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REVIEW ARTICLE

Herbal Medicines for Liver Diseases

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Herbal medicines have been used in the treatment of liver diseases for a long time. A number of herbal preparations are available in the market. This article reviews four commonly used herbal preparations: (1) *Phyllanthus*, (2) *Silybum marianum* (milk thistle), (3) glycyrrhizin (licorice root extract), and (4) Liv 52 (mixture of herbs). *Phyllanthus* has a positive effect on clearance of HBV markers and there are no major adverse effects; there are no data from randomized controlled trials on clinically relevant outcomes, such as progression of chronic hepatitis to cirrhosis and/or liver cancer, and on survival. Silymarin does not reduce mortality and does not improve biochemistry and histology among patients with chronic liver disease; however, it appears to be safe and well tolerated. Stronger neominophagen C (SNMC) is a Japanese preparation that contains 0.2% glycyrrhizin, 0.1% cysteine, and 2% glyceine. SNMC does not have antiviral properties; it primarily acts as an anti-inflammatory or cytoprotective drug. It improves mortality in patients with subacute liver failure and improves liver functions in patients with subacute hepatic failure, chronic hepatitis, and cirrhosis with activity. SNMC does not reduce mortality among patients with cirrhosis with activity. SNMC may prevent the development of hepatocellular carcinoma in patients with chronic hepatitis C, however, prospective data are lacking. Liv 52, an Ayurvedic hepatoprotective agent, is not useful in the management of alcohol-induced liver disease. Standardization of herbal medicines has been a problem and prospective, randomized, placebo-controlled clinical trials are lacking to support their efficacy. The methodological qualities of clinical trials of treatment with herbal preparations are poor. The efficacy of these herbal preparations need to be evaluated in rigorously designed, larger randomized, double-blind, placebo-controlled multicenter trials.

KEY WORDS: hebal products; *Phyllanthus*; *Silybum marianum*; milk thistle; glycyrrhizin; Stronger neominophagen C; Liv 52; hepatoprotective agent; complementary and alternative medicine.

The use of herbal medicine can be traced back to 2100 BC in ancient China at the time of the Xia dynasty and during the Vedic period in India. The first written reports are timed to 600 BC with Charaka Samhita in India and to 400 BC with the early notes of the Eastern Zhou dynasty in China (1–3). Herbal medicines for liver disease have been in use in India for a long time and have been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they have not become acceptable treatment modalities for liver diseases. The limiting factors that contribute to this eventuality are (i) lack of standardization of the herbal drugs and lack of identification of this active ingredient(s), (ii) lack of randomized controlled clinical trials (RCTs), and (iii) lack of toxicological evaluation (1).

A number of herbal preparations are available on the market. This article reviews four commonly used herbal preparations: (1) *Phyllanthus*, (2) *Silybum marianum* (milk thistle), (3) glycyrrhizin (lecorice root extract), and (4) Liv 52 (a mixture of herbs).

The recommendations provide a data-supported approach. They are based on the following: (1) a review of the recently published world literature on the topic (Medline search), (2) a review of recently published systematic reviews and meta-analyses, and (3) personal communication (Professor Subrat K. Acharya, Department of

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TABLE 1. QUALITY OF EVIDENCE ON WHICH RECOMMENDATION IS BASED (4)

Grade	*Definition*
I	Randomized, controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case–control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

Gastroenterology, All India Institute of Medical Sciences, New Delhi). The recommendations are graded from I to III (Table 1) (4).

PHYLLANTHUS

The plants of the genus *Phyllanthus* are widely distributed in most tropical and subtropical countries and have long been used in traditional medicine to treat chronic liver disease. Phytochemical studies carried out on these plants isolate and characterize a number classes of compounds, including alkaloids, avonoids, lignans, phenols, and terpenes, which are responsible for the pharmacological actions. An aqueous extract of *P. amarus* inhibits woodchuck hepatitis virus DNA polymerase and surface antigen expression (5–7) and several protein kinases such as cAMP-dependent protein kinase, protein kinase C, and myosin light chain kinase in rate liver (8).

