A Review of Plants Used in the Treatment of Liver Disease: Part 1

by Scott Luper, N.D.

Abstract

Botanicals 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. Basic scientific research has uncovered the mechanisms by which some plants afford their therapeutic effects. *Silybum marianum* (milk thistle) has been shown to have clinical applications in the treatment of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis via its antioxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating, and liver regenerating effects. *Picrorhiza kurroa*, though less well researched than Silybum, appears to have similar applications and mechanisms of action. When compared with Silybum, the hepatoprotective effect of Picrorhiza was found to be similar, or in many cases superior, to the effect of Silybum. (*Altern Med Rev* 1998;3(6):410-421)

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 counsel watchful waiting for many of their patients, waiting in fact for the time when the disease has progressed to the point that warrants the use of heroic measures. Physicians and patients are in need of effective therapeutic agents with a low incidence of side-effects. Plants potentially constitute such a group.

In recent years many 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 confirmed traditional experience and wisdom by discovering the mechanisms and modes of action of these plants as well as reaffirming 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. Just a handful have been fairly well researched. The latter category of plants include: *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), *Chelidonium majus* (greater celandine), *Glycyrrhiza glabra* (licorice), and *Allium*

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sativa (garlic). This review will be divided into two parts. *Silybum marianum* and *Picrorhiza kurroa*, will be reviewed in Part One. *Curcuma longa*, *Camellia sinensis*, *Chelidonium majus*, *Glycyrrhiza glabra*, and *Allium sativa* will be reviewed in Part Two.

Silybum marianum (milk thistle)

Silybum marianum is currently the most well researched plant in the treatment of liver disease (with over 450 published peer review papers). The genus Silybum is a member of the daisy family (Compositae). The plant itself is a stout thistle, growing one to three meters tall in rocky soils, with large purple flowering heads (Figure 1). The leaves are characterized by distinct white "milky" veins that give the plant its common name.

Figure 1. Milk Thistle

History, Early Authors

Silybum is cited as one of the oldest known herbal medicines. Dioscores first described the plant. In Roman times, Pliny the Elder (A.D. 77), a noted naturalist, described the medicinal uses of milk thistle, indicating it was "excellent for carrying off bile."[1] Culpeper (1650) wrote of its effectiveness in removing obstructions of the liver and spleen.[2] But it has been relatively recent clinical research, especially in Germany, which has brought the use of Silybum to prominence in the treatment of chronic or acute liver disease, as well as protecting the liver against toxicity.

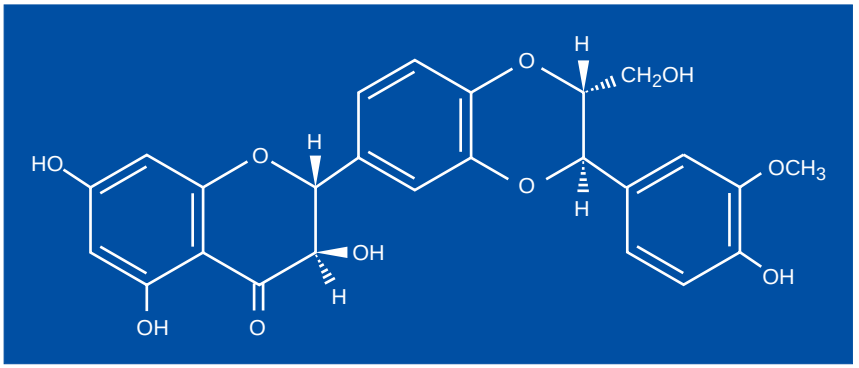
Active Constituents

The active constituents of milk thistle are flavonolignans including silybin, silydianin, and silychristine, collectively known as silymarin. Silybin (Figure 2) is the component with the greatest degree of biological activity, and milk thistle extracts are usually standardized to contain 70-80 percent silybin. Silymarin is found in the entire plant but is concentrated in the fruit and seeds. Silybum seeds also contain betaine (a proven hepatoprotector) and essential fatty acids, which may contribute to silymarin's anti-inflammatory effect.

