



Glycyrrhiza glabra

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. 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 soothe and heal skin eruptions, such as psoriasis and herpetic lesions.

Description

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.¹ Glycyrrhiza is derived from the ancient Greek term glykos, meaning sweet, and rhiza, meaning root.

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. This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances.² Glycyrrhizin, a triterpenoid compound, accounts for the sweet taste of licorice root. 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.² The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone), and other compounds.³ The isoflavones glabridin and hispaglabridins A and B have significant antioxidant activity,⁴ and both glabridin and glabrene possess estrogen-like activity.⁵

Pharmacokinetics

After oral administration of licorice in humans, the main constituent, glycyrrhizic acid, is hydrolyzed to glycyrrhetic acid by intestinal bacteria possessing a specialized β -glucuronidase.^{6,7} Glycyrrhetic acid is 200-1,000 times more potent an inhibitor of 11- β -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.⁸ 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.³

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 A⁹ and C,^{10,11} herpes zoster,¹² HIV,^{13,14} *Herpes simplex*,^{15,16} and CMV.¹⁷

Glycyrrhizin and its metabolites inhibit hepatic metabolism of aldosterone and suppress 5- β -reductase, 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.¹⁸

Licorice constituents also exhibit steroid-like 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.^{19,20}



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.^{21,22} *In vitro* studies have demonstrated licorice isoflavones, hispaglabridin A and B, inhibit Fe³⁺-induced mitochondrial lipid peroxidation in rat liver cells.²³ Other research indicates glycyrrhizin lowers lipid peroxide values in animal models of liver injury caused by ischemia reperfusion.²⁴ Licorice constituents also exhibit hepatoprotective activity by lowering serum liver enzyme levels and improving tissue pathology in hepatitis patients.²⁵

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,²⁶ liver,²⁷ and skin^{28,29} cancer.

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.^{30,31}

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. In two clinical trials, SNMC has been shown to significantly lower aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyltransferase (GGT) concentrations, while simultaneously ameliorating histologic evidence of necrosis and inflammatory lesions in the liver.^{25,32} In recent years, several studies have been performed supporting this action.^{10,11} Presently, interferon (IFN) therapy is a predominant treatment for chronic hepatitis. Because its efficacy is limited, an alternative treatment is desirable. SNMC has profound effects on the suppression of liver inflammation and is effective in improving chronic hepatitis and liver cirrhosis. It also appears to have considerably fewer side effects than IFN.³³

In a double-blind, randomized, placebo-controlled trial investigating IV infusions of SNMC, short-term efficacy of licorice was confirmed with regard to ALT levels. The study showed the need for daily IV administration of SNMC, which may be impractical for patients. The study also demonstrated that after cessation of therapy the ALT-decreasing effect of licorice disappeared, suggesting the need for long-term administration.²⁵

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. In an open clinical trial, 17 hepatitis C-positive patients with oral lichen planus were given either routine dental care or 40 mL IV glycyrrhizin daily for one month. Among nine patients taking glycyrrhizin, six (66.7%) 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.³⁴

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.¹⁵

Hepatitis A virus (HAV) causes acute hepatitis, a major public health concern in numerous countries. *In vitro* research with glycyrrhizin and a human hepatoma cell line has demonstrated glycyrrhizin completely suppresses the expression of the HAV antigen. 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. Glycyrrhizin also exhibited a five-fold greater cell selectivity than ribavirin in that it was less cytotoxic to the hepatoma cells. These results indicate glycyrrhizin may be a potential therapeutic adjunct in fighting HAV infections.⁹

Studies show licorice and its constituents, specifically glycyrrhizin, have antiviral activity against *Herpes simplex* and are capable of irreversibly inactivating the virus.^{16,35,36} Glycyrrhizin has also been shown to inhibit viral replication and infectivity of HIV,^{14,36} herpes zoster,³⁷ *Varicella zoster*,¹² and CMV.^{17,38,39}

