [53].

Although licorice has many medicinal and flavoring properties it also has many side effects like hypertension, hypocalcaemia and metabolic alkalosis Licorice is believed to be blocking the action of the enzyme involved in breakdown of corticoids, which ultimately help in maintenance of blood balance in the body else it may cause swelling and high blood pressure [54-56].

## CONCLUSIONS

Root of *Glycyrrhiza glabra* is a potential source of plethora of biologically important secondary metabolites. Several isoflavons like licochalcone, glabrene glabridin, isoliquiritigenin, triterpenoids, polyphenolics and chalcones have been isolated from the roots. Glycyrrhizin is the most important, interesting and medicinally active component of the plant, which is a water-soluble triterpenoid glycoside, responsible for the medicinal importance of the plant. It is 50 times sweeter than sugar (Sucrose), upon hydrolysis the glycoside looses its sweet taste and is converted to aglycone glycyrrhetinic acid or glycyrrhizic acid and two molecules of glucuronic acid. Glycyrrhizin may prove an unlikely ally in the fight against Severe Acute Respiratory Syndrome (SARS). The chemical makes it difficult for the SARS virus to attach and invade the target cell. It hinders virus reproduction, slowing its spread from one cell to next. It hampers the growth of the other viruses including the herpes and helps in restoring liver function in patients suffering from hepatitis C. It is currently being assessed as a treatment of HIV infection, as it slows the replication of virus in culture cell. Glycyrrhizin inhibits the infection of Vero cells induced by eleven different pathogenic flavi viruses belonging to principle virus group of medicinal importance: dengue, Japanese encephalitis, tick borne encephalitis and yellow fever virus.

A novel flavonoid licochalcone isolated from licorice root show significant antitumor activity in various malignant human cell lines as in prostate cancer cell so licochalcone can be considered as a chemopreventive and

anticancer agent. Another isoflavon from the root is glabridin which has shown to improve women's health by mimicking the critical benefits of estrogens to the bones and the cardiovascular system but avoiding deleterious effects on breast and uterus. Licorice is reported to be beneficial in reducing the depression in pre and post-menopausal women caused by ovarian steroid hormone. Glabrene and isoliquiritigenin acts as tyrosinase, which is known as key enzyme in melanin biosynthesis. It is involved in determining the color of mammalian skin and hairs. It is suggested that glabrene can inhibit both mono and diphenolase tyrosinase activity inhibiting melanin formation in melanocytes and serve as skin lightening agents.