Pharmacokinetics

Silymarin is not water soluble and so cannot be taken as a tea. It is typically administered as an encapsulated standardized extract. The absorption with oral administration is rather low with only two to three percent of the silybin recovered in 24 hours from rat bile.[3,4] The peak plasma levels after an oral dose are achieved in four to six hours in both animals and humans.[3-5] Silymarin is cleared from the body predominantly via the bile and to a lesser extent the kidney. The clearance half-life is six to eight hours.[5]

Figure 2. Silybin



Clinical Indications

Mushroom Poisoning: The most remarkable use of silymarin is in the treatment of Amanita mushroom poisoning. The Amanita genus is widespread in Europe and North America, and several species are considered choice by mushroom collectors. Unfortunately, the genus also contains several of the most toxic mushrooms in existence. Amanita mushrooms possess two extremely powerful hepatotoxins, amanitin and phalloidin (the LD50 of amanitin is 0.1 mg/kg body weight). Historically, the accidental ingestion of mushrooms containing these toxins results in about 60 cases of poisoning per year in the United States and Europe, with a mortality rate of about 30 percent.[6]

In mice, silymarin was 100 percent effective in preventing liver toxicity if given before or up to ten minutes after Amanita toxin poisoning. Severe liver damage (and death) was avoided if silymarin was administered within 24 hours.[7] In a study with dogs (who model human Amanita poisoning quite well), none of the dogs died when given silymarin 5-24 hours after ingesting an LD50 dose of *Amanita phalloides* (85 mg/kg). In comparison, untreated dogs experienced a mortality rate of 33 percent. Liver enzyme studies and liver biopsies in the controls and treated dogs demonstrated a significant hepatoprotective effect for the silymarin.[6]

The hepatoprotective effects of silymarin in humans after ingestion of Amanita toxins have been repeatedly demonstrated. In one series of 18 patients treated with silymarin, all patients survived except one particularly high-dose suicide. The authors concluded, "Administration of silymarin even up to 48 hours after mushroom ingestion appears to be an effective measure to prevent severe liver damage in *Amanita phalloides* poisoning."[8] In a 1995 study of 41 mushroom poisoning victims, none died in the group which included silymarin in the treatment regimen.[9]

A 1996 report made the case that silymarin may be useful even three days post toxification. A family of four poisoned by Amanita mushrooms was admitted to the hospital with severe liver damage. Although all were treated with standard therapy, there was a worsening of the clinical picture until the third day, when it was decided to add silybin dihemisuccinate by intravenous route to the therapy. After the beginning of silybin administration the patients showed a favorable course with a rapid resolution of the clinical picture, although the prognosis appeared severe on the basis of hepatochemical examination results.[10]

A particularly dramatic case of a very severe accidental poisoning in a seven-year-old girl resulted in her entering a hepatic coma. The authors reported the girl's survival was due in large part to treatment with silymarin in combination with high doses of G-penicillin.[11]

General Hepatoprotective: Many studies have demonstrated the beneficial hepatoprotective effects of treatment with silymarin. In a Finnish military hospital study on consecutive patients with elevated serum liver enzymes (mostly due to ethanol ingestion), 420 mg/day silymarin was found to significantly lower liver enzymes – aspartate aminotransferase (AST), alanine aminotransferase (ALT) – after four weeks. Histologic examination of liver biopsies also

demonstrated a statistically significant improvement.[12]

In an Italian study of 20 patients with chronic active hepatitis, 240 mg/day of silybin-phosphatidylcholine complex for only seven days was found to significantly lower serum liver enzymes – AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase, and total bilirubin.[13]

In a Hungarian study of 36 patients with chronic alcoholic liver disease, 420 mg/day of silymarin resulted in a normalization in serum liver enzymes (AST, ALT, GGT), total bilirubin, and an improvement in the histological examination of liver biopsies after six months of treatment. In addition, procollagen III peptides (a marker of active fibrosis) were found to be significantly decreased in the treatment group.[14]

In an Austrian study involving 170 patients with liver cirrhosis, 420 mg/day of silymarin for an average of 41 months resulted in a significant improvement in survival (58% in silymarin-treated patients and 39% in the placebo group ($P = 0.036$)). No side-effects of silymarin were noted in this study[15] or in others cited above.

