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Review Article

PHYTOCHEMICAL CONSTITUENT, PHARMACOLOGICAL ACTIVITIES AND MEDICINAL USES THROUGH THE MILLENIA OF *GLYCYRRHIZA GLABRA* LINN: A REVIEW

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ABSTRACT

Liquoris, *Glycyrrhiza glabra Linn*, is a herb belonging to the family Leguminoceae.It is widely used in ayurvedic formulations. This review article is presented to phytochemical constituents and pharmacological activities, which were performed by widely different methods. It contains glycyrrhizin, which is a saponin glycoside, flavanoides, Carbenoxolone etc. *Glycyrrhiza glabra Linn* possesses different pharmacological activities such as antibacterial, antioxidant, antimalerial, expectorant, anti-tussive, antispasmodic, anti-inflammatory and anti hyper glycemic properties. Various other effects like antiulcer, antiviral, antihapatotoxic, antifungal and herpes simplex have also been studies. These results are very encouraging and indicate this herb should be studies more extensively to confirm these results and reveal other potential therapeutic effects. Medicinal uses of Glycyrrhiza glabra Linn through the millennia as well as drug-botanical interaction, side effect and toxicity also included under this review article.

Keyword: *Glycyrrhiza glabra* Linn, Glycyrrhizin, expectorant, anti-tussive etc.

INTRODUCTION

Glycyrrhiza glabra, also known as licorice and sweetwood, is native to the Mediterranean and certain areas of Asia. Historically, the dried rhizome and root of this plant were employed medicinally by the Egyptian, Chinese, Greek, Indian, and Roman civilizations as an expectorant and carminative. *Glycyrrhiza glabra Linn* is a hardy perennial shrub, attaining a height up to 2.5 m. The leaves are compound, imparipinnate, alternate, having 4-7 pairs of oblong, elliptical or lanceolate leaflets. The flowers are narrow, typically papilionaceous, borne in axillary spikes, lavender to violet in colour. The calyx is short, campanulate, with lanceolate tips and bearing glandular hairs. The fruit is a compressed legume or pod, up to 1.5 cm long, erect, glabrous, somewhat reticulately pitted, and usually contains 3-5 brown, reniform seeds. The taproot is approximately 1.5 cm long and subdivides into 3-5 subsidiary roots, about 1.25 cm long, from which the horizontal woody stolons arise. These may reach 8 m and when dried and cut, together with the root, constitute commercial liquorice. It may be found peeled or unpeeled. The pieces of root break with a fibrous fracture, revealing the yellowish interior with a characteristic odour and sweet taste[1]. In modern medicine, licorice extracts are often used as a flavoring agent to mask bitter taste in preparations, and as an expectorant in cough and cold preparations. 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. The licorice shrub is a member of the pea family and grows in subtropical climates in rich soil to a height of four or five feet. It has oval leaflets, white to purplish flower clusters, and flat pods. Below ground, the licorice plant has an extensive root system with a main taproot and numerous runners. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior[2]. Glycyrrhiza is derived from the ancient Greek term glykos, meaning sweet, and rhiza, meaning root.

CLASSIFICATION

Kingdom : Plantae
Division : Angiospermae
Class : Dicotyledoneae
Order : Rosales
Family : Leguminosae
Genus : Glycyrrhiza
Species : glabra Linn

(A)

(B)

Figure1. (A)Plant of Glycyrrhiza glabra (B) Root

VERNACULAR NAMES

Sanskrit : Yashti-madhuh. Madhuka
Bengali : Jashtimadhu, Jaishbomodhu
Gujarat : Jethimadhu
Hindi : Jothi-madh, Mulhatti
Kannada : Yastimadhuka, atimaddhura
Malayalam: Iratimadhuram
Marathi : Jeshtamadha
Oriya : Jatimadhu
Tamil : Atimaduram

Telugu : Atimadhuranu, Yashtimadhukam
English : Licorice, Liquorice, Sweet wood
Arab : Aslussiesa
Persia : Ausareha mahaka
France : Boisdoux

PHYTOCHEMICAL CONSTITUENTS:

The roots of *Glycyrrhiza glabra Linn* contain glycyrrhizin, which is a saponin glycoside that is 60 times sweeter than cane sugar; Flavonoid rich fractions include liquirtin, isoliquertin liquiritigenin and rhamnoliquirilin and five new flavonoids- glucoliquiritin apioside, prenyllicoflavone A, shinflavanone, shinpterocarpin and 1-methoxyphaseolin[3,4] isolated from dried roots. Isolation and structure determination of licopyranocoumarin, licoarylcoumarin, glisoflavone and new coumarin-GU-12 also isolated. Four new isoprenoid-substituted phenolic constituents – semilicoisoflavone B, 1-methoxyficifolinol, isoangustone A, and licoriphenone isolated from roots[3]. A new prenylated isoflavan derivative, kanzonol R was also isolated[4]. The presence of many volatile components such as pentanol, hexanol, linalool oxide A and B, tetramethyl pyrazine, terpinen-4-ol, α-terpineol, geraniol and others in the roots is reported. Presence of propionic acid, benzoic acid, ethyl linoleate, methyl ethyl ketine, 2,3-butanediol,furfuraldehyde, furfuryl formate, 1-methyl-2-formylpyrrole, trimethylpyrazie,maltol and any other compounds is also isolated from the essential oil[4]. The Indian roots show various 2-methyliso - flavones, and an unusual coumarin, C liquocoumarin, 6 - acetyl- 5, hydroxy- 4 - methyl coumarin. Asparagine is also found[5]. Glycyrrhizin (glycyrrhizic acid; glycyrrhizinate) constitutes 10–25% of licorice root extract and is considered the primary active ingredient. Glycyrrhizin is a saponin compound comprised of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid; enoxolone) conjugated to a disaccharide of glucuronic acid. Both glycyrrhizin and glycyrrhetic acid can exist in the 18α and 18β stereoisomers[6]. As a tribasic acid, glycyrrhizin can form a variety of salts and occurs naturally in licorice root as the calcium and potassium salts. The ammoniated salt of glycyrrhizin, which is manufactured from licorice extracts, is used as a food flavoring agent and specifications for this salt form have been established in the Food Chemicals Codex[7]. Carbenoxolone (18-β glycyrrhetinic acid hydrogen succinate), an analog of glycyrrhetic acid, is used in the treatment of some alimentary tract ulcerative conditions, such as peptic ulcers[8].

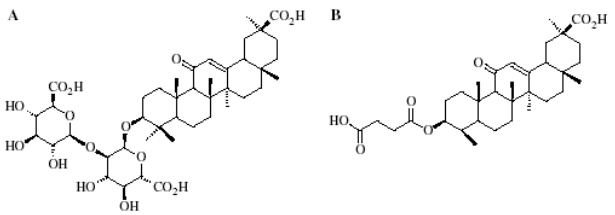

Figure 2: Chemical structure of Glycyrrhizin (A) and Carbenoxolone (B).

Physicochemical Parameters

Total ash (not less than 7%), cid insoluble ash (not less than 2%), Sulfated ash (not less than 10%) Water soluble extractive (not more than 20%), Diluted alcohol-soluble Extractive, (not more than 25%), Moisture (5.25%), Ether extracts (16.85%), Albuminoids (37.00 %(containing nitrogen5.92%)) Soluble carbohydrates (31.00%) Woody fiber (5.05%) [9].