## REFERENCES


1. Crusheva, R. and R. Parvanov, 1978. Album of rare protected plants, Bulgaria, pp: 27-28.
2. Olukoga, A. and D. Donaldson, 1998. Historical perspective on health. The history of licorice: the plant, its extracts, cultivation, commercialisation and etymology. J. Roy. Soc. Health., 118(5): 300-304.
3. Duke, J.A., 1981. Handbook of legumes of world economic importance, Plenum Press, New York, pp: 90-92.
4. Olukoga, A. and D. Donaldson, 1998. Historical perspectives on health. The history of liquorice: the plant, its extract, cultivation and commercialisation and etymology. J. R. Soc., Health, 118:300-304.
5. Poehlman, M.A., 1977. Breeding Field Crops. Avi Publishing Company Inc, USA.
6. Obolentseva, G.V., V.I. Litvinenko, A.S. Ammosov, T.P. Popova and A.M. Sampiev, 1999. Pharmacological and therapeutic properties of licorice preparations (a review). Pharm. Chem. J., 33:24-31.
7. Yamamura, Y., J. Kawakami, T. Santa, H. Kotaki, K. Uchino, Y. Sawada, N. Tanaka and T. Iga, 1992. Pharmacokinetic profile of glycerrhizin in healthy volunteers by a new high-performance liquid chromatographic method. J. Pharm. Sci., 81: 1042-1046.
8. Vaya, J., P.A. Belinky and M. Aviram, 1997. Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. Free Radic. Biol. Med., 23: 302-313.
9. Tamir, S., M. Eizenberg, D. Somjen, S. Izrael and J. Vaya, 2001. Estrogen like activity of glabrene and other constituents isolated from licorice root. J. Steroid Biochem. Mol. Biol., 78: 291-298.
10. Hattori, M., T. Sakamoto, T. Yamagishi, K. Sakamoto, K. Konishi, K. Kobashi and Namba, 1985. Metabolism of glycyrrhizin by human intestinal flora. II. Isolation and characterization of human intestinal bacteria capable of metabolizing glycyrrhizin and related compounds. Chem. Pharm. Bull. (Tokyo), 33: 210-217.
11. Akao, T., T. Akao, M. Hattori, M. Kanaoka, K. Yamamoto, T. Namba and K. Kobashi, 1991. Hydrolysis of glycyrrhizin to 18 beta-glycyrrhetyl monoglucuronide by lysosomal beta-D glucuronidase of animal livers. Biochem. Pharmacol., 41: 1025-1029.
12. Ploeger, B., T. Mensinga, A. Sips, W. Seinen, J. Meulenbelt and J. DeJongh, 2001. The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. Drug Metab. Rev., 33: 125-147.
13. Crance, J.M., E. Biziagos, J. Passagot, H.V. Cuyck-Gandré and R. Deloince, 1990. Inhibition of hepatitis A virus replication in vitro by antiviral compounds. J. Med. Virol., 31: 155-160.
14. Van Rossum, T.G., A.G. Vulto, W.C. Hop, J.T. Brouwer, H.G. Niesters and S.W. Schalm, 1999. Intravenous glycyrrhizin for the treatment of chronic hepatitis C: a double-blind, randomized, placebo-controlled phase I/II trial. J. Gastroenterol. Hepatol., 14: 1093-1099.
15. Su, X.S., H.M. Chen, L.H. Wang, C.F. Jiang, J.H. Liu and M.Q. Zhao, 1984. Clinical and laboratory observation on the effect of glycyrrhizin in acute and chronic viral hepatitis. J. Tradit. Chin. Med., 4: 127-132.
16. Baba, M. and S. Shigeta, 1987. Antiviral activity of glycyrrhizin against Varicella-zoster virus *in vitro*. Antiviral Res., 7: 99-107.
17. Hattori, T., S. Ikematsu, A. Koito, S. Matsushita and Y. Maedfa, 1989. Preliminary evidence for inhibitory effect of glycyrrhizin on HIV replication in patients with AIDS. Antiviral Res., 11: 255-261.
18. Ito, M., A. Sato, K. Hirabayashi, F. Tanabe, S. Shigeta, M. Baba, E. De Clercq, H. Nakashima and N. Yamamoto, 1988. Mechanism of inhibitory effect of glycyrrhizin on replication of human immunodeficiency virus (HIV). Antiviral Res., 10: 289-298.
19. Pompei, R., O. Flore, M.A. Marccialis, A. Pani and B. Loddo, 1979. Glycyrrhizic acid inhibits virus growth and inactivates virus particles. Nature, 281: 689-690.

