A Review of Plants Used in the Treatment of Liver Disease: Part Two

Scott Luper, ND

Abstract

Botanical medicines have been used traditionally by herbalists and indigenous healers worldwide for the prevention and treatment of liver disease. Clinical research in this century has confirmed the efficacy of several plants in the treatment of liver disease, while basic scientific research has uncovered the mechanisms by which some plants provide their therapeutic effects. This article is Part Two in a review of botanicals used in the treatment of liver disease. *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), and *Glycyrrhiza glabra* (licorice) are reviewed in this installment. *Silybum marianum* (milk thistle) and *Picrorhiza kurroa* (kutkin) were reviewed in Part One.
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Introduction

Treatment options for common liver diseases such as cirrhosis, fatty liver, and chronic hepatitis are problematic. The effectiveness of treatments such as interferon, colchicine, penicillamine, and corticosteroids are inconsistent at best, and the incidence of side-effects profound. All too often the treatment is worse than the disease. Conservative physicians often use a "wait and see approach" for many of their patients, waiting for the time when the disease has progressed to the point to warrant the use of heroic measures. Physicians and patients are in need of effective therapeutic agents with a low incidence of side effects. Several botanical medicines potentially constitute such a group.

In recent years, researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to support liver function and treat diseases of the liver. In most cases, research has borne out the traditional experience and wisdom by discovering the mechanisms and modes of action of these plants, as well as confirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies.

Several hundred plants have been examined for use in a wide variety of liver disorders. Only a handful have been fairly well researched. These plants include *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), and *Glycyrrhiza glabra* (licorice). *Silybum marianum* and *Picrorhiza kurroa* were reviewed in Part One. *Curcuma longa*, *Camellia sinensis*, and *Glycyrrhiza glabra* are reviewed in this article.

Scott Luper, N.D., is Chair of Diagnostics at Southwest College of Naturopathic Medicine, where he teaches and supervises clinical education. Correspondence address: 2140 East Broadway Rd, Tempe, AZ 85282. E-mail:lupers@cwix.com.

Curcuma longa

Description: *Curcuma longa* is a member of the ginger family. It is a tropical plant extensively cultivated in the tropical areas of Asia, and to a lesser extent in Africa. It is the source of the spice turmeric, which is derived from the dried, ground rhizome.

History and Folk Use: Turmeric has a long tradition of use in both the Chinese and Ayurvedic systems of medicine. Traditional applications include the treatment of gastrointestinal colic, flatulence, hemorrhage, hematuria, menstrual difficulties, and jaundice.[1] The anti-inflammatory and hepatoprotective characteristics of turmeric and its constituents have been widely researched.

Active Constituents: The most well-researched component of turmeric is curcumin (diferuloylmethane). Raw turmeric contains from 0.3 to 5.4 percent curcumin.[1] Turmeric also contains 4-14 percent volatile oils, including tumerone, atlantone, and zingiberone. These oils have medicinal properties and may be the primary active component of turmeric in some conditions. Tumeric also contains sugars (28 percent glucose, 12 percent arabinose), proteins, and resins.[1,2]

Pharmacokinetics: Curcumin is poorly absorbed following oral administration. It has been found to be far more active with parenteral administration than with oral administration.[2] This difference between enteral and parenteral activity may be due to several factors. Animal studies have found 40-75 percent of curcumin passes through the digestive system unchanged.[3,4] Much of what is retained is actively metabolized in the intestinal mucosa and liver.[5] Only traces of curcumin were found in the blood after oral administration of a single, two-gram dose in humans, and even larger doses in rats.[2,5]

Oral absorption may be improved by concurrent administration of piperine (from black pepper). Piperine was shown to increase the bioavailability of orally administered curcumin 2,000 percent [5] In dosages used in the referenced study, piperine enhanced the absorption, bioavailability, and serum concentration of curcumin in both rats and humans, with no adverse effects. Based on clinical experience, a typical recommended dose of curcumin is 400-600 mg three times per day.