PHARMACOLOGICAL ACTIVITIES:

Although a lot of pharmacological investigations have been carried out based on the ingredients present but a lot more can still be explored, exploited and utilized. A summary of the findings of these studies is presented below.

Anti-bacterial Activity

Shirazi M.H. et al. had studied the in vitro inhibitory effects of G. glabra extract against the growth of Salmonella typhi, S. paratyphi B, Shigella sonnei, S. flexneri and enterotoxigenic E. coli (ETEC E. coli) was investigated using well and disc diffusion method. Salmonella paratyphi B showed no susceptibility to liquorice with concentrations lower than 7.5%, however all tested bacterial strains exhibited susceptibility to high concentration of liquorice[10]. The antibacterial activities of the alcohol, ethyl acetate, acetone and chloroform extracts of 5 plant species were studied by Ates D. A. et al. The extracts of *Glycyrrhiza glabra Linn* (liquorice) (root), was tested in vitro against 13 bacterial species and strains by the agar diffusion method. The extracts of *Glycyrrhiza glabra Linn* roots showed various antibacterial activities (7-11 mm/20 µl inhibition zone) against the microorganisms tested. The alcohol extracts did not inhibit B.subtilis var.niger, B. brevis, E. faecalis, L. monocytogenes, P. aeruginosaand Y. enterocolitica. The ethyl acetate extracts did not inhibit B. subtilis or Y. enterocolitica, and the acetone extracts did not inhibit E. faecalis, L. monocytogenes, P. aeruginosaor Y. enterocolitica. The chloroform extracts showed no inhibition effect against P. aeruginosaor Y. enterocolitica[11]. Alonso J. had studies the glycyrrhizin is habitually used as a vehicle in orally administered products, where it inhibits the growth of some bacteria, as well as dental plaque formation. In regards to its antibacterial action, *in vitro* studies have demonstrated inhibitory effects for licorice aqueous and ethanolic extracts on *Staphylococcus aureus* and *Streptococcus pyogenes* cultures, the first one showing the strongest inhibition with 10-15mm halo diameters[12]. It exhibited antimicrobial activity against both Gram-positive and Gram-negative bacteria by Gupta V K. et al[13].

Antioxidant Activity

Ashawat M.S. et al. had studied the relative reducing activity in terms of antioxidant activity of extracts was determined by using individual extract (15mg) as well as its combination with equal amount of ascorbic acid. The extracts and ascorbic acid were dissolved separately in 1.0 ml of deionised water with phosphate buffer. The mixture was incubated at 50 0C for 20 min. aliquot of trichloroacetate acid were added to the mixture and centrifused at 3000 rpm for 10 min. the upper layer of solution was mixed with distilled water and a freshly prepared FeCl3 solution. The absorbance was measured at 700nm by making 500µg mL extract aliquot. Increased absorbance of the reaction mixture indicated increased antioxidant activity via reducing power with reference to equal amount of standard ascorbic acid[14]. Visavadiya N. P. et al. showed antioxidant property of *Glycyrrhiza glabra Linn* root extracts using *in vitro* models. The dosedependent aqueous and ethanolic extracts demonstrated the scavenging activity against nitric oxide (concentration that caused 50% inhibition of nitric oxide radicals [IC50] =72 and 62.1 µg/ml, respectively), superoxide (IC50=64.2 and 38.4 µg/ml, respectively), hydroxyl (IC50=81.9 and 63 µg/ml, respectively) radicals. Further, both extracts showed strong reducing power and iron-chelating capacities. In the Fe2+/ascorbate system, both extracts were found to inhibit mitochondrial fraction lipid peroxidation. In copper-catalyzed

human serum and low-density lipoprotein oxidation models, both extracts significantly ($P<0.05$) lengthened the lag phase along with a decline in the oxidation rate, conjugated dienes, lipid hydroperoxides and thiobarbituric acid reactive substance formation. So, ethanolic extract of *G. glabra* possess considerable antioxidant activity and protective effect against the human lipoprotein oxidative system[15]. Glycyrrhetic acid is used in cosmetics as a wound healer, anti-inflammatory and decongestant agent; it is applied as emulsion, talcum powder or toothpaste. Its antioxidant properties have been evidenced through its inhibition of lipid peroxidation in rat liver, and its protective action on mitochondrial functions under oxidative stress. A marked decrease in the catalase enzyme activity was detected in the blood of these animals. Thus, licorice-eco extract is helpful to formulate cosmetic products for the protection of skin and hair against oxidative processes[12]. The hydroalcoholic extracts of *Glycyrrhiza glabra Linn* which exhibited different anti-inflammatory activities were evaluated by Herold A et al. for the possible mode of action by studying their antioxidant potential. In the present study we investigated if standardized hydroalcoholic extracts of plants such as *Glycyrrhiza glabra Linn* produced by Hofigal Stock Company could modulate the respiratory burst of human activated neutrophils, as a consequence of their antioxidant capacity[16].

Enzyme Inhibitory Activity

Zuidhoff H. W. et al. had studies licorice methanolic extract has shown *in vitro* inhibition of the tyrosinase enzyme, with 21.2 µg/ml inducing 50% inhibition. Active principles able to inhibit tyrosinase act by modifying the action site of the enzyme, thus reducing its activity. Licorice root extract is known to inhibit tyrosinase. Most of tyrosinase inhibitors are reducing agents, which produce their effects through their reducing capacity. Thus, licorice-eco extract is of great use to formulate cosmetic products with depigmenting activity[17]. Isoliquiritigenin inhibited rat lens aldose-reductase using DL-glyceraldehyde as substrate. Licochalcones A and B, licopyranocoumarin, licoarylcoumarin, licocoumarone, glycyrrhisoflavone and glisoflavone inhibited xanthine oxidase[3].

Anti fungal activity

Hojo A and Sato J. were screening for antifungal compounds from various plant material, licorice (*Glycyrrhiza glabra Linn*) extracts with 80% methanol (oil-based extract of licorice; OEL) was found to have high fungicidal effect against Arthrinium sacchari M001 and Chaetomium funicola M002, and its active compound was identified as glabridin (3-(2',4'- dihydroxyphenyl)-8-dimethylpyranochroman). OEL was effective against not only filamentous fungi but also some bacteria, especially thermo-resistant bacilli such as genera of Bacillus and Alicyclobacillus[18]. Glabridin to be active against both yeast and filamentous fungi and also showed resistance modifying activity against drug resistant mutants of Candida albicans at a minimum inhibitory concentration of 31.25-250 mcg/mL by Fatima A. et al[19]. In regards to its antifungal action, *in vivo* inhibition of *Mycobacterium smegmatis* and *Candida albicans* has been reported, which was attributed to the action of isoflavonoids such as glabridin, glabrol and derivatives of these. A recent study demonstrated the inhibitory effects of a licorice root aqueous extract (CIM=1.56 mg/ml) on cultures of *Candida albicans*, which had been obtained from mouth lesions of 5-months old infants. These results support the use of licoricebased mouthwash to treat candida-induced lesions in HIV patients[12]. Therefore, licorice-eco extract is of great use to formulate cosmetic products with purifying and antiseptic activities.