20. Partridge, M. and D.E. Poswillo, 1984. Topical carbenoxolone sodium in the management of herpes simplex infection. Br. J. Oral. Maxillofac. Surg., 22: 138-145.
21. Numazaki, K., M. Umetsu and S. Chiba, 1994. Effect of glycyrrhizin in children with liver dysfunction associated with cytomegalovirus infection. Tohoku J. Exp. Med., 172: 147-153.
22. Armanini, D., I. Karbowiak and J.W. Funder, 1983. Affinity of liquorice derivatives for mineralocorticoid and glucocorticoid receptors. Clin. Endocrinol. (Oxf), 19: 609-612.
23. Okimasu, E., Y. Moromizato, S. Watanabe, J. Sasaki, N. Shiraishi, Y.M. Morimoto, M. Miyahara and K. Utsumi, 1983. Inhibition of phospholipase A2 and platelet aggregation by glycyrrhizin, an antiinflammation drug. Acta. Med. Okayama., 37: 385-391.
24. Ohuchi, K. and A. Tsurufuji, 1982. A study of the anti-inflammatory mechanism of glycyrrhizin. Mino. Med. Rev., 27: 188-193.
25. Akamatsu, H., J. Komura, Y. Asada and Y. Niwa, 1991. Mechanism of anti-inflammatory action of glycyrrhizin: effect on neutrophil functions including reactive oxygen species generation. Planta Med., 57: 119-121.
26. Wang, Z.Y. and D.W. Nixon, 2001. Licorice and cancer. Nutr. Cancer, 39: 1-11.
27. Haraguchi, H., N. Yoshida, H. Ishikawa, Y. Tamura, K. Mizutani and T. Kinoshita, 2000. Protection of mitochondrial functions against oxidative stresses by isoflavans from Glycyrrhiza glabra. J. Pharm. Pharmacol., 52: 219-223.
28. Nagai, T., T. Egashira, Y. Yamanaka and M. Kohno, 1991. The protective effect of glycyrrhizin against injury of the liver caused by ischemia-reperfusion. Arch. Environ. Contam. Toxicol., 20: 432-436.
29. Van Rossum, T.G., A.G. Vulto, W.C. Hop and S.W. Schalm, 2001. Glycyrrhizin-induced reduction of ALT in European patients with chronic hepatitis C. Am. J. Gastroenterol., 96: 2432-2437.
30. Tamir, S., M. Eizenberg, D. Somjen, N. Stern, R. Shelach, A. Kaye and J. Vaya, 2000. Estrogenic and antiproliferative properties of glabridin from licorice in human breast cancer cells. Cancer Res., 60: 5704-5709.
31. Shiota, G., K. Harada, M. Ishida, Y. Tomie, M. Okubo, S. Katayama, H. Ito and H. Kawasaki, 1999. Inhibition of hepatocellular carcinoma by glycyrrhizin in diethylnitrosamine-treated mice. Carcinogenesis, 20: 59-63.
32. Nishino, H., K. Kitagawa and A. Iwashima, 1984. Antitumorpromoting activity of glycyrrhetic acid in mouse skin tumor formation induced by 7,12 dimethylbenz [a] anthracene plus teleocidin. Carcinogenesis, 5: 1529-1530.
33. Liu, W., M. Kato, A. Akhand, A. Hayakawa, M. Takemura, S. Yoshida, H. Suzuki and I. Nakashima, 1998. The herbal medicine Sho-saiko-to inhibits the growth of malignant melanoma cells by up-regulating Fas mediated apoptosis and arresting cell cycle through down regulation of cyclin dependent kinases. Int. J. Oncol., 12: 1321-1326.
34. Van Marle, J., P.N. Aarsen, A. Lind, J. van Weeren-Kramer, 1981. Deglycyrrhizinised liquorice (DGL) and the renewal of rat stomach epithelium. Eur. J. Pharmacol., 72: 219-225.
35. Da Nagao, Y., M. Sata, H. Suzuki, K. Tanikawa, K. Itoh and T. Kameyama, 1996. Effectiveness of glycyrrhizin for oral lichen planus in patients with chronic HCV infection. J. Gastroenterol., 31: 691-695.
36. Hirabayashi, K., S. Iwata, H. Matsumoto, T. Mori, S. Shibata, M. Baba, M. Ito, S. Shigeta, N. Nakashima and N. Yamamoto, 1991. Antiviral activities of glycyrrhizin and its modified compounds against human immunodeficiency virus type 1 (HIV-1) and Herpes simplex virus type 1 (HSV-1) in vitro. Chem. Pharm. Bull. (Tokyo), 39: 112-115.
37. Pompei, R., A. Pani, O. Flore, M.A. Marcialis and B. Loddo, 1980. Antiviral activity of glycyrrhizic acid. Experientia, 36: 304.
38. Aikawa, Y., T. Yoshiike and H. Ogawa, 1990. Effect of glycyrrhizin on pain and HLA-DR antigen expression on CD8-positive cells in peripheral blood of herpes zoster patients in comparison with other antiviral agents. Skin Pharmacol., 3: 268-271.
39. Numazaki, K. and S. Chiba, 1993. Natural course and trial of treatment for infantile liver dysfunction associated with c y tomegalovirus infections. *In Vivo*, 7: 477-480.
40. Numazaki, K., 1998. Glycyrrhizin therapy for liver dysfunction associated with cytomegalovirus infection in immunocompetent children. Antimicrobics Infect. Dis. Newsl., 17: 70-71.
41. Arase, Y., K. Ikeda, N. Murashima, K. Chayama, A. Tsubota, I. Koida, Y. Suzuki, S. Saitoh, M. Kobayashi and H. Kumada, 1997. The long term efficacy of glycyrrhizin in chronic hepatitis C patients. Cancer, 79: 1494-1500.
42. Peterson, W.L., 1991. Helicobacter pylori and peptic ulcer disease. N. Engl. J. Med., 324: 1043-1048.