Phyllanthus appears to be promising in patients with chronic hepatitis B virus (HBV) infection (9–11). In seven clinical trials involving 213 patients with chronic HBV carriers, a mean HBsAg clearance rate of 25.6% and a mean HBeAg seroconversion rate of 55.3% were observed (1, 11). However, only three of these seven trials were controlled trials, recruiting 78, 22, and 16 patients (9, 11). The largest trial, which included 78 patients, did not examine HBeAg seroconversion. The results of this study are yet to be reproduced (9).

Liu *et al.* (12) published a meta-analysis of the effect on and safety of genus *Phyllanthus* for chronic HBV infection. Twenty-two RCTs ($n = 1947$) were included; quality was high in 5 double-blind trials (Jadad score [13] 3 or 4 in 5 trials and low in the remaining 17 trials [1 in 13 trials and 2 in 4 trials]). Of these 22 RCTs, only 6 trials had a follow-up duration of more than 3 months after the end of treatment. Thirteen trials studied single herbs and nine studied compound *Phyllanthus* herbs. None of the trials reported mortality or incidence of liver cirrhosis and/or hepatocellular carcinoma. Nine of 22 RCTs compared *Phyllanthus* herb with placebo; 7 RCTs, with conventional treatment (interferon and thymosin); and 6 RCTs, with other herbal medicines. The combined results showed that *Phyllanthus* species had a positive effect on clearance of serum HBsAg (relative risk, 5.64%; 95% CI, 1.85–17.21) compared with placebo or no intervention. There was no significant difference on clearance of HBsAg, HBeAg, and HBV DNA between *Phyllanthus* and interferon. *Phyllanthus* plus interferon was better than interferon alone. *Phyllanthus* species were better than nonspecific treatment or other herbal medicines for the clearance of serum HBsAg, HBeAg, and HBV DNA and liver enzyme normalization. No serious side effects were reported. This meta-analysis shows that *Phyllanthus* has antiviral properties, however, the evidence is weakened due to the general low methodological quality of majority of trials. They provided only a limited description of randomization and allocation concealment insufficient to allow a judgment of whether or not they had been conducted properly (12). There may also be a publication bias, as the majority of trials published from China have unusually high proportions of positive results, while negative trials remain unpublished.

There are negative studies as well, reporting no efficacy of *P. amarus* in chronic HBV carriers (14–18). The discrepancy between these studies could be related to different varieties of *P. amarus* being used (1, 14–18), which may not contain biological active substances (1).

In conclusion, *Phyllanthus* has a positive effect on clearance of HBV markers (Grade I). There are no major adverse effects (Grade I). Though the active compound remains to be identified, significant progress has already taken place in standardization of the extract to ensure the bioefficacy of *P. amarus* (1). The long-term goal of treatment for chronic hepatitis B is to prevent ALT fares and progression to cirrhosis and/or liver cancer and, ultimately, to prolong survival. There are no data from RCTs on these clinically relevant outcomes. Due to the low methodological quality of most of the trials and the limited follow-up, *Phyllanthus* cannot be recommended for clinical use in patients with chronic HBV infection, until large-scale prospective multicenter, randomized, controlled trials show consistent benefits. Rigorous efforts should also continue to identify the active ingredient(s), in order to avoid interspecies differences in biological activities.

SILYMARIN (MILK THISTLE)

Silybum marianum is the most well-researched plant in the treatment of liver disease. In Roman times, Pliny the El-der (A.D. 77), a noted naturalist, reported that milk thistle was "excellent for carrying off bile" (19). Culpeper (1650) wrote of its effectiveness in removing obstruction of the liver and spleen (19).