Anti hyper glycemic Activity

Kalaiarasi P. et al. had studies the antihyperglycemic effect of 18β-glycyrrhetinic acid, aglycone of glycyrrhizin, on streptozotocin-diabetic rats. Diabetes was induced in adult male albino rats of the Wistar strain, weighing 180–200 g, by administration of streptozotocin (40 mg/kg of body weight) intraperitoneally. Diabetic rats showed increase of plasma glucose and glycosylated haemoglobin (HbA1c) and a decrease of plasma insulin and haemoglobin (Hb). Activities of gluconeogenic enzymes such as glucose 6-phosphatase, fructose 1, 6-bisphosphatase increased and glucokinase, glucose 6-phosphate dehydrogenase decreased in the liver along with glycogen. Oral administration of 18β-glycyrrhetinic acid (50, 100, or 200 mg/kg/body weight) or glibenclamide (600 µg/kg/body weight) in 5% dimethyl sulfoxide, for 45 days, prevented the above changes and improved towards normalcy[20, 21].

Anti malarial Activity

The Chinese pharmacopoeia accepts three species of *Glycyrrhiza*, *G. glabra, G. uralensis* and *G. inflata*, as sources of Gan Cao. The chalcone licochalcone A can be isolated from all *Glycyrrhiza* species in different amounts and has been shown to exhibit good antimalarial activity. In *invivo* tests against *P. yoelii* in mice, oral doses of 1000 mg kg-1 resulted in the complete eradication of the malaria parasite and no toxicity was noted[22]. The burden of this disease is getting worse, mainly due to the increasing resistance of *Plasmodium falciparum* against the widely available antimalarial drugs. There is an urgent need for new, more affordable and accessible antimalarial agents possessing original modes of action. Natural products have played a dominant role in the discovery of leads for the development of drugs to treat human diseases. This present review covers most of the recently-published nonalkaloidal natural compounds from plants with antiplasmodial and antimalarial properties, belonging to the classes of terpenes, limonoids, flavonoids, chromones, xanthones, anthraquinones, miscellaneous and related compounds[23]. Licochalcone A inhibited in vitro growth of both chloroquine-susceptible (3D7) and chloroquine-resistant (Ddz) strains of Plasmodium falciparum to same extent in [3H] hypoxanthine uptake assay[3].

Anti-viral and Immunostimulatory effects

Ammonium glycyrrhinate (amide of the glycyrrhetinic acid) showed antiviral activity against vaccinia, herpes simplex 1 and the vesicular stomatitis virus. In chicken embryos, licorice root saponins inhibited the development of type A influenza virus, possibly due to interferon production, as it was found in other studies about the saponin glycyrrhizin. An *in vitro* study evidenced the inhibitory action of glycyrrhizin on HIV cultures. An *in vitro* assay carried out in Germany, demonstrated that glycyrrhizin inhibited the SARS virus (coronavirus, which causes atypical pneumonia), more efficiently than synthetic drugs (ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid). Even when the action mechanism is still unclear, evidences indicate that glycyrrhizin acts by stimulating nitric oxide synthesis, via nitric oxide synthase[12]. Most of the *Glycyrrhiza* phenols reduced the viable cell number of mock-infected and HIV-infected MT-4 cells to comparable extents[24]. *Glycyrrhiza glabra Linn* showed immunostimulatory effects *in vitro* (at 100µg/ml concentration) by increasing TCD69 lymphocytes

production and macrophage production from human granulocytes. Additionally, glycyrrhizin has been reported to be involved in the decrease of IgG and IgA ($P<0.01$), which plays an essential role in hypersensitivity mechanisms. Recent studies carried out with rats, demonstrated that glycyrrhizin inhibited the Arthus phenomenon and the Schwartzman reaction, and that the alcoholic extract of licorice root inhibited type I allergic reactions induced by injection of Ascaris lumbricoides IgE containing serum. Furthermore, *in vivo* assays have shown that licorice root extracts prevented the rise in the amount of immune-complexes associated to some autoimmune conditions, such as systemic lupus erythematosus. It is known that the activation of the immune system slows down with age, which results in decreased cell regeneration. Therefore, licorice-eco extract is helpful to treat aged skin[12]. The immunostimulatory properties of glycyrrhizin were also studies Utsunomiya T. et al. BALB/c mice infected with influenza virus A2 (H2N2) were unable to survive 10 times the mean lethal dose (LD50) of virus[25]. The authors reported that the transplanting of splenic T-cells from glycyrrhizin-treated mice conferred resistance to infected mice that had not been treated with glycyrrhizin. The transplanting of other splenic cell subsets did not improve the survival of infected mice, indicating that glycyrrhizin was a specific inhibitor of the cell-mediated immunological response. The administration of γ-interferon monoclonal antibody to infected mice blocked the anti-viral activity of glycyrrhizin treatment[25]. These results confirm that the anti-viral activity of glycyrrhizin is due to its stimulating of γ- interferon production by T-cells. Glycyrrhizin has also been demonstrated as effective in the treatment of herpes simplex-induced encephalitis in mice[26]. Licorice and glycyrrhizate compounds have long been used in the treatment of chronic viral hepatitis in China and Japan but the possible mechanism of anti-viral activity remains unknown. *In vitro* studies have demonstrated that glycyrrhizin is effective at inhibiting the growth of a host of viruses under culture conditions including pathogenic flaviviruses[27], alphaviruses[28],and herpes simplex virus[29], Studies such as these suggest a direct effect of glycyrrhizin on viral growth, possibly through an inhibition of viral particle to cell membrane binding, replication mechanisms, or through cellular signal transduction mechanisms. *In vivo* and human studies tend to agree with the anti-viral efficacy of glycyrrhizin, but the mechanism of action may be more complex and promote an immune response. Aqueous extract of the root is reported to inhibit the spinach mosaic virus[4].

Memory Enhancing Activity

Dhingra D. et al. had studied to investigate the effects of *Glycyrrhiza glabra Linn* (popularly known as liquorice) on learning and memory in mice. Elevated plus-maze and passive avoidance paradigm were employed to test learning and memory. Three doses (75, 150 and 300 mg/kg p.o.) of aqueous extract of *Glycyrrhiza glabra Linn* were administered for 7 successive days in separate groups of animals. The dose of 150 mg/kg of the aqueous extract of liquorice significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by diazepam (1 mg/kg i.p.) and scopolamine (0.4 mg/kg i.p.). Antiinflammatory and antioxidant properties of liquorice may be contributing favorably to the memory enhancement effect. Since scopolamine-induced amnesia was reversed by liquorice, it is possible that the beneficial effect on learning and memory was due to facilitation of cholinergictransmission in mouse brain. However, further studies are necessitated to identify the exact mechanism of action. In the present investigation, *Glycyrrhiza glabra Linn* has shown promise as a memory enhancing agent in all the laboratory models employed[30].

Expectorant Activity

While the specific mechanism of action remains unknown, *Glycyrrhiza* has been shown to work as effectively as codeine in the throat, decreasing irritations and producing expectorant effects. One proposed explanation is that in the same way that carbenoxolone, a semisynthetic compound derived Murray from *Glycyrrhiza*, is able to stimulate gastric mucus secretion, it is also able to stimulate tracheal mucus secretions and hence produce demulcent and expectorant effects[31]. Licorice is a helpful remedy for coughs as it facilitates the movement of mucus from the respiratory tract[32].

Spasmolytic Activity

Mills S. Y. et al. showed liquiritin present in the roots of *Glycyrrhiza* is inactive as an antispasmodic. However when hydrolysed by heat and converted to isoliquiritigenin, it was shown to exhibit strong spasmolytic activity[33].

Antiallergic activity

Glycyrrhiza glabra Linn (Glycyrrhizin, 18β glycyrrhetinic acid and Liquiritigenin) have antiallergic activity, which can relive IgE – induced allergic diseases such as dermatitis and asthma[34].