43. Parsonnet, J., 1996. Helicobacter pylori in the stomach-a paradox unmasked. N. Engl. J. Med., 335: 278-280.
44. Fukai, T., A. Marumo, K. Kaitou, T. Kanda, S. Terada and T. Nomura, 2002. Anti-Helicobacter pylori flavonoids from licorice extract. Life Sci., 71: 1449-1463.
45. Armanini, D., M.J. Mattarello, C. Fiore, G. Bonanni, C. Scaroni and P. Sartorato, 2004. Licorice reduces serum testosterone in healthy women. Steroids, 69: 763-766.
46. Evans, F.Q., 1958. The rational use of glycyrrhetinic acid in dermatology. Br. J. Clin. Pract., 12: 269-274.
47. Amer, M. and M. Metwalli, 2000. Topical liquiritin improves melasma. Int. J. Dermatol., 39: 299-301.
48. Takeda, H., K. Ohta and H. Niki, Y. Matsumoto, K. Tanaka, H. Machimura, M. Yagame, W. Inoue, M. Endoh and H. Kaneshige, 1991. Eosinophilic peritonitis responding to treatment with glycyrrhizin. Tokai J. Exp. Clin. Med., 16: 183-186.
49. Basso, A., L. Dalla Paola, G. Erle, M. Boscaro and D. Armanini, 1994. Licorice ameliorates postural hypotension caused by diabetic autonomic neuropathy. Diabetes Care, 17: 1356.
50. Kolarski, V., K. Petrova-Shopova, E. Vasileva, D. Petrova and S. Nikolov, 1987. Erosive gastritis and gastroduodenitis-clinical, iagnostic and therapeutic studies. Vutr. Boles., 26: 56-59.
51. Chen, M., T.G. Theander, S.B. Christensen, L. Hviid, L. Zhai and A. Kharazmi, 1994. Licochalcone A, a new anti-malarial agent, inhibits in vitro growth of the human malaria parasite Plasmodium falciparum and protects mice from P. yoelii infection. Antimicrob. Agents Chemother., 38: 1470-1475.
52. Christensen, S.B., C. Ming, L. Anderson, U. Hjorne, C.E. Olsen, C. Cornett, T.G. Theander and A. Kharazmi, 1994. An antileishmanial chalcone from Chinese licorice roots. Planta Med., 60: 121-123.
53. Parle, M., D. Dhingra and S.K. Kulkarni, 2004. Memorystrengthening activity of Glycyrrhiza glabra in exteroceptive and interoceptive behavioral models. J. Med. Food., 7: 462-466.
54. Hoes, A.W., D.E. Grobbee, T.M. Peet and J. Lubsen, 1994. Do non-potassium-sparing diuretics increase the risk of sudden cardiac death in hypertensive patients? Recent evidence. Drugs, 47: 711-733.
55. Clyburn, E.B. and D.J. DiPette, 1995. Hypertension induced by drugs and other substances. Semin. Nephrol., 15: 72-86.
56. Olukoga, A. and D. Donaldson, 2000. Liquorice and its health implications. J. R. Soc. Health, 120: 83-89.