The active complex in mile thistle is a lipophilic extract from the seeds of the plant and is composed of three isomer

flavonolignans—silybin, silydianin, and silychrstine—collectively known as silymarin (19). Silybin is the component with the greatest degree of biological activity and makes up 50 to 70% of silymarin. Silymarin is found in the entire plant but is concentrated in the fruit and seeds.

Silymarin acts as an antioxidant by reducing free radical production and lipid peroxidation (20–22), has antifibrotic activity (23), and may act as a toxin blockade agent by inhibiting binding of toxins to heptocyte cell membrane receptors (24, 25). In animals, silymarin reduces liver injury caused by acetaminophen, carbon tetrachloride, radiation, iron overload, phenylhydrazine, alcohol, cold ischemia, and *Amanita phalloides* (26).

Silymarin has been used to treat alcoholic liver disease, acute and chronic viral hepatitis, and toxin-induced liver diseases. Jacobs *et al.* (26) published a systematic review and meta-analysis to determine the efficacy and safety of silymarin for the tratment of liver disease. Fourteen RCTs ($n = 1209$) were included; quality was high in 10 RCTs (Jadal score ≥ 3) and low in the remaining 4-trials (Jadal score <3). Patients with acute liver disease were studied in one trial; the remaining trials studied patients with chronic liver disease. The etiology of liver disease was hetrogeneous and included viral in three studies, alcohol in seven, mixed or unknown in three, and drugs in 1. Four studies reported outcomes for mortality among 433 patients; there was no reduction in mortality. Three studies evaluated histology; there was no improvement in histology at liver biopsy. There was also no improvement in liver function tests with silymarin. The frequency of adverse effects was low and was indistinguishable from that with placebo (26).

There are no RCTs of silymarin treatment aimed at specific forms of chronic liver disease, e.g., chronic hepatitis C or B. The role of silymarin in reducing HCV RNA or HBV DNA levels has not been evaluated.

In conclusion, silymarin appears to be safe and well tolerated (Grade I). It does not reduce mortality among patients with chronic liver disease (Grade I). It does not improve histology at biopsy among patients with chronic liver disease (Grade I). It does not improve biochemical markers among patients with chronic liver disease (Grade I). At present data do not support recommending this herbal compound for the treatment of liver disease.

GLYCYRRHIZIN (LICORICE ROOT EXTRACT)

Glycyrrhizin is an aqueous extract of the licorice root, *Glycyrrhizin glabra*. Its major constituents are glycyrrhetic acid, multiple flavonoids, isoflavonoids, hydroxycoumarins and sterols, including β-sitosteroid, which may have glucocorticoid and mineralocorticoid activities (27). Stronger neominophagen C (SNMC), a Japanese preparation that contains 0.2% glycyrrhizin, 0.1% cysteine, and 2% glyceine, is marketed in India.

Glycyrrhizin prevents several forms of experimental liver injury in animals (28). This compound has anti-inflammatory and antioxidant activities. Glycyrrhizin inhibits $CD4^+$ T cell- and tumor necrosis factor (TNF)-mediated cytotoxicity (29). However, a recent study from Japan shows augmentation of cytotoxicity mediated by NK cells, NKT cells, and TNF-α in mice (30). Glycyrrhizin has a membrane stabilizing effect (31) and also stimulates endogenous production of interferon (32).

There are few RCTs with glycyrrhizin (33–36). Abe *et al.* (33), in a randomized trial, have shown that an interferon and glycyrrhizin combination is more effective than interferon alone (33 versus 13%) in treating patients with chronic hepatitis C who have not responded to interferon monotherapy. Two reports suggest that long-term treatment with SNMC has the potential of preventing the development of hepatocellular carcinoma in patients with chronic hepatitis, especially with chronic hepatitis C (37, 38). However, these studies were retrospective and varying doses of SNMC were used. SNMC has also been reported to be useful in patients with subacute hepatic failure (39) and moderate to severe acute sporadic hepatitis E (40). A higher iv dose of 100 ml/day is better than 40 ml/day in normalizing liver enzymes (35, 36).