Not every study found a beneficial effect of silymarin administration. In a French study on 116 patients with histologically proven alcoholic hepatitis, 420 mg/day of silymarin for three months was not found to significantly alter the course of the disease. Both the treated and the placebo groups had similar rates of abstinence (46%), and significant improvement in the score of alcoholic hepatitis and serum amino transferase activity, irrespective of treatment with silymarin or placebo. Four patients died of hepatic failure during the trial, one in the treatment group and three in the placebo group (not statistically significant). As usual, no side-effects were noted.[16]

It is interesting to note that while silymarin has been shown to have a profound hepatoprotective effect on chronic exposure to ethanol, it has no direct effect on ethanol metabolism. When studied, silybin had no effect on reducing blood ethanol levels or the rate at which ethanol is removed from the body.[17]

Mechanism of Action

Silymarin has been reported to protect liver cells from a wide variety of toxins, including acetaminophen, ethanol, carbon tetrachloride, and D-galactosamine.[18-23] Silymarin has also been found to protect liver cells from ischemic injury,[24] radiation,[25] iron toxicity,[26] and viral hepatitis.[27]

The mechanisms which provide silymarin's hepatoprotective effects are many and varied, and include antioxidation,[21,26,28] anti-lipid peroxidation,[19,28,29] enhanced detoxification,[30-32] and protection against glutathione depletion.[33,23] Silymarin has been found to inhibit the formation of leukotrienes from polyunsaturated fatty acids in the liver, via its inhibition of the enzyme lipoxygenase. These leukotrienes are known to be some of the most damaging chemicals found in man.[34]

Studies also demonstrated that silymarin increased hepatocyte protein synthesis,[35,36] decreased the activity of tumor promoters,[37] stabilized mast cells,[38] modulated immune functions,[39,40] and was anti-inflammatory[41-43] and antifibrotic.[44-46]

Stimulation of Liver Regeneration: One of the mechanisms to explain the ability of silymarin to stimulate the regeneration of hepatic tissue is the increase in protein synthesis in damaged livers. In both *in vivo* and *in vitro* experiments, significant increases in the formation of ribosomes and DNA synthesis were measured in addition to the increase in protein synthesis. Interestingly, the increased protein synthesis was only measured in damaged livers (partial hepectomy), not in controls.[35] The mechanism of increased protein synthesis is currently not known but some authors speculate silymarin imitates a

physiologic regulator, so the silybin fits into a specific binding site on the polymerase, thus stimulating ribosome formation.[36]

The potential for stimulation of protein synthesis by silymarin was investigated in malignant liver tissue, and no increases in protein synthesis, ribosome formation, or DNA synthesis were found in malignant cell lines.[35]

Anti-inflammatory Effects: The mainstays of the current medical management of nonviral chronic hepatitis are immunosuppressive/anti-inflammatory medications (e.g., prednisone, azathioprine). While use of these drugs may be lifesaving, long-term use may result in debilitating, life-threatening side-effects. Doctors and patients need safe and effective alternative anti-inflammatory medications. Botanical anti-inflammatories may constitute such a group.

Silymarin has been shown to have significant anti-inflammatory effects on hepatic tissue. Several studies have demonstrated a variety of anti-inflammatory effects, including mast cell stabilization,[38] inhibition of neutrophil migration,[47] Kuppfer cell inhibition,[43] strong inhibition of leukotriene synthesis, and prostaglandin formation.[41-43]

Antifibrotic Effects: Hepatic stellate cells play a central pathogenic role in liver fibrogenesis. In response to some fibrotic influences (e.g., chronic ethanol exposure, carbon tetrachloride, etc.), they proliferate and transform into myofibroblasts, which are responsible for the deposition of collagen fibers in the liver. One recent study investigated the effect of silybin on the transformation of hepatic stellate cells into myofibroblasts. Silybin [10^{-4} mol/l concentration] was found to reduce the proliferation of freshly isolated rat hepatic stellate cells by about 75 percent. It also reduced the conversion of stellate cells into myofibroblasts and down-regulated the gene expression of extracellular matrix components necessary for fibrosis.[44]