Toxicity: The toxicity of turmeric has been found to be quite low. No toxic reactions have been reported at standard doses in humans or animals. No mortality or teratogenicity was found at any dose for turmeric, its alcohol extracts, or curcumin in animal studies using rats, mice, guinea pigs, and monkeys.[6] The toxicity of the extract and the oil of a closely related species, *Curcuma kwangsinenis*, was also found to be very low. The oral LD50 is 86.8 ± 12 g crude herb/kg (ethanolic extract) and 1.10 ± 0.08 g/kg (essential oil) [7]

Hepatoprotective Activity: *In vitro* and *in vivo* animal studies provide evidence for the hepatoprotective effects of turmeric: however, there are no human clinical studies. Like silymarin, turmeric has been found to protect animal livers from a variety of hepatotoxic substances, including carbon tetrachloride,[7,8] galactosamine,[9] pentobarbitol, 1-chloro-2,4-dinitrobenzene,[7] 4-hydroxynonenal,[10] and acetaminophen (paracetamol).[11]

The hepatoprotective effects of turmeric may stem from its potent antioxidant effects. Turmeric contains several water- and fat-soluble antioxidant compounds, of which curcumin was found to be the most active.[12,13] The antioxidant effects of other components of turmeric are also significant. A heat-stable protein isolated from the aqueous extract of turmeric was found to be more effective against superoxide than curcumin, and more effective in inhibiting oxidative damage to DNA.[14-16]

Dietary supplementation of turmeric in rats (one percent by weight turmeric for 10 weeks) was found to significantly protect

Curcuma longa

against iron-induced lipid peroxide formation. The activities of superoxide dismutase, catalase, and glutathione peroxidase were higher (by 19, 19, and 20 percent, respectively) in liver homogenates of rats fed the turmeric-containing diet in comparison with controls.[17]

When compared to other known antioxidants, including butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and ellagic acid, turmeric extract and curcumin were more active in protecting against the effects of aflatoxin B1 on rat livers.[18] Turmeric and curcumin were also found to reverse the aflatoxin-induced liver damage produced by feeding aflatoxin B1 (5 micrograms/day for 14 days) to ducklings. Fatty changes, necrosis, and biliary hyperplasia produced by aflatoxin B1 were reversed by curcumin.[19]

In addition to its antioxidant effects, curcumin has also been shown to enhance liver detoxification by increasing the activity of glutathione S-transferase,[10,20] an enzyme which conjugates glutathione with a wide variety of toxins to facilitate their removal from the body.

Anti-inflammatory Activity: Both the volatile oil and curcumin exhibit powerful anti-inflammatory effects.[21-23] Orally administered, curcumin was found to be as effective as cortisone or phenylbutazone in acute inflammation, and one-half as effective in chronic inflammation as these drugs, without toxic side-effects.[23] One mechanism of curcumin's anti-inflammatory activity may be its ability to block the production of pro-inflammatory arachidonic acid. Curcumin significantly inhibited the conversion of dihomo-gamma-linolenic acid to arachidonic acid in the fungus *Mortierelle alpina* and in rat liver microsomes.[24]

Choleretic Activity: Curcumin also has choleretic effects on the liver. Bile acid production was increased over 100 percent in rats after oral curcumin administration.[2] Increased production of other constituents of bile, including cholesterol, bile salts, and bilirubin, was also demonstrated.[25]

Green Tea *(Camellia sinensis)*

Description: Green, black, and oolong teas all derive from of the leaves of *Camellia sinensis*, which is cultivated widely in China, India, Japan, and Indonesia. When cultivated, it grows as a well-trimmed bush with alternating evergreen leaves. Originally from East Asia, the wild plant grows as a large shrub or tree. Green tea is made from unfermented leaves which are lightly steamed to inactivate the enzymes which would allow fermentation, then dried. The leaves of oolong tea are partially fermented, and black tea is fully fermented. The greater the fermentation, the lower the polyphenol content and the higher the caffeine content. Black tea has 2-3 times the caffeine content of green tea.[26]

History and Folk Use: Tea has been used as both a drink and a medicine for approximately 5000 years in China. Historical uses of tea are as a stimulant, an astringent for clearing phlegm, and as a digestive aid.[27]

Active Constituents: Tea contains a wide assortment of bioactive constituents, most of which are contained in two groups, alkaloids and polyphenols. Examples of alkaloids found in tea include caffeine, theobromine, and theophylline.[28] These alkaloids provide the stimulant effects of tea and figure prominently in the experience of tea drinking, although they are not thought to be central to tea's medicinal effects.