The largest experience from India is from the All India Institute of Medical Sciences, New Delhi. Acharya and coworkers (41) have evaluated the efficacy of SNMC in treatment of subacute hepatic failure (42), chronic hepatitis, and cirrhosis with activity.

Fifty-six patients with subacute hepatic failure in an open-label trial were treated with SNMC at a dose of 100 ml/day, for 30 days, then every other day for 8 weeks (41). The survival was better in these patients (73%) than in 98 patients with similar disease treated only with supportive treatment during the previous 10-year period (historical control). While there was a significant improvement in biochemical and liver failure-related complications, no effect was observed on development of chronic sequallae (67 versus 70%) and on HCV RNA or HBV DNA clearance.

Twenty-seven patients with chronic hepatitis (etiology: HBV, 14; HCV, 5; HBV and HCV, 2; and cryptogenic, 6) were also treated in a RCT (41). Patients in the SNMC group received SNMC, 60 ml/day iv, for 1 month, then every other day for 5 months. While there was an improvement in biochemical markers in the SNMC group, virological (HBV DNA or HCV RNA) clearance among SNMC

and control group, members was nonexistent, suggesting that glycyrrhizin is predominantly a cytoprotective (anti-inflammatory) rather than an antiviral agent.

In a RCT, 43 patients with cirrhosis with histological and/or biochemical features of active necroinflammatory activity (etiology: HBV, 25; HCV, 8; HBV + HCV, 2; cryptogenic, 8) were also treated with SNMC under the same dose regimen as used in patients with chronic hepatitis (41). The majority of patients showed biochemical improvement compared with controls, however, 36% relapsed after discontinuation of SNMC. There was no effect on overall mortality and complications or on HBV or HCV clearance.

HCV infection runs an accelerated course in renal allograft recipients. Interferon is not recommended in renal allograft recipients due to risk of graft rejection. Anand *et al.* (43) treated 10 patients with a combination of SNMC (40 mL daily for 8 weeks, followed by every other day for 8 weeks, then twice a week for 8 weeks) and ribavirin (1000 mg daily in two divided doses) and 15 patients with ribavirin (1000 mg daily in two divided doses) monotherapy. Six of 10 patients with combination therapy and 12 of 15 patients with ribavirin therapy completed the study. Biochemical response was seen in 4 of 6 (67%) patients with combination therapy and 3 of 12 (25%) patients with ribavirin monotherapy. The cause of dropout was rising serum creatinine in two patients on combination therapy and drug noncompliance in the remaining two patients on combination therapy and in three patients with ribavirin monotherapy. The results were inconclusive, however, larger studies should be planned to confirm this observation.

Treatment with SNMC is not without side effects, which are seen in a minority of patients; the main side effects are hypertension, sodium and fluid retention, worsening ascites, and hypokalemia (44, 45). Glycyrrhizin should be used cautiously in patients with a history of hypertension or renal failure or currently using cardiac glycosides.

In conclusion, SNMC does not have antiviral properties; it primarily acts as an anti-inflammatory or cytoprotective drug (Grade I). It improves mortality in patients with subacute liver failure compared to historical controls, however, it does not prevent chronic sequallae (Grade II-3). It improves liver function in patients with subacute hepatic failure (Grade II-3) and in chronic hepatitis and cirrhosis with activity (Grade I). SNMC does not reduce mortality among patients with cirrhosis with activity (Grade I). It prevents the development of hepatocellular carcinoma in patients with chronic hepatitis C (Grade II-3). Ribavirin and SNMC in combination are more effective than ribavirin monotherapy in renal allograft recipients with chronic hepatitis C (Grade II-1).

Future studies in patients with chronic hepatitis B and C must look at its effect on HBV DNA and HCV RNA levels and improvement of histological parameters in a large number of patients. Further, the active ingredients of licorice root warrant better characterization.