Silymarin has been shown to slow or reverse liver fibrosis in animals. Rats were subjected to a complete bile duct occlusion which consistently causes progressive liver fibrosis without inflammation. Silymarin was able to reduce the fibrosis by 30-35 percent in comparison with controls (50 mg/kg/day, human dose = 3500 mg/day). Silymarin worked equally if used continuously for six weeks after the bile duct occlusion or only for the final two weeks. Dosage at 25 mg/kg/day (human dose = 1750 mg/day) was not found to be effective.[45]

Colchicine is currently used to inhibit fibrosis of the liver. It functions as an antifibrotic and anti-inflammatory by inhibiting macrophage stimulation of fibrosis. Unfortunately, colchicine has a narrow, unpredictable therapeutic window, and serious, life-threatening side-effects, including liver failure, renal failure, myocardial injury, severe gastrointestinal damage, shock, and death. In a rat study using carbon tetrachloride-induced liver fibrosis, silymarin was found to be very similar to colchicine for the prevention of chronic liver fibrosis, but without any side-effects.[46]

Inhibition of P450: Paradoxically, silymarin may have an inhibitory effect on the cytochrome P450 (Phase I) detoxification system. In a recently published animal study, silybin was found to inhibit several specific induced P450 enzymes in mice.[30] Other researchers have noted the lack of stimulatory effect on the P450 detoxification system.[29,31] This effect may explain some of the hepatoprotective effects of silymarin, especially against Amanita poisoning. Amanitin toxin becomes deadly to hepatocytes only after it becomes bioactivated by the P450 system. The inhibition of the bioactivation of amanitin could reduce its toxic effects. In addition, silymarin and other antioxidants afford some protection against the free radicals generated by P450 enzymes.[48]

Enhanced Glucuronidation: Glucuronidation is an important Phase II liver detoxification pathway. More toxins are removed from the body via glucuronidation than any other single detoxification pathway.[48] Glucuronic acid is conjugated with toxins to facilitate their elimination from the body via the bile. In addition, many other substances, including estrogen, are removed from the body via glucuronidation. Unfortunately, some intestinal bacteria (mostly pathogenic) possess an enzyme, beta-glucuronidase, that enables them to remove glucuronic acid from the conjugated substance and use it as an energy source. This allows the original molecule to be reabsorbed through the GI mucosa, thus re-exposing the person to the removed substance. Silymarin was found to inhibit the activity of beta-glucuronidase 53 percent in healthy humans and in one patient with colon cancer.[32]

Immunomodulation: Researchers have investigated the immunomodulatory effects of silymarin on the diseased liver. A pair of Hungarian studies demonstrated a positive effect of silymarin on immune function. The first study looked at patients with histologically proven chronic alcoholic liver disease. These patients originally had low T-cell percentage, high CD8+ cell percentage, and an enhanced antibody-dependent increase in lymphocyte cytotoxicity. All of these abnormal immune findings were normalized by a six-month course of silymarin. No significant changes were found after six months in the control group.[39]

The second study looked at the hepatoprotective effect of silymarin in addition to its effects on normalizing immune function. Forty patients with alcoholic cirrhosis of the liver were given either silymarin, aminoimidazole-carboxamide-phosphate, or placebo in a one-month, double-blind clinical trial. In the treated groups, silymarin normalized elevated levels of AST, ALT, and total bilirubin, markedly reduced the high level of GGT, decreased the percentage of OKT8+ cells, and suppressed lymphocytotoxicity.[40]

Dosage/Toxicity

Silybum marianum is not water soluble and is typically administered as an encapsulated standardized extract (70-80% silymarin). In animals, silymarin has proven to be non-toxic when administered at high doses for short periods of time and long term dosage in rats has also failed to demonstrate any toxicity. Human studies have shown silymarin to be generally without side-effects. The typical adult dosage for silymarin is 240-900 mg/day in two or three divided doses. At higer doses (>1500 mg/day) silymarin may produce a laxative effect due to increased bile flow and secretion. Mild allergic reactions have also been noted, but neither of these side-effects was severe enough to discontinue treatment.[49-51]

Picrorhiza kurroa

History/Traditional Use

Picrorhiza kurroa (fam. Scrophulariaceae) is a small perennial herb that grows in northwest India on the slopes of the Himalayas between 3000 and 5000 meters. It is an important herb in the traditional Ayurvedic system of medicine, and has been used to treat liver troubles and bronchial problems. Other traditional uses include dyspepsia (similar to gentian in its bitter quality), bilious fever, chronic dysentery, and scorpion sting. The roots and rhizomes are the part of the plant used medicinally.