The polyphenols found in all tea give it its astringent, somewhat bitter flavor. The hepatoprotective and other health effects of green tea are believed to be chiefly dependent on the polyphenol content.[29-31] The polyphenols contained in teas are classified as catechins, which are considered to be bioflavonoids, which in turn is a subcategory of the larger group of polyphenols.[28] Green tea contains six primary catechin compounds: (+)-catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate. Epigallocatechin gallate (also known as EGCG) is considered to be the most active component, and is the best researched of the green tea polyphenols (GTP).[30,32]

Green tea contains about 30-40 percent polyphenols (dry weight), whereas the polyphenol content of black tea is 3-10 percent. The average cup of green tea contains 50 to 150 mg of polyphenols.[28]

Pharmacokinetics: The bioactive constituents of green tea are absorbed following oral administration in a dose dependent manner. The catechins are metabolized by the liver and kidneys, and cleared from the body chiefly by the kidneys. The plasma half-life of epigallocatechin gallate is 5.5 hours.[26,33] Based on the author's clinical experience, a typical recommended dose of green tea solids with polyphenols standardized to 50 percent is from 100 to 300 mg three times daily.

Hepatoprotective Activity: Green tea has been found to provide protection to the liver against a variety of toxic insults, including the industrial solvent 2-nitropropane (also found in cigarette smoke),[34] alcohol,[35] d-galactosamine,[36] and 1,4-naphthoquinone.[31] In addition, the anti-carcinogenic effect of green tea on the liver and other organs has been well researched.[32,34,37,38]

Much is known about the hepatoprotection afforded by green tea. Catechins have been discovered to be powerful antioxidants, which is though to be at least in part responsible for green tea's hepatoprotective activity. In 2-nitropropane poisoning, epigallocatechin gallate administration lowered hepatic lipid peroxide levels 100 percent at six hours and 30 percent at 15 hours. Histopathological examination revealed effective protection against induction of hepatic degenerative changes by 2-nitropropane at 15 hours.[37] Catechins have also been shown to inhibit lipid peroxidation due to other toxins, including tert-butyl hydroperoxide and bromotrichloromethane,[29] 1,4-naphthoquinone,[31] and singlet oxygen.[39]

The hepatoprotective effect of green tea is not dependent on its direct antioxidant effects alone. Green tea catechins have been shown to maintain intracellular protein thiol levels.[31] Protein thiols help maintain the intracellular reduction-oxidation (redox) balance. Protein tertiary configuration (shape), and therefore cellular function, is dependent on the maintenance of the redox balance. In rat liver cells exposed to 1,4-naphthoquinone, green tea extract prevented the expected cellular damage. This protective effect was suggested to be due to maintenance of protein thiol levels by green tea.[31]

Detoxification Activity: Glucuronidation, the predominant human Phase II liver

detoxification pathway, has been shown to be enhanced with green tea administration.[40,41] Glucuronic acid is conjugated with toxins to facilitate their elimination from the body via the bile. Examples of toxins eliminated in this manner include aflatoxin and acetaminophen metabolites. Green tea administration in rats (as their only drinking fluid) increased glucuronidation by 100 percent. The authors of the study suggest the increase in glucuronidation may contribute to the anti-carcinogenic effect of green tea by facilitating the metabolism of chemical carcinogens into inactive, readily-excretable products.[40]

The effect of green tea on other detoxifying and antioxidant enzymes is controversial. Some researchers found oral feeding of green tea in drinking water (0.2%, w/v) to mice for 30 days significantly increased the activities of glutathione peroxidase, catalase, and quinone reductase in small bowel, liver, and lungs, and glutathione S-transferase in small bowel and liver. GTP feeding to mice also resulted in considerable enhancement of glutathione reductase activity in the liver.[38]

Other researchers reported no increase in glutathione peroxidase, catalase, or superoxide dismutase following a much larger exposure of rats to green tea in drinking water (2.5%, w/v, as the sole drinking fluid, for four weeks).[40]

Green Tea and Hepatitis: One of the polyphenols present in green tea, (+)-catechin, has been studied for its effects on animal models of hepatitis, as well as in human clinical studies. Pure (+)-catechin (also known as (+)-cyanidanol-3 – trade name Catergen) has been used to treat hepatitis since 1976.[42] This compound has been shown to be an efficient immune stimulator, promoting activation of macrophages, cytotoxic-T-lymphocytes, and natural killer cells in mice in a dose-dependent manner.[42]