Anti Ulcer Activity

Pepticare, a herbomineral formulation of the Ayurveda medicine consisting of the herbal drugs: *Glycyrrhiza glabra Linn*, *Emblica officinalis* and *Tinospora cordifolia*, was tested for its antiulcer and anti-oxidant activity in rats. Bafna PA were studied that effects of various doses (125, 250, 500 and 1000mg/kg, p.o.) of Pepticare on gastric secretion and gastric ulcers in pylorusligation and on ethanol-induced gastric mucosal injury in rats. The reduction in ulcer index in both the models along with the reduction in volume and total acidity, and an increase in the pH of gastric fluid in pylorus-ligated rats proved the anti-ulcer activity of Pepticare. It was also found that Pepticare was more potent than G. glabra alone in protecting against pylorus-ligation and ethanol-induced ulcers. The increase in the levels of superoxide dismutase, catalase, reduced glutathione and membrane bound enzymes like Ca2+ ATPase, Mg2+ ATPase and Na+ K+ ATPase and decrease in lipid peroxidation in both the models proved the anti-oxidant activity of the formulation. Thus it can be concluded that Pepticare possesses anti-ulcer activity, which can be attributed to its anti-oxidant mechanism of action[35]. Glycyrrhizic acid and its aglycon occurs in the form of the two stereoisomers, 18β (cis) and 18ά (trans). The 18β GA isomer extracted from the root of licorice have anti viral, expectrorant, antitumor and antiulcer effects[36]. Perhaps the most predominant and consistent medicinal use for licorice has been as a demulcent for the digestive system. Indeed, carbenoxolone, a widely used pharmaceutical treatment for gastric ulcers, is a synthetic derivative of glycyrrhetic acid. The anti-ulcer activity of deglycyrrhizinated licorice Bennett A et al[37].was demonstrated using a rat model of aspirin-induced gastric mucosal damage. Male Wistar rats were administered 60mg of aspirin by gastric tube and divided into four different treatment groups of saline (control), 50mg deglycyrrhizinated licorice, 5mg/kg cimetidine, or both deglycyrrhizinated licorice and cimetidine. Four hours after treatment the stomachs were removed and gastric mucosal damage was scored. The anti-ulcer effects of licorice extract may be due

to reduced gastric secretions caused by an inhibition of gastrin release. The results from clinical studies evaluating the efficacy of deglycyrrhizinated licorice suggest that several components exist in the extracts which promote gastric healing, although inconsistencies are apparent between these studies. Botanical compounds with anti-ulcer activity include flavonoids (i.e. quercetin, naringin, silymarin, anthocyanosides, sophoradin derivatives) saponins (i.e. from *Panax japonicus* and *Kochia scoparia*), tannins (i.e. from *Linderae umbellatae*), gums and mucilages (i.e. gum guar and myrrh). Among herbal drugs, liquorice, aloe gel and capsicum (chilli) have been used extensively and their clinical efficacy documented[38, 39].

Hepatoprotective Effecets

Watari N. studied that in animal and human models glycyrrhetic acid plays a protective role when liver cells are challenged. It decreases inflammatory states by reducing cytokines like tumor necrosis factor-alpha and increasing protective antioxidants like heme oxygenase-1. These shielded tissues release fewer markers of liver damage, repairing and regenerating themselves more rapidly. The hepatoprotective properties of glycyrrhizin in hepatotoxin treated mice. In this study, animals were administered the hepatic carcinogen 3'- methyl-4-dimethylaminoazobenzene in the diet and injected 1mg glycyrrhizin twice per week for a period of three months. Animals treated with glycyrrhizin had a reduced incidence of hepatic cells showing morphological evidence of injury, including degenerated mitochondria, increased number of lysosomes, atrophied Golgi apparatus, pseudonuclear inclusions and increased mitotic cells[40]. Glycyrrhizin, at concentrations of 25–200 μg/ml, was found to significantly inhibit the CCl4- induced release of AST and LDH. The authors speculated that this function was due to an alteration of membrane fluidity by the glycyrrhizin, or perhaps an inhibition of CCl4 induced membrane lipid peroxidation. Glycyrrhizin exhibited no significant suppressive activity of free radical generation, whereas 18β-glycyrrhetic acid inhibited this activity at 1mg/ml. Hepatoprotective mechanism of glycyrrhizic acid is due to its aglycone, 18β-glycyrrhetic acid, which inhibits both free radical generation as well as lipid peroxidation. The *in vivo* protection of glycyrrhizin against CCl4- induced hepatotoxicity was more recently illustrated by Jeong[41]. Extracts of herbal plants *Glycyrrhiza glabra Linn* (GL), they showed a novel hepatoprotective effects against diclofenac – induced hepatotoxicity in rats[42]. Glycyrrhizin reduced the mortality of acetaminophen overdosed mice more effectively, attenuate acetaminophen-induced hepatotoxicity, and reduced the number and area of γ-GT positive foci, thus protecting liver function was illustrated by Xu-ying[43].

Anticonvulsant

The anticonvulsant activity of ethanolic extract of roots and rhizomes of *Glycyrrhiza glabra Linn* (10, 30, 100 and 500 mg/kg, *i.p.*) in mice was assessed using maximum electroshock seizure (MES) test and pentylenetetrazol (PTZ) using albino mice. The lithium-pilocarpine model of status epileptics was also used by Shirish DA et al. to assess the anticonvulsant activity in rats. The ethanolic extract of *G. glabra* did not reduce the duration of tonic hind leg extension in the MES test even in the dose of 500 mg/kg. However, the extract significantly and dose dependently delayed the onset of clonic convulsions induced by pentylenetetrazol. The dose of 100 mg/kg afforded protection to all animals. The extract also protected rats against seizures induced by lithium-pilocarpine[44].

Antiinflammatory

Glycyrrhizin has long demonstrated its strengthening action on hydrocortisone anti-inflammatory activity in rats. Alonso showed anti-inflammatory activity of aglycone (glycyrrhetic acid) with 1/8 potency as compared to cortisol; this activity reaches 1/5 potency, if glycyrrhetic acid is administered as sodium hemisuccinate (whose chemical structure is identical to carbenoxolone). Other flavonoid components of licorice root, such as liquiritoside, have also shown *in vitro* anti inflammatory activity. The activity of 18-α-glycyrrhetic acid was found to be stronger than that of its β isomer, and similar to that of glucocorticoids. Both glycyrrhizin and its aglycone have mineralocorticoid effects due to the inhibition of hepatic D'-5-β-reductase. The modifications that glycyrrhetic acid and hydrocortisone produce on the activity of certain enzymes have been correlated with their anti-arthritis effects, due to the structural similarity of both compounds and their activity at the suprarenal level. Both glycyrrhizic acid and its aglycone (glycyrrhetic acid) inhibited leukocyte migration towards swollen areas in animal models. Glycyrrhizin inhibited activated peritoneal macrophages, phospholipase A activity and prostaglandin E2 synthesis. Liquiritoside demonstrated experimental inhibition of cyclooxygenase, lipooxygenase and platelet peroxidase. In animal assays, glyderinine (a glycyrrhizic acid derivative) showed stronger antipyretic, analgesic and anti-inflammatory activities than hydrocortisone and amidopyrine; unlike other anti-inflammatory drugs, it did not damage the gastroduodenal mucosa. Applied as an ointment, it showed very good penetration in the skin and tolerability. In this regard, a 0.1% glycyrrhizin concentration in a gel or an emulsion, increased penetration of externally applied Diclofenac sodium[12]. Glycyrrhetinic acid inhibits the enzyme 11-betahydroxy steroid dehydrogenase, which is responsible for converting cortisol, the active form into its inactive metabolites. Thus inhibition of the enzyme by glycyrrhetinic acid significantly increases the levels of cortisol and also stimulation of the glucocorticoid receptors. This in turn potentiates the action of hydrocortisone, the main glucocorticoid secreted by the adrenal cortex. Hydrocortisone is associated with, and accounts for glyrrhizin and glycyrrhetinic acid's antiinflammatory[45].