A case report demonstrated a two-percent topical glycyrrhizic acid cream (carbenoxolone sodium) applied six times daily in 12 patients with acute oral herpetic (*Herpes simplex*) infections resolved pain and dysphagia within 24-48 hours of beginning use. Moreover, the accompanying ulceration and lymphadenopathy gradually healed within 24-72 hours.¹⁶

A clinical study of three HIV patients with hemophilia investigated the effect of glycyrrhizin on HIV replication. Glycyrrhizin was administered IV at 400-1600 mg on six separate occasions over a one-month period. The HIV p24 antigen was detected in all patients at the beginning of treatment courses. At the end of one month, p24 antigen levels had either decreased significantly or become negative. Tapering of the glycyrrhizin dose resulted in an immediate elevation in p24 antigen levels, suggesting the higher doses of glycyrrhizin were responsible for decreased antigen levels, probably via suppressed viral replication.¹³

In a clinical trial of 31 patients with severely painful herpes zoster lesions, 12 patients were given 20 mg IV glycyrrhizin on six separate occasions. The remaining 19 patients received either zoster immune gamma-globulin, recombinant interferon- β , or acyclovir. Glycyrrhizin ranked next to acyclovir for pain resolution at the end of one month.³⁷

CMV is the most common cause of congenital and perinatal viral infections throughout the world. It manifests with profound liver dysfunction and poor weight gain. In a series of studies, both oral and IV preparations of licorice (SNMC) were administered to infants with CMV. Liver dysfunction and weight gain improved in nearly all cases compared to groups without treatment.^{17,38,39}

Hepatocellular Carcinoma

In a retrospective study, long-term licorice administration for hepatitis C infection was effective in preventing hepatocellular carcinoma (HCC). Four hundred fifty-three patients diagnosed with hepatitis C were divided into three groups and given either licorice, in the form of SNMC at a dose of 100 mL daily for two months, or other natural treatments, such as vitamin K. The remaining group of patients was treated with a wider number of agents, including SNMC, corticosteroids, and immunosuppressive agents; as a result of the mixed medication regimen, this group was excluded from the study. After 10 years, analysis of the results showed 30/84 patients (35.7%) employing SNMC had normalized AST levels, compared with seven patients (6.4%) not treated with IV SNMC. Moreover, the 10- and 15-year appearance rate of HCC was 7 and 12 percent in the treated group compared to 12 and 25 percent in the untreated group, respectively.⁴⁰ A summary of the literature on HCC and the use of SNMC has confirmed that IV glycyrrhizin not only decreases ALT levels but also improves liver histology and decreases incidence of hepatic cirrhosis.⁴¹

Aphthous Ulcers

In a double-blind, placebo-controlled trial, 24 patients with recurrent aphthous ulcers were randomly allocated to consume 2 g glycyrrhizin (carbenoxolone sodium) in 30 mL of warm water or a

placebo three times daily following meals for four weeks. In contrast to the placebo group, the use of the oral licorice mouthwash significantly reduced the average number of ulcers per day, pain scores, and the development of new ulcers.⁴² In a study of 20 patients instructed to use a DGL mouthwash four times daily, 15 experienced 50-75 percent clinical improvement after only one day, with complete healing of canker sores after three days.⁴³

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. In a double-blind, placebo-controlled study, 70 patients with endoscopically-confirmed gastric or duodenal ulcers were given carbenoxolone sodium 300 mg or placebo daily during the first seven days, followed by 150 mg daily over the next 3-5 weeks. The authors concluded the carbenoxolone group had an increase in pH at the stomach antrum from 1.1 to 6.0, and a reduction in basal and histamine-induced gastric acid secretion at pH 3 and 5. Overall, 70 percent of ulcers in the glycyrrhizin group healed within 3-5 weeks of beginning therapy, compared to 36 percent employing placebo.⁴⁴