Several clinical studies demonstrate the effectiveness of (+)-catechin in the treatment of viral hepatitis. One double-blind study found a significant drop in antibodies to hepatitis B e antigen (HBeAg) in patients with HBeAg positive hepatitis B. Patients were given 1.5 g for two weeks, followed by 2.25 g for 14 weeks. HBeAg antibody titers decreased at least 50 percent in 31 percent of patients, ($P < 0.01$), and HBeAg completely disappeared in approximately 11 percent ($P < 0.05$). The patient group responding best to the treatment had higher initial values of SGPT, SGOT and gamma-globulin than the patients whose HBeAg titers remained unchanged. Mean values for these liver enzymes also fell significantly in the treatment group. The compound was reported to be well tolerated in this study, the only notable side-effect being a transient febrile reaction in 13 patients. [43]

In another double-blind study, 12 patients with chronic hepatitis B were treated with the combination of recombinant human alpha-interferon and (+)-catechin — three million units of interferon twice per week and 2.5 g of (+)-catechin daily for 24 weeks. Four patients experienced clinical improvement in which HBeAg and DNA polymerase disappeared from sera, and aminotransferase activities fell to normal levels. Side-effects were minimal, and all patients tolerated the treatment. [44]

Pure (+)-catechin has been found to cause hemolysis in some patients,[45,46] possibly by the promotion of antibody formation against (+)-catechin, which might cross-react with red blood cells.[47] However, there are no reports in the literature of green tea, green tea extracts, or green tea polyphenols causing this side-effect.

In an animal model of viral hepatitis, pre-treatment with green tea extract significantly prevented increases in hepatic transaminases and alkaline phosphatase levels in a dose-related manner.[48] With this information, as well as the research on (+)-catechin, one might surmise that green tea could be used as

part of a hepatitis treatment protocol, although more human research is needed in this area before a solid recommendation can be made.

Green Tea and Liver Cancer: Much of the green tea research involves its effects on cancer prevention and treatment. A full review of the anti-cancer properties of green tea is beyond the scope of this review, but at least a passing mention must be made on the subject with regard to liver cancer.

Green tea has been found to reduce or prevent the growth of hepatic neoplasms in rodents. One study used mice which had been exposed to the known carcinogen diethylnitrosamine (DENA) (50 micrograms/kg bw, i.p., once per week for eight weeks). The mice were treated with green (and black) tea for 40 weeks. After treatment, the mice were examined for pulmonary and hepatic tumors. Mice treated with both DENA and tea displayed a significant decrease in the mean number of lung and liver tumors, compared to DENA-only treated animals. Mice receiving 0.63 or 1.25 percent green tea, or 1.25 percent black tea, exhibited a reduction in the incidence of liver tumors of 54, 50, and 63 percent, respectively, compared to DENA-only treated mice.[32]

Other researchers found similar results in rats,[49,50] although one research group found a slight, but significant increase in the number of liver tumors in rats treated with green tea catechins and a decrease in intestinal cancer in the same animals.[51]

Toxicity: Green tea has not been found to be toxic at any dose. Animal studies (and the experience of a billion tea drinkers) have found no toxicity.[29] Single doses of decaffeinated green tea solids up to 4.5 g/day (equal to 45 cups of tea) have been well tolerated by humans.[34]

Glycyrrhiza glabra (licorice)

Description: *Glycyrrhiza glabra* originated in the Mediterranean and Middle East and has been used medicinally since at least 500 BC.[52] It has been cultivated in Europe since at least the 16th century. It was one of the most commonly prescribed herbs then, as it is today. It is sometimes known as "the grandfather of herbs." It is a perennial with compound pinnate leaves and grows three to seven feet high in temperate climate zones. The root is used, preferably from plants three to four years old which have not borne fruit. The roots are collected in the Fall.[53]