Anti-carcinogenic Effects

Wang ZY Studied to evaluate the potential anti-carcinogenic effects of licorice extract and glycyrrhizate compounds[46,7]. The *in vitro* anti-mutagenic properties of triterpene compounds, such as glycyrrhizin, have been well documented, although the mechanism of this action is still poorly understood. An early report on the anti-mutagenic effects of glycyrrhizin and glycyrrhetic acid demonstrated, using a modified Ames test, that both of these compounds inhibited the mutagenicities of 3-amino-1-methyl-5*H*-pyrido[2,3-*b*]indol (Trp-p-2), 2-acetyl aminofluorene, and benzo(α)pyrene, in the presence S9 fraction hepatic enzymes[47]. When the assay was repeated using mutagens not requiring metabolic activation, such as methyl glyoxal, glyceraldehyde and glucose pyrolysate, glycyrrhizin inhibited the number of induced *Salmonella typhimurium* TA98 revertants, whereas glycyrrhetic acid promoted the number of revertants per plate. Ikken Y et al. speculate that glycyrrhetic acid may act by inhibiting the metabolic activation of some mutagens. Both licorice extract and glycyrrhizin inhibited the mutagenic effects of Trp-p-1 and Trp-p-2 in *S. typhimurium* TA98 whereas licorice extract exerted a moderate to strong antimutagenic effect against several *N*-nitrosamine

mutagens[48]. Licorice extract and glycyrrhizin were also effective at inhibiting the mutagenic effects of metabolically pre-activated Trp-p-1, suggesting that the antimutagenic effects are not due solely to the inhibition of the activating enzymes. In order to elucidate the inhibition mechanism of chemically induced mutagenicity by licorice extract, glycyrrhizin, 18β and 18α glycyrrhetic acid. Only the licorice extract was antimutagenic towards ribose–lysine, suggesting that a nonglycyrrhizin compound is the active antimutagenic component of this extract. The antimutagenic activity of licorice extract was confirmed in the *rec*-assay in *Bacillus subtilis* strain M45, which is deficient in the genetic recombination function. However, licorice extract was not antimutagenic to the activities of the frame shift mutagens 9-aminoacridine or acriflavine, suggesting specificity in its mechanism of action. These results led to the possibility that the root extract might be acting as an antimutagen either by enhancing a DNA repair response or by directly interfering with the mutagen. Glycyrrhetic acid inhibited the growth of B16 cells in a concentration-dependent manner and caused the complete inhibition at concentrations over 10 μg/ml (approx. 21μM), while 200 μg glycyrrhizin/ml (243 μM) inhibited growth by 40%.

Anti-Cariogenic Studies

Several studies have been conducted on the effects of licorice and glycyrrhizin on the growth and acid production of oral bacteria associated with the development of dental caries. Glycyrrhizin could significantly reduce the growth and acid production of *Streptococcus*, *Actinomyces*, and *Bacterionema* species. Licorice powder, ammoniated glycyrrhizin, and monoammonium glycyrrhetic acid competitively reduced the metabolism of sucrose, glucose, and fructose, but were themselves minimally fermentable. In contrast to these results, Segel R et al. reported that neither licorice "juice," nor glycyrrhizin inhibited the growth of seven *Streptococcus mutans* strains. In the presence of sucrose, 0.5–1% glycyrrhizin had no effect on growth, but significantly inhibited bacterial adherence to glass by nearly 100% at the highest concentration tested[49]. Licorice juice had similar anti-adherent properties with concentrations of 5 and 10% providing almost 100% activities. The buffering capacity of glycyrrhizin was not sufficient to affect the fall in pH caused by bacterial sucrose degradation. In an additional study evaluating the mechanism of the anti-adherent property of glycyrrhizin[50], examined by Sela MN et al its effect on bacterial glucosyltransferase activity —an enzyme required in the formation of insoluble glucans required in plaque development. A crude preparation of *S. mutans* glucosyltransferase was significantly inhibited by glycyrrhizin in a concentration-dependent manner. At 12mM glycyrrhizin there was a 50% inhibition of total glucan formation and a 90% inhibition of adhered glucans formation. Although glycyrrhizin was able to inhibit the activity of the soluble glucan-forming glucosyltransferase, the IC50 was 36mM. The authors concluded that inhibition of bacterial glucosyltransferase activity may be a mechanism by which glycyrrhizin inhibits oral bacterial adherence, but that additional enzyme systems may also be affected.

Miscellaneous Studies

Glycyrrhizin is classified as a saponin compound, and this property has been tested to determine its interaction with cellular membranes of erythrocytes and hepatic lysosomal preparations. Glycyrrhizin was found to protect erythrocytes against the hemolysis induced by other saponin compounds including digitonin, excin, tomatin, and saponin A[51]. The effect of glycyrrhizin was concentration-dependent but it was only effective at preventing hemolysis at concentrations approximately 400 times greater than the hemolysin. Glycyrrhizin was found to be as efficacious against the sapogenins digitogenin, tomatidine, and sapogenin A, indicating that its mechanism of action is not the result of the inhibition of membrane glycosidases of erythrocytes. The possibility remains that glycyrrhizin prevents access of hemolysin to its receptor, or alters membrane fluidic dynamics at these high concentrations. To test this possibility, Nakagawa K investigated the effects of glycyrrhizin on the release and activity of acid phosphatases from hepatic lysosomal preparations. Both glycyrrhizin and 18β glycyrrhetic acid attenuated acid phosphatase activity, but did not affect β-*N*-acetylglucosaminidase activity. The reduction of lysosomal acid phosphatase activity was due to its release from the lysosomes rather than a direct inhibition of the enzyme suggesting an alteration in membrane fluidity[52].

MEDICINAL USES OF LICORICE THROUGH THE MILLENNIA:

Licorice continues to be used as a pharmacological agent as well as an ingredient in tobacco and confectionery throughout countries in the East and West. Studies over the past 50 years have yielded information which has prompted new interest in the pharmacological and physiological effects of this plant. This research has revealed that the chemical structure of one of the principle agents in the root of the licorice plant is a glycoside of a triterpene called glycyrrhetinic acid. Originally its structure and activity were thought to be similar to adrenal steroid hormones such as aldosterone and cortisol, since ingestion of licorice mimicked hyperaldosteronism and was suggested as a treatment for Addison's disease[53,54]. It is now thought that the presence of intact adrenals is required for licorice ingestion to cause sodium retention leading to subsequent hypertension[55]. This recent insight into the effects of licorice on adrenal function and steroid metabolism has led us to examine the uses of licorice historically and culturally in order to arrive at a better understanding of its many possible functions. In realizing how widely licorice has been used in many societies throughout the millenia, not only can we gain insight into its possible medicinal functions, but we can also learn to what extent licorice may pose as a potential threat to the individual. Further-more, it is fascinating to account for some of its uses in the past in view of our present knowledge of its biochemical structure and physiological effects. The licorice with which we are familiar in the Western part of the world comes from the plant *Glycyrrhiza glabra.* The plant is indigenous to Greece, Turkey, Spain, Iraq, Caucasian and Transcaspian Russia, and northern China[56]. According to Lucas in his book entitled *Nature's Medicines*[56], the earliest evidence we have of the employment of licorice comes from the stores of licorice found in the ancient tombs of Egyptian pharaohs, including that found in the 3000-year old tomb of King Tut. Lucas claims that this was an Egyptian ritual which allowed the spirits of the kings to prepare a sweet drink called *mai sus* in the afterlife. An iced drink, *Mai sus,* is still consumed today by the Egyptians and is made available by 'itinerant venders'[56, 57]. References to licorice have also been made on Assyrian tablets dating back to the second or third millenia B.C. Other accounts date back to ancient Greece and Rome where licorice was commonly used as a tonic and cold remedy, as well as for other purposes less familiar to us. In the fourth century B.C., the Greek botanist and contemporary of Aristotle,