LIV 52

Liv 52 is considered to be an Ayurvedic hepatoprotective medicine that contains the following ingredients. *Capparis spinosa* (Himsara), *Cichorium intybus* (Kasani), Mandur bhasma, *Solanum nigrum* (Kakamachi), *Terminalia arjuna* (Arjuna), *Cassia occidentalis* (Kasamarda), *Achillea millefolium* (Biranjasipha), and *Tamarix gallica* (Jhavaka).

The manufacturer of Liv 52 recommends its usefulness in the following conditions: (1) in the prevention and treatment of (a) viral hepatitis, (b) alcoholic liver disease, (c) precirrhotic conditions and early cirrhosis, (d) protein energy malnutrition, (e) loss of appetite, and (f) radiation- and chemotherapy-induced liver damage, (2) as an adjuvant with hepatotoxic drugs, and (3) as an adjuvant during convalescence and prolonged illness. (*www.himalayahealthcare.com/products/liv_drops.htm*; accessed July 1, 2004)

Liv 52 has been on the market for over 50 years and has been claimed to be useful in a variety of conditions, as listed above; this is not well supported by well-planned RCTs. The majority of studies have been performed in a small number of patients and published in journals which are not indexed. A total of 49 papers on Liv 52 were found using a Medline search covering 1966 to June 2003 and approximately half of the studies were experimental; there are very few RCTs.

Experimental data suggest that Liv 52 inhibits lipid peroxidation (46, 47), may have a protective effect on alcohol-induced fetotoxicity (48), and inhibits TNF activity (49). In healthy adults consuming alcohol it has been shown to reduce the levels of acetaldehyde (50) Well-designed prospective RCTs in humans are lacking. However, two prospective randomized placebo-controlled trials did not show any benefit of Liv 52 in patients with alcohol liver disease (51, 52). Fleig *et al.* (51) performed a prospective, randomized, placebo-controlled trial in 188 patients with alcohol-related cirrhosis of the liver. The study consisted of 127 patients with Child–Pugh grades A and B and 59 patients with Child–Pugh grad C. While no effect on mortality of Child Pugh class A and B patients was observed, mortality of Child–Pugh grade C patients treated with Liv 52 was 81%, compared with 40% in the placebo group (23 vs 11 deaths). In another well-conducted RCT in patients with alcohol liver disease,

Liv 52 was not superior to placebo in terms of clinical outcome (52).

Liv 52 has been claimed to be useful as an adjuvant to hepatotoxic drugs; however, there are no supportive data in humans. Liv 52 is not useful in the management of alcohol liver disease (Grade I). In this era of evidence-based medicine, there is hardly any evidence to suggest that Liv 52 is useful in the treatment of any of the liver conditions that have been claimed. Thus, large-scale, urgent prospective, double blind, placebo-controlled, and randomized trials are required in patients with liver disease of various etiologies; if Liv 52 is found to be useful, then every effort should be made to isolate its active ingredient(s).

RCTs and meta-analysis are considered to be the "gold standards" in evaluating the efficacy of a drug. If one goes by these gold standards, then none of these herbal preparations passes the acid test. Though *Phyllanthus* has been evaluated in the most RCTs that showed a positive effect on clearance of HBV markers, the majority of the trials were of a poor quality and small sample size, which makes the results of meta-analysis less reliable. Silymarin is not useful in the treatment of liver disease. Glycyrrhizin merits further evaluation in large multicenter RCTs, especially in patients with subacute liver failure and chronic hepatitis. Two RCTs (51, 52) with Liv 52 in patients with alcoholic liver disease did not show any benefit of this herbal preparation.

The methodological quality of clinical trials of treatment with herbal preparations needs to be improved. The efficacy of these herbal preparations must be evaluated in rigorously designed, larger, randomized, double-blind, placebo-controlled trials. The outcome measures should include molecular methods, such as HBV DNA and HCV RNA estimation, liver histology, and end-point events. Long-term adverse events should also be monitored by a standardized, effective report system.

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