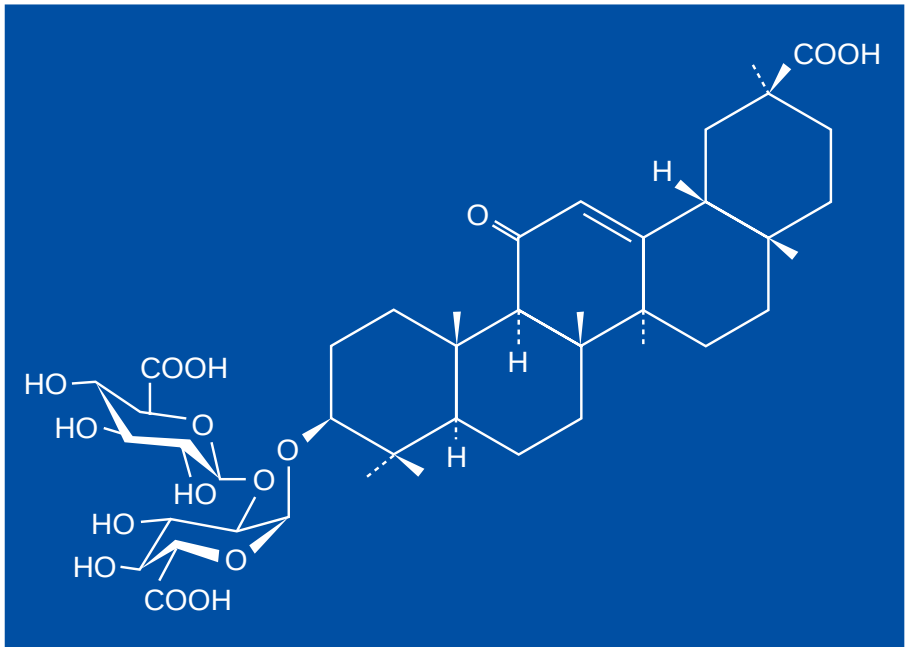
History and Folk Use: Glycyrrhiza is part of both Western and Eastern herbal traditions. Traditional uses include the treatment of peptic ulcers, asthma, pharyngitis, malaria, abdominal pain, and infections. The traditional medicinal properties of Glycyrrhiza include demulcent, expectorant, antitussive, and mild laxative activity.[54] Licorice is used to flavor a wide variety of candies, gum, tobacco products, and drinks.

Active Constituents: The primary active constituent of Glycyrrhiza, as it relates to hepatic disorders, is the triterpene glycoside glycyrrhizin (also known as glycyrrhizic acid or glycyrrhetinic acid) (figure 1). Other constituents of Glycyrrhiza include flavonoids (liquiritin and isoliquiritin), isoflavonoids (isoflavonol, kumatakenin, licoricone, and glabrol), chalcones, coumarins (umbelliferone, herniarin), triterpenoids, and phytosterols.[53,55]

Glycyrrhizin is found in concentrations in Glycyrrhiza ranging from 6-14 percent. It is 50 times sweeter than sucrose, which explains why Glycyrrhiza is commonly used in combination with other medications to mask their bitterness. The surfactant property of the steroidal saponins may also facilitate absorption of poorly-absorbed compounds, such as carotenes and anthraquinone glycosides.[53]

Pharmacokinetics: After oral administration, glycyrrhizin is metabolized predominantly in the liver and removed from the body via the bile. Better absorption and higher plasma concentrations might be achieved by administering glycyrrhizin alone rather than

Figure 1. Chemical structure of glycyrrhizin.



in licorice extract. Significantly lower concentrations of glycyrrhizin were found in bile samples from rats treated with licorice extract compared to pure glycyrrhizin. This could be attributed to an interaction during intestinal absorption between the glycyrrhizin constituent and several components in the licorice extract.[56,57]

Toxicity: Glycyrrhiza has a well known pseudoaldosterone effect when large doses are ingested. The symptoms of pseudoaldosterone syndrome include hypertension, hypokalemia, sodium and water retention, low plasma renin activity, and suppressed urine and serum aldosterone levels.[58,59] The amount of glycyrrhizin needed to produce these symptoms is variable. In one study in which 14 healthy volunteers ate 100-200 grams of a licorice product (equivalent to approximately 10-14 grams of the crude herb or 0.7-1.4 g glycyrrhizinic acid), for one to four weeks, four subjects withdrew from the study due to hypokalemia. Plasma renin activity or urinary aldosterone concentrations were decreased in all subjects, revealing a significant effect of licorice root on the renin-angiotensin-aldosterone axis at these doses.[59]

This effect is not thought to be due to a direct mineralcorticoid activity on the part of Glycyrrhiza (although Glycyrrhiza possesses mineralcorticoid activity about four orders of magnitude lower than aldosterone), but rather by enhancing the endogenous activity of mineralocorticoids by inhibiting their breakdown in the liver.[60] Glycyrrhizin has been shown to suppress the activity of 11-beta-hydroxysteroid dehydrogenase, the main enzyme in humans responsible for inactivating cortisol and progesterone.[61] Glycyrrhiza alone is without significant mineralcorticoid effect in adrenalectomized animals or in humans with severe adrenocorticoid insufficiency, which illustrates the need for endogenous cortisol to be present to have this effect.[62]

Glycyrrhiza is well tolerated by most patients at normal doses (1-4 g/d crude herb). Glycyrrhiza should probably not be used in patients with a history of hypertension, renal failure, or current use of cardiac glycosides.[63]

Hepatoprotective Activity: Glycyrrhiza has been shown to have a direct hepatoprotective effect. Glycyrhhiza flavonoids provided protection to hepatocytes exposed to carbon tetrachloride,[64] and galactosamine.[65] The researchers pointed to the anti-lipid peroxidation effect of Glycyrrhiza as the central mechanism contributing to its protective action against carbon tetrachloride-induced hepatotoxicity.[64,66] Glycyrrhiza has also been shown to have a significant free-radical-quenching effect.