Theophrastus (ca. 370-288/5 B.C.), refers to licorice as 'Scythian root' or 'sweet root' in his *Enquiry into Plants*[58]. This ancient herbalist, also interested in the history of licorice, claims that the Scythians, whose civilization was established early in the first millennium B.C., used licorice and mare's milk cheese and could subsequently abstain from drinking for 11 or 12 days[58]. Theophrastus also mentions that licorice is useful in treating asthma when administered in honey. The root heals wounds[58]. In the first century B.C., Pliny the Elder also makes mention of the various functions of licorice root. Pliny alleges that licorice in the form of a lozenge clears the voice and postpones hunger and thirst[59,60]. He agrees with Theophrastus, suggesting that cheese 'made of mare's milk and licorice' in 'small quantities' will assuage these symptoms of hunger and thirst 7f. Furthermore, according to Pliny, the root of the licorice plant was appropriately referred to as atiipsos [g] by the ancients. a word which can be translated as 'not suffering from or causing thirst'. Pliny states that, because of its association with thirst, licorice has served as a remedy for patients suffering from dropsy. He continues, 'it is for this reason that the powder of it is often sprinkled on ulcerous sores of the mouth and films on the eyes; it heals too excrescences of the bladder, Pains in the kidneys and ulcerous sores of the genitals.' [60,61]. As reported by Lucas in *Nuture'.y Medicines*[56], the ancient Hindus believed that licorice increased sexual vigor and they prepared the concoction as a beverage, mixing the licorice with milk and sugar. The ancient Chinese thought that licorice root gave them strength and endurance, and they prepared it most often in tea for medicinal purposes. According to W.T. Fernie in his *Herbal Sinzples (1897),* the Chinese found that the licorice root contains 'tonic. Alterative (bringing about slow gradual change) and expectorant properties' and the root serve as 'a mild aperient'; Fernie also indicates that the Chinese ascribe rejuvenating and nutritive qualities. Early popular books on herbal medicines, both English and American, provide some of the most thorough accounts of Western uses of *Glycyrrhiza glabra,* having been native to warmer European countries, is recorded as having been cultivated in England for the first time in 1562. Fernie, unlike his predecessors, presents a description of the competition of the licorice root: a sugar called glycyrrhizine (a demulcent starch), asparagin, phosphate and malate of lime and magnesia, albumen, and woody fibre. Fernie regrets to say that 'liquorice is commonly adulterated with potato starch. Miller's sweepings mixed with sugar, and any kind of rubbish'[62]. He suggests that the sugar of licorice is safe for diabetics and claims that licorice in porter and stout supposedly both adds sweeteness, thickeness, and blackness to drinks and simultaneously prevents their fermenting. Fernie also mentions the employment of black licorice in tobacco. both chewing and smoking. Nicholas Culpepper[63], one of the most popular and enduring English herbalists of the seventeenth and eighteenth centuries, as well as the early nineteenth century American herbalists. Samuel Stearns[64] and John Monroe[65], give almost identical accounts of the pharmacological attributes of the licorice root. They assert, as do other herbalists and historians, that the root serves as an emollient, demulcent, attenuant, expectorant, detergent. And a diuretic. The root 'abates thirst in dropsies', 'helps defluctions of the breast', 'softens acrimonious humours'. ' temperates salt'. 'allays the heat of the blood', promotes urine, and thickens the sanguinary fluid, when too thin'. Moreover, the root is 'good for pleurisy, gravel, dysury and intense pain'. Earlier accounts by William Langham[66] and Robert Love11[67] reveal that as far back as the early seventeenth century licorice was believed to alleviate sickness and pain when administered in combinations with other food. Most interesting are their recipes for internal sores and ulcers, including the 'running of sores' inside the ears; Lovell, in rather vague terms claims that licorice root, when applied (perhaps as an ointment), remedies 'green wounds'. Furthermore, licorice bread is said to assuage the 'heat of stomach and mouth', a consequence of thirst and dehydration[67]. *Glycyrrhiza glabra* was probably introduced to the Native Americans by early English settlers[56] and consequently adopted into their traditional pharmacopoeia. Diabetes, which affects at least 25% of the adult population, has been commonly treated with *Glycyrrhiza glabra.* The medicine man will prescribe licorice to 'keep sugar down', a practice which demonstrates that the inherent sweetness of licorice is thought to reflect the plant' medicinal function to treat diseases caused by high sugar levels[68]. As in the Western cultures previously described, ***Glycyrrhiza glabra*** continues to be employed by non-Western cultures for treatment of similar ailments. In India licorice is believed to ease thirst in an antitussive and a demulcent, and it serves as a treatment for influenza, uterine complaints, and biliousness[69]. The Chinese and their Far Eastern neighbors have traditionally used licorice most extensively. While the typical European licorice or 'Spanish licorice' as it is sometimes called, comes from the plant ***Glycyrrhiza glabra,*** the licorice used in the Far East comes from the plant ***Glycyrrhiza uralensis.*** Indigenous to Northern China, Mongolia, and Siberia, it is referred to as 'gan cao' (or 'kan ts'ao') by the Chinese[70, 71]. The root is considered to benefit all organs of the body. The general composition of ***Glycyrrhiza uralensis*** includes 66.14% glycerrhizin, glycyrramarin, liquiritin, iso-liquiritin, mannitol, glucose, sucrose, and starch[71]. In modern Chinese medicine, many medicinal remedies contain licorice as an ingredient. Extracts of licorice root are distributed easily within the body, where it is broken down and absorbed slowly [72,73]. Chinese herbal medicine instructs that again ***Glycyrrhiza uralensis*** be employed as a tonic, an antipyretic, an antidote (e.g. counteracting mushroom poisoning), a demulcent to the lungs, an expectorant, an analgesic, to soothe sore throats and coughs, to treat asthma, and to alleviate toxic abscesses as well as acute abdominal pains. In addition, ***Glycyrrhiza uralensis*** is used in Chinese recipes for food treating acne and pimples, frost bite, heat stroke, and nervous disorders such as hysteria, irritability, epilepsy, manic depression, violent temper, etc., and curiously, hypertension. It should be noted that while licorice is used in recipes which treat symptoms of hypertension related to nervous disorders and stress, licorice is not present specifically in the recipe for high blood pressure that is discussed in ***Chinese Herbal Medicine*** by Reid[71]. Licorice continues to serve as a flavoring agent, sweetening the bitter taste of many drugs, as filler for pills, and as an 'essential ingredient in ointments for treating skin diseases'. Licorice also slows and prolongs the effects of strong tonic medicines. Because the Chinese recognize the capacity of licorice to imitate the activity of adrenocortical hormones, they use licorice to treat Addison's disease[70]. Most common is the employment of licorice 'as an emollient for duodenal and peptic ulcers'. Until approximately ten years ago when cimetidine was marketed, licorice was a primary antipeptic ulcer drug[72]. Licorice extract is also used as a flavoring agent in soy sauce in both China and Japan. Very large quantities of ***Glycyrrhiza glabra,*** both root and extract