Active Constituents

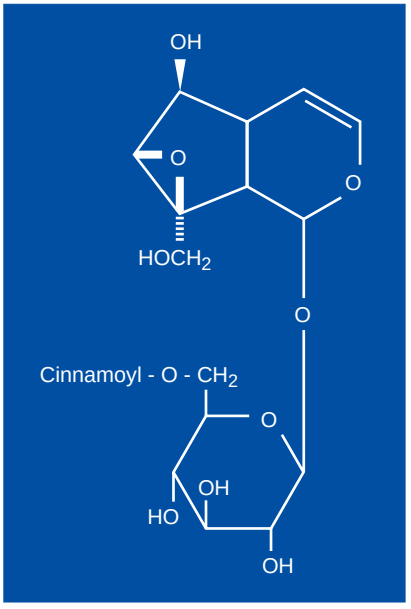
The most important active constituents of Picrorhiza are the iridoid glycoside picrosides I, II, III (Figure 3), and kutkoside, known collectively as kutkin.[52] Many other active constituents have been identified, including nine cucurbitacin glycosides, apocynin, and drosin.[53]

Clinical Indications

General Hepatoprotective: Picrorhiza has been shown to protect liver cells from a wide variety of insults including Amanita poisoning,[54,55] carbon tetrachloride,[56-58] galactosamine,[59-61] ethanol,[62] aflatoxin B1,[63] acetaminophen,[64] thioacetamide,[59,65] oxytetracyline,[66] and monocrotaline,[67] in both *in vitro* and *in vivo* experiments. When compared with silymarin, the hepatoprotective effect was found to be similar, or in many cases, superior to the effect of silymarin.[58,61,64-66]

Picrorhiza has demonstrated significant hepatoprotective effects against Amanita mushroom poisoning in *in vivo* animal models.[54,55] There are significantly fewer clinical studies on Picrorhiza than Silybum. One study, however, found the protective effect of Picrorhiza was comparable to silybin, and the curative efficacy of Picrorhiza appeared to be slightly superior.[55]

Figure 3. Picroside I



Viral Hepatitis: Picrorhiza may be of value in the treatment of viral hepatitis. In an Indian study on 32 patients diagnosed with acute viral hepatitis (HBsAg negative), 15 patients in the treatment group were given Picrorhiza root powder, 375 mg three times daily for two weeks. Liver enzymes (AST and ALT) and bilirubin were significantly lower in the treatment group. The number of days required for total serum bilirubin to drop to an average value of 2.5 milligrams percent was 75.9 days in the placebo group, as compared to 27.4 days in the treatment group.[68]

Another study investigated *in vitro* anti-hepatitis B virus surface antigen (anti-HBs)-like activity. HbsAg-positive serum samples obtained from hepatitis B virus (HBV)-associated acute and chronic liver diseases and healthy HBsAg carriers were used to evaluate the anti-HBs-like activity of Picrorhiza and other compounds. Promising anti-HBsAg activity was noted with Picrorhiza. Picrorhiza also inhibited purified HBV antigens prepared from healthy HBsAg carriers.[69]

Mechanisms of Action

Antioxidant: The mechanism by which Picrorhiza affords protection to the liver is not completely understood, but several possibilities have come to light. Like silymarin, Picrorhiza does possess significant antioxidant activity *in vitro* which may contribute to the hepatoprotective effect by reducing lipid peroxidation and free radical damage.[70] Chander et al found that Picrorhiza and its main constituents, picroside-I and kutkoside, inhibited the non-enzymatic generation of O_2-anions in a phenazine methosulphate NADH system, inhibited oxidative malonaldehyde generation by both the ascorbate-Fe^{2+} and NADPH-ADP-Fe^{2+} systems, and scavenged superoxide (O_2) anions generated in a xanthine-xanthine oxidase system. In other words, Picrorhiza demonstrated antioxidant activity similar to that of superoxide dismutase, metal-ion chelators, and xanthine oxidase inhibitors.[70]