Detoxification: Recent studies have brought to light the ability of Glycyrrhiza to enhance the detoxification of medications and

toxins. Several mechanisms seem to be involved, one of which is increased liver glucuronidation. Rats pretreated with Glycyrrhiza tincture (1 g/kg, p.o., for six days) significantly increased the cumulative biliary (156 percent) and urinary (132 percent) excretion of acetaminophen-glucuronide conjugate within 120 minutes after the administration of acetaminophen (150 mg/kg, i.v.)[67] However, the dose in this study was extremely high (equivalent to a 70-gram dose in humans) and would likely cause significant side-effects in humans.

Another mechanism is an activation of p450, phase I detoxification. Daily doses of licorice root extract (3,138 or 6,276 mg/kg b.w., orally) or glycyrrhizin (240 or 480 mg/kg b.w., orally), were administered to different groups of Swiss Albino CD1 mice for one, four, or 10 consecutive days. The detoxification of a wide variety of substances (testosterone, ethoxyresorufin, methoxyresorufin, pentoxyresorufin, p-nitrophenol, and aminopyrine) were found to be enhanced.[68]

In a Russian study, hepatotoxicity reactions in patients being treated for tuberculosis were significantly reduced in patients who received herbal liver support, including a combination of Glycyrrhiza, nettle (Urtica), tansy (Tanacetum), and mint (Mentha).[69]

Viral Hepatitis: Glycyrrhiza exerts antiviral activity in vitro toward a number of viruses, including hepatitis A,[70] varicella-zoster,[71] HIV,[72] herpes simplex type 1, Newcastle disease, and vesicular stomatitis[73,74] viruses.

Intravenous glycyrrhizin has been shown to be effective in a double blind study against viral hepatitis, in particular chronic viral hepatitis.[75] Administered in a physiologic saline solution in combination with cysteine and glycine (a product called Stronger Neo Minophagen-C, or SNMC), Glycyrrhiza has been shown to stimulate endogenous interferon production in addition to its antioxidant and detoxifying effects.[76] An impressive 72.2 percent survival rate was noted for patients with subacute hepatic failure due to viral hepatitis who received SNMC treatment for 12 weeks, compared to a survival rate of 31.1 percent in patients who received standard supportive therapy ($P < 0.01$).[76]

Oral dosing of a Glycyrrhiza extract may also be of benefit in acute and chronic hepatitis. Eighty patients with hepatitis, 40 acute and 40 chronic, were given oral glycyrrhizin (approximately 750 mg, equivalent to 7.5 g of crude herb) or Poly I:C (polyinosinic-polycytidylic acid, an antiviral) and inosine intramuscularly. In the glycyrrhizin group, all indicators of liver function returned to normal in 85 percent of subjects with acute hepatitis within 30 days, compared to 35 percent in the control group. In patients with chronic hepatitis, 75 percent experienced normalization of liver function, versus 10 percent in the control group.[77]

Conclusion

Modern society has inherited knowledge about the herbal treatment of liver disease from many cultures. The dominant Western medical culture has largely ignored this knowledge until recently. Research into plants traditionally used in the treatment of liver disease has significantly advanced in the past 15 years, and much of what has been discovered supports traditional knowledge.

There continues to be a need for safe, effective treatments of liver disease. The two botanical medicines reviewed in Part One of this series, milk thistle and Picrorhiza, are the best-researched plants for the treatment of liver disease, with many human therapeutic trials available to the practicing physician to assess their potential effectiveness. Much research is yet to be done, but these plants appear to have a place in the treatment of liver poisoning, viral hepatitis, and cirrhosis of the liver. The research on turmeric, green tea, and licorice root is much less complete, with published human

trials still a rarity. However, those human clinical studies which exist, in addition to animal research and *in vitro* studies, support further investigation into the use of these plants in the prevention and treatment of liver disease.

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