(greater than 40,000.000 lbs. per year were reported for 1952[56], are imported to the U.S.A. from Iraq, Turkey, Russia, Syria, Italy, Spain, and East Africa. The largest portion of licorice extract imported to the United States is employed by tobacco industries as a conditioning and flavoring agent[56 ,57]. Because licorice cures tobacco, it has been used for approximately 100 years in cigars, pipe tobacco, cigarettes and chewing tobacco and is even present in snuff[57, 74]. We are most familiar with the role of licorice in the confectionery industry in Western countries where varieties of licorice candies are prepared by a simple process. Licorice is extracted from the root with water and vacuum concentrated. It is from this 'block juice' that all licorice candies are made. Once licorice juice is combined with sugar, corn syrup, and flour. it forms a paste which can be moulded into any desirable shape. However, many licorice candies in the United States now contain anethole, a major constituent in the aniseed plant, as a substitute flavoring agent for licorice. Aside from its universal role as an expectorant and demulcent in many familiar over-the-counter remedies, licorice root has been featured in powdered form as filler for pills in the U.S.A. as well, both enhancing the consistency of the pill and coating the surface. Some commercial hand. body, and skin lotions contain licorice as an ingredient. Furthermore, it is also used in ointments as a remedy for various skin disorders since glucocorticoid action is potentiated by either glycyrrhizin or glycyrrhetinic acid[57,75]. Other possible pharmacological actions of licorice have been evaluated by the early work performed by Costello and Lynn[76] in 1949 who extracted estrogenic constituents from ***Glycyrrhiza glabra;*** they suggested that this plant might be a source of low-cost estrogens to be used for medicinal purposes in treating hormone imbalances associated with menstruation. However, in contrast, the glycoside of glycyrrhetinic acid has also been shown to possess anti-estrogenic activity, inhibiting the effect of estradiol on uterine growth in ovariectomized animals[77]. Since 1906, licorice extract residues have been used successfully to extinguish fires in a fire-foam suspension[57]. For similar reasons, licorice as an emulsifier has been used in the United Kingdom to create foam in drinks and alcoholic beverages[56, 57]. Licorice by-products have also been used as an excellent compost medium for mushrooms, the reasons for which still remain unknown[56, 57]. Beginning in the late 1940s and extending well into the 1950s. There was a growing interest in the metabolic activity of glycyrrhetinic acid. Investigations into various side-effects of licorice treatment of adrenal and electrolyte disorders, such as Addison's disease, peptic ulcers and rheumatoid arthritis, showed that licorice can produce a syndrome mimicking h~eraldosteronism, which may lead to subsequent hypertension. As mentioned before, licorice extracts have been commonly used and still continue to be used in many European countries to relieve gastric and duodenal ulcers, supposedly as an inhibitor of gastric secretion. The anti-peptic ulcer drug carboxolone sodium, developed in the early 1960s by a team from Biorex Laboratories, London, headed by Dr. S. Gottfried and L. Baxendale, is a succinate derivative of glycyrrhetinic acid which is the major chemical triterpenoid constituent in licorice[78]. This drug evolved from the widespread usage of licorice in Holland and other European countries throughout the middle Ages and earlier for the treatment of peptic ulcers. Save for the United States, which was concerned with the possible blood-pressure elevating properties of the drug, carbenoxolone sodium has been extensively employed for the purpose of alleviating ulcers throughout the world. Interestingly, as early as 1948, Revers[79] reported his observations that approximately one out of five patients who were treated with licorice paste for peptic ulcers developed edema. Molhuysen et al. (1950) also noticed the side effects associated with the use of licorice which generally resulted in the retention of water, sodium, and chloride, and were accompanied by increased excretion of potassium[80]. They also concluded that licorice extracts exhibit effects similar to that of large injections of deoxycorticosterone (DOC). but the effects are more persistent, even after the drug has been discontinued until a salt-free diet is given. However, they did not observe a positive response, but rather a slight negative response, to licorice extract in a patient suffering from Addison's disease who did not respond to ACTH. These observations inspired Card et al. (1953) to examine further the effects of licorice on normal subjects as well as on patients who suffered from Addison's disease, and to investigate the DOC-like activity of licorice[81]. Their results differed from those of the previous examiners, and they concluded that licorice appeared to have positive results in reversing the effects of Addison's disease. In 1957, Kumagai et al. [82]were encouraged by the observations made by Molhuysen et al.[80] concerning the effect of licorice extract on rheumatoid arthritis. They established in their report that when glycyrrhizine is administered along with ACTH or cortisone, favorable effects of glycyrrhizine on rheumatoid arthritis are achieved. Without the concomitant use of glucocorticoids or equivalents such as cortisone or ACTH, respectively, licorice has little effect on acute rheumatic episodes or electrolyte balance. The product of these and other investigations culminated in the realization that an intact adrenal gland was required for many of the effects of licorice; the demonstration that carbenoxolone and glycyrrhetinic acid can themselves bind to mineralocorticoid receptors at very high levels[83, 84]suggests that such doses are rarely achieved therapeutically, and that the main effect of licorice is to potentiate rather than mimic endogenous steroids. There has been a variety of other studies on the pharmacological effects of licorice. Yamamoto et al. [85], for example, discovered that glycyrrhizin promotes the biosynthesis of cholesterol in rat liver. The excretion of cholesterol in the liver appears to be proportional to a subsequent decrease of cholesterol levels in the blood. These findings are cited by H. Wagner and P. Wolff[85]. Morris, Davis, and Latif[86], and Guthrie et al.[87] have recently demonstrated the potential dangers of licorice used as a flavoring agent in many brands of chewing tobacco in the United States. Because glycoside derivatives of glycyrrhetinic acid induce symptoms of mineralocorticoid excess through the inhibition of llp-hydroxysteroid dehydrogenase (llfi-OHSD). the continual use of chewing tobacco can result in hypertension, sodium retention, and hypokalemia. In their report, Morris et al.[86] claim that glycyrrhetinic acid present as its glycoside in chewing tobacco inhibits hepatic A4.5 p-steroid-reductase in addition to lip-OHSD, thereby preventing the reduction of the A ring of steroids, a major metabolic pathway for the inactivation of both glucocorticoids and mineralocorticoids. Hypertensive children with the syndrome of apparent mineralocorticoid excess (AME) lack ll/%hydroxysteroid dehydrogenase (1 l/%OHSD) enzyme activity, a condition resulting in reduced peripheral metabolism of cortisol. Stewart and Edwards et al[55, 88]. realized that licorice ingestion causes biological consequences and changes in the pathways of adrenal steroid metabolism similar to those demonstrated by Ulick, New and