Glutathione is vital to maintaining a variety of intracellular functions, including detoxification, antioxidation, tertiary protein configuration, and redox balance.[71] Picrorhiza was found to restore depleted glutathione levels in African desert rats infected with

Plasmodium berghei (malaria). Several enzymes associated with glutathione function were also restored, including glutathione-S-transferase, glutathione reductase, and glutathione peroxidase.[72] Generation of lipid peroxides in African desert rats infected with *Plasmodium berghei* was significantly reduced by Picrorhiza at the oral dose of 6 mg/kg for two weeks, revealing Picrorhiza also possesses anti-lipid peroxidative effects.[73]

Stimulation of Liver Regeneration: Like silymarin, Picrorhiza may have an effect on liver regeneration. A 1992 study demonstrated stimulation of nucleic acid and protein synthesis in rat liver with oral administration of Picrorhiza. The authors stated the results were comparable to silymarin.[74]

Anti-inflammatory: Another factor in the hepatoprotection of Picrorhiza may be its anti-inflammatory effects. Picrorhiza extracts were found to have an inhibitory effect on such pro-inflammatory cells as neutrophils, macrophages, and mast cells.[75] The authors suggested Picrorhiza extract inhibited membrane-mediated activation of these cells (inhibited 8-adrenergic receptors).[76,77] The researchers found no effect of the Picrorhiza extract on prostaglandin production.[75]

Picrorhiza contains apocynin, a catechol, as one of its minor constituents. Apocynin has been found to exhibit powerful anti-inflammatory effects on a variety of inflammatory models. Apocynin was found to inhibit neutrophil oxidative burst *in vitro* without affecting beneficial activities such as chemotaxis, phagocytosis, and intracellular killing of bacteria.[78,79]

In *in vivo* animal models, apocynin inhibited lipopolysaccharide-induced emphysema in hamsters.[80] Apocynin prevented the formation of ulcerative lesions in rats injected intracutaneously with Freund's complete adjuvant,[81] and reduced swelling in collagen-immunized rats. No effects on humoral and cellular immunity were observed after treatment with apocynin.[82,83] What is remarkable about the last study is the effective daily dose of apocynin was only 0.024 mg/kg. Such a dose is readily achieved from normal use of Picrorhiza root instead of the concentrated apocynin extract.[82,83]

Choleretic: Several hepatotoxins, including paracetamol and ethynylestradiol, have a cholestatic effect on the production of bile. Picrorhiza has been shown to reverse acetaminophen and ethynylestradiol-induced cholestasis, maintaining both bile volume and flow. Silymarin was tested simultaneously for comparison. Picrorhiza was found to be a more potent choleretic and anticholestatic agent than silymarin.[84]

Dosage/Toxicity

Picrorhiza is poorly soluble in water and so is usually not taken as a tea. It is soluble in ethanol and so can be taken in tincture form (very bitter), but is usually administered as an encapsulated standardized extract (4% kutkin).[85] The usual adult dosage is 400 to 1500 mg/day, although daily doses as high as 3.5 g/day have been recommended for fevers.[86]

Picrorhiza use is widespread in India and no major adverse reactions have been reported. The oral LD50 of kutkin is greater than 2600 mg/kg in rats.[87] The LD50 of picrocide and kutkoside is greater than 1000 mg/kg in rats.[87] By comparison, the maximum dose achievable with oral ingestion of Picrorhiza root is about 3-6 mg/kg.

Conclusion

Clinical research has confirmed the efficacy and safety of several botanicals for the treatment of liver disease. Both *Silybum marianum* and *Picrorhiza kurroa* have a long tradition of use as hepatoprotective herbs. Scientific research has elucidated many of the mechanisms by which these two herbs provide their hepatoprotective effect. As a result these plants are now being more widely used in the

treatment of liver diseases such as toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis.

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