Unfortunately, the side effects of licorice limit its potential to be used on a long-term basis for treatment of peptic ulcer disease. A processed form of licorice, DGL (removal of the glycyrrhizin), was produced to eliminate potential adverse effects, including licorice-induced hypertension.⁴⁵ In a double-blind trial, 100 patients were randomly chosen to chew Caved S (DGL plus antacid), 760 mg three times daily, or take cimetidine (Tagamet®) 200 mg three times daily and 400 mg at night for 12 weeks. Endoscopy showed the healing rate between the two regimens was comparable at six (63 percent) and 12 (91 percent) weeks. Although both therapies reduced pain symptom scores in a comparable fashion during the day, cimetidine was more effective during the first two weeks at reducing nighttime pain.⁴⁶ A two-year follow-up trial comparing the two therapies in the prevention of gastric ulcer recurrence noted the out-

comes were similar, with a reported relapse rate of 29 percent (9/31) in the Caved S group and 25 percent (8/32) in the cimetidine group.⁴⁷

Other clinical trials have demonstrated the effectiveness of DGL for gastric ulcer.^{48,49} A four-week clinical trial by Turpie et al demonstrated a statistically significant greater reduction in ulcer size in patients receiving 760 mg of a DGL preparation compared to placebo.⁴⁸

Helicobacter pylori infection is prevalent in individuals with peptic ulcer and is also a known risk factor for gastric cancer.^{50,51} Consequently, an *in vitro* study was performed to investigate the effects of licorice flavonoids on the growth of *H. 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.⁵²

Other studies have demonstrated DGL's benefit in healing duodenal ulcers. In a trial of 40 patients receiving either 3.0 or 4.5 g DGL daily for eight weeks, all patients showed significant improvement after 5-7 days. Patients were assessed for relief from epigastric pain, nausea, vomiting, x-ray of ulcer craters to determine changes in size, and frequency of relapse (return of ulcer pain for two days per week). Patients receiving the higher DGL dose showed the most improvement.⁵³ In a large study of 874 patients with chronic duodenal ulcers, patients received either DGL, cimetidine, or antacids. Ninety-one percent of all ulcers healed, regardless of treatment type. Differences among treatment groups were not statistically significant, but patients in the DGL group experienced the fewest relapses.⁵⁴

Other Therapeutic Considerations

In a trial of 15 normal-weight subjects (seven males, eight females, ages 22-26), 3.5 mg of a commercial licorice preparation daily for two months resulted in a decrease in body fat mass. Plasma renin activity and aldosterone were also suppressed. No changes in body mass index were noted. These results indicate licorice and its constituents can reduce body fat by inhibiting 11- β -hydroxysteroid dehydrogenase in fat cells.⁵⁵

Armanini et al investigated the effect of licorice on serum testosterone in nine healthy women, ages 22-26, using the same licorice preparation as above, and found total serum testosterone decreased from 27.8 (\pm 8.2) to 19.0 (\pm 9.4) ng/dL after one month, and further decreased to 17.5 (\pm 6.4) ng/dL after the second month of therapy. This is likely due to inhibition of 17-hydroxysteroid dehydrogenase, indicating licorice may be of benefit in treating women with hirsutism and polycystic ovary syndrome.⁵⁶

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.²⁶⁻²⁹

Studies also show licorice constituents to be effective in the treatment of eczema,⁵⁷ melasma,⁵⁸ eosinophilic peritonitis,⁵⁹ postural hypotension,⁶⁰ erosive gastritis,⁶¹ and as anti-malarial⁶² and anti-Leishmanial agents.⁶³ 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.⁶⁴

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.⁶⁵

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 β -hydroxysteroid dehydrogenase.⁶⁶

Hypokalemia, commonly associated with metabolic acidosis, may co-present with essential benign hypertension in patients using diuretics and licorice simultaneously.⁶⁷

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 phenomenon

is 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.²⁵ Many studies report no side effects during the course of treatment.^{32,33} 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.⁶⁸

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.⁶⁹ Studies of DGL for peptic ulcers employed dosages ranging from 760-2,280 mg DGL daily.

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