co-workers[89, 90, 91] in these children with the syndrome of AME. Glycyrrhetinic acid, present as its glycoside in licorice has been shown to be a potent competitive inhibitor of ll/%OHSD[91]. Their experiments together with those of Funder et al. suggest[89,-92] that lowered lip-OHSD activity results in higher peripheral and intrarenal concentrations of corticosterone in experimental animals and cortisol in humans, which may then interact with mineralocorticoid (MC) receptors and promote Na+ reabsorption. However, other processes may also be involved. Souness and Morris[93] reported that indeed acute pretreatment of adrenalectomized male rats with carbenoxolone sodium, the water-soluble succinate derivative of glycyrrhetinic acid, caused both cortisol and corticosterone to display significant mineralocorticoid-like activity, particularly Nat retention. They also showed that the same dosage of carbenoxolone sodium, which does not affect Na+ or Kt excretion on its own, amplifies the antinatriuretic but not the kaliuretic activity of the two mineralocorticoids, aldosterone and lldeoxycorticosterone[94]. The latter steroid is particularly significant since it does not possess a hydroxyl group at the c-11 position in the steroid nucleus and therefore is not a substrate for the enzyme 11/3-OHSD. Glycyrrhetinic acid has also been shown by Latif et al. [95] to be a potent inhibitor of the important steroid metabolizing enzyme, S/3-reductase and also as an inhibitor of 3P-hydroxysteroid dehydrogenase, to a lesser extent, It does not inhibit Sa-reductase. Thus licorice derivatives reroute the metabolism of aldosterone, deoxycorticosterone. and glucocorticoids resulting in the accumulation of unmetabolized hormones and their corresponding Sa-dihydro and 3a,5atetrahydro derivatives (as in children with the syndrome of AME). Thus after almost half a century, it is no wonder that there has been a resurgence of interest in licorice, since many of the properties ascribed to this plant by several cultures throughout history now need to be re-examined in another light. Who knows what new insight into a host of medicinal cures and clinical problems may once more be focussed around extracts of ***Glycyrrhiza giabra.***

Drug-Botanical Interactions

There is an increased likelihood of cardiac arrhythmias, particularly in individuals with ischemic heart disease, when licorice is used in conjunction with digoxin[96]. Estrogen-based oral contraceptives may enhance the mineralocorticoid side effects of licorice in susceptible individuals. This may be due in part to estrogens reacting with mineralocorticoid receptors or inhibition of 11-hydroxysteroid dehydrogenase[97]. Hypokalemia, commonly associated with metabolic acidosis, may co-present with essential benign hypertension in patients using diuretics and licorice simultaneously[98].

Side Effects and Toxicity

One of the most commonly reported side effects with licorice supplementation is elevated blood pressure. This is thought to be due to the effect of licorice on the renin-angiotensin-aldosterone system. It is suggested licorice saponins are capable of potentiating aldosterone action while binding to mineralocorticoid receptors in the kidneys. The phenomenonis known as "pseudoaldosteronism." In addition to hypertension, patients may experience hypokalemia (potassium loss) and sodium retention, resulting in edema. All symptoms usually disappear with discontinuation of therapy[99].Many studies report no side effects during the course of treatment[100, 101].Generally, the onset and severity of symptoms depend on the dose and duration of licorice intake, as well as individual susceptibility. Patients with delayed gastrointestinal transit time may be more susceptible to these side effects, due to enterohepatic cycling and reabsorption of licorice metabolites. The amount of licorice ingested daily by patients with mineralocorticoid excess syndromes appears to vary over a wide range, from as little as 1.5 g daily to as much as 250 g daily[102].

Dosage

Because individual susceptibility to various licorice preparations is vast, it is difficult to predict a dose appropriate for all individuals. Nevertheless, a daily oral intake of 1-10 mg of glycyrrhizin, which corresponds to 1-5 g licorice (2% glycyrrhizin), has been estimated to be a safe dose for most healthy adults[103].Studies of DGL for peptic ulcers employed dosages ranging from 760-2,280 mg DGL daily.

REGULATORY ASSESSMENT OF *GLYCYRRHIZA GLABRA* LINN:

Licorice and licorice derivatives, including ammoniated glycyrrhizin, are affirmed as Generally Recognized as Safe (GRAS) for use in foods by the U.S. FDA (21 CFR 184.1408). This chapter of the regulations includes descriptions, specifications, and maximum use levels (Table 1) for licorice and licorice derivatives.

TABLE 1: US Food and Drug Administration limitations for the use of liquorice and its derivatives in Foods (21 CFR 184.1408c)

S.N.	Food category	Maximum allowable levels in foods as % glycyrrhizin content	Functional use
1.	Baked goods	0.05	Flavor enhacer, flavouring agent
2.	Alcoholic beverages	0.10	Flavor enhacer, flavouring agent, surface active agent
3.	Non alcoholic beverages	0.15	Flavor enhacer, flavouring agent, surface active agent
4.	Chewing gum	1.10	Flavor enhacer, flavouring agent
5.	Hard candy	16.0	Flavor enhacer, flavouring agent
6.	Soft candy	3.10	Flavor enhacer, flavouring agent
7.	Herbs and seasonings	0.15	Flavor enhacer, flavouring agent
8.	Plant protein products	0.15	Flavor enhacer, flavouring agent
9.	Vitamin or mineral dietary Supplements	0.50	Flavor enhacer, flavouring agent
10.	All other foods, except sugar substitutes	0.10	Flavor enhacer, flavouring agent

FDA assumes that glycyrrhizin levels in foods do not pose a health hazard, provided that these foods are not consumed in excess or by individuals who are sensitive to low levels of glycyrrhizin. Licorice extract and its derivatives are also approved for use in some over the counter drugs (21 CFR 310.528; 310.544; 310.545), and licorice is included as a GRAS ingredient in animal feeds (21 CFR 582.10; 582.20). Licorice root, licorice extract, licorice extract powder and glycyrrhizin were included in the Flavor and Extract Manufacturers' Association (FEMA) list of GRAS substances. At the 1977 meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), a decision on an acceptable daily intake (ADI) for licorice was held in abeyance. Glycyrrhizinic acid was evaluated during a more recent JECFA meeting[104]. Although a formal ADI was not established, the committee indicated that consumption of

100mg/day would be unlikely to cause adverse effects in the majority of adults and recognized that a subset of the population may be more susceptible to its physiological effects even at lower doses. Both the Council of Europe and the UK Food Additive and Contaminants Committee consider licorice as a natural plant product intended for use in small quantities as a food additive with the intention that its consumption be limited by the glycyrrhizin levels and not to exceed those occurring naturally in foods[105]. A limit of less than 50 ppm glycyrrhizin was established by these organizations.

CONCLUSION

Glycyrrhizin is used as a traditional medicine, folk remedies, and as a sweetening and flavoring agent. Pharmacological studies have evaluated several of the traditional health from history. Glycyrrhizin is extracted from Licorice (*Glycyrrhiza glabra Linn*) root. The presence of active ingredients other than glycyrrhizin, although other studies have shown it has no beneficial effects. Licorice and glycyrrhizinate compounds have been used as antibacterial, antioxidant, antimalerial, antispasmodic, anti-inflammatory and anti hyper glycemic properties. Various other effects like antidiuretic, antihapatotoxic, antifungal and herpes simplex viral infections such as hepatitis. Although these studies indicated favorable changes in hepatic function, they do not all demonstrate a reduction in viral load. The potential mechanisms of anti-ulcer and anti-viral action of glycyrrhizin are unknown; however, modulation of the immune response seems to be indicated. *Glycyrrhiza glabra* produced by Hofigal Stock Company could modulate the respiratory burst of human activated neutophils. It can be concluded that *Glycyrrhiza glabra Linn* can be used as prophylactic as well as therapeutic drug for major body ailments at any age group irrespective of sex.

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