Herbal Products for Liver Diseases: A Therapeutic Challenge for the New Millennium

DETLEF SCHUPPAN,1 JI-DONG JIA,1,2 BENNO BRINKHAUS,1 AND ECKHART G. HAHN1

Use of herbal drugs in the treatment of liver diseases has a long tradition, especially in Eastern medicine. Standardization has been a problem, and randomized, placebo-controlled clinical trials to support efficacy are lacking. Some herbal extracts promoted for gastrointestinal or biliary disorders contain potent hepatotoxic alkaloids and are harmful. However, some of these extracts have yielded molecules, often related to flavonoids, with proven antioxidant, antifibrotic, antiviral, or anticarcinogenic properties, including glycyrrhizin, phyllanthin, silibinin, picroside, and baicalin, which derive from licorice root, *Phyllanthus amarus*, milk thistle, *Picrorhiza kurroa*, and sho-saiko-to, respectively, that can serve as primary compounds for the development of specific hepatotropic drugs.

BACKGROUND

Natural remedies represent a $1.8 billion market in the United States, and a single herbal preparation, silymarin, which is used almost exclusively for liver diseases, amounts to $180 million in Germany alone.1 Marketing of herbal products tripled between 1992 and 1996,1 and nearly a third of outpatients attending liver clinics use these products.2 This is reflected in the internet home pages of hepatitis foundations. Herbal products have been classified as food supplements and thus are exempt from regulations on quality control and proof of efficacy that govern standard pharmaceuticals. This is contentious in view of the biological activity of many herbals and, more worrisome, their occasionally severe toxicity.

Use of herbal medicines can be traced back as far as 2100 B.C. in ancient China (Xia dynasty) and India (Vedic period). The first written reports date back to 600 B.C. with the Caraka Samhita of India and the early notes of the Eastern Zhou dynasty of China that became systematized around 400 B.C. The recipes, once formulated, were usually expanded rather than abandoned during subsequent centuries. Expansion was stimulated by a growing understanding of the natural evolution of frequently encountered diseases and by emerging hypotheses regarding their causes. Hepatitis was and continues to be prominent. Biliary stasis in patients with jaundice, often associated with ascites and encephalopathy, led to the discovery that the liver is responsible for bile production and excretion. However, contrary to the Aristotelian Western world, which preferred the analytical approach to medicine, even when based on unfounded assumptions, the Eastern hemisphere always considered disease a manifestation of a more general imbalance of the dichotomous energies that govern life as a whole and human life in particular. In China these energies are represented by the complementary Yin (representing earth and moon, moistness, darkness and passivity the female aspect) and Yang (representing sun, dryness, light, and activity the male aspect), the balance and timely sequence of which is necessary to maintain health. In the Ayurveda (sanskrit: ayur; life; veda, knowledge) of India, similar forces are agni (strength, health, and innovation) and ama (weakness, disease, and intoxication).

With the revolution of the natural sciences and evidence-based medicine, the divide between Western and Eastern medicines appeared to widen. However, given the limitations of conventional treatment for chronic diseases and tumors, both patients and scientifically trained physicians are giving increased attention to the more holistic approach of Eastern medicine. Although this may represent in part a trend towards mysticism in our modern world, the effectiveness of Eastern medicine is amenable to Western analysis. One explanation is the placebo effect, part of which can be explained by modulation of neurotransmitters or the immune system in the brain, and another is the fact that some herbal drugs contain ingredients that specifically treat disease.

EFFICACY AND SAFETY OF HERBAL PRODUCTS

Any evaluation of herbal products faces major problems. The first is the use of mixed extracts (concoctions) and variations in methods of harvesting, preparing, and extracting the herb, which can result in dramatically different levels of certain alkaloids. The biologically active substances have been structurally defined and standardized for only a few of the herbs. Even then, it may not be known if this molecule is the sole active principle or if efficacy depends on the mixture of compounds.

The second problem is a lack of randomized, placebo-controlled clinical studies. Traditional Eastern medicine relies on empiricism and a holistic philosophy, and controlled studies are considered unnecessary. This is a view shared by many Western supporters of alternative medicine. Also, trials may not use end points, such as death from liver disease, histological fibrosis or inflammation, cancer, and transplantation.
Related to these issues is concern about the safety of herbal remedies. Numerous reports of toxic effects contradict the popular view that herbs are natural and therefore harmless. A survey of the National Poison Information Service for the years 1991-1995 documented 785 cases of possible or confirmed adverse reactions to herbal drugs, among which hepatotoxicity was the most frequent. The real number is probably much higher because of underreporting. Although abnormal liver function tests mostly return to normal once the offending drug is withdrawn, cases of chronic disease and acute liver failure requiring transplantation have been reported.

There are groups of plant alkaloids with well established hepatotoxicity (Table 1). There are groups of plant alkaloids found in herbal teas or enemas containing Crotalaria, Senecio, Heliotropium, or Symphytum damage the hepatic central vein endothelia, causing veno-occlusive disease that may be lethal or require transplantation. Germander (Teucrium chamaedrys L.), broadly used in France as an antipyretic for treatment of abdominal discomfort and for weight reduction, contains hepatotoxic alkaloids identified as furano-diterpenoids that, after activation by the hepatic cytochrome P450 3A, deplete glutathione and precipitate hepatocyte necrosis, apoptosis, and cytoskeletal disorganization. Greater celandine (Chelidonium majus) has resulted in acute hepatitis; extracts of this herb are broadly used in Europe to treat gallstone disease and dyspepsia. Hepatotoxicity can result also from misidentification or mislabeling of a plant, contamination by chemicals such as heavy metals, and incorrect storage that leads to microbial or fungal growth and toxin production. Safety testing is needed. Before this can be implemented, however, preparations must be standardized and must replace in the market the uncontrolled and individualized concoctions currently being offered. Safety concerns notwithstanding, sufficient scientifically useful data have accumulated during the last few years to allow an overview of herbal compounds, some of which appear to be beneficial and may serve as a basis for future drug development.

STUDIES OF DEFINED FORMULATIONS OF HERBAL MEDICINES

Some herbal preparations exist as standardized extracts with major known ingredients or even pure compounds, for which pharmacodynamic and pharmacokinetic data are usually available. These resemble the medications of traditional Western medicine. In only a few cases, however, have studies documented their efficacy using accepted parameters of disease progression.

Glycyrrhizin. This group of related, sulfated saponins and lectins from the licorice root has been used for over 20 years to treat chronic viral hepatitis in Japan. It has a well-documented transaminase-lowering effect. The standardized aqueous extract (Stronger Neo-Minophagen C) has to be administered parenterally. A daily dose of 80 mg given for 2 weeks can normalize aspartate transaminase and alanine transaminase in over 60% of patients. The preparation has immunosuppressive and anti-inflammatory effects in cell culture, where glycyrrhizin inhibits CD4+ T cell- and tumor necrosis factor-mediated cytotoxicity. Furthermore, the extract modifies glycosylation and blocks sialylation of hepatitis B surface antigen (HBsAg), which leads to its retention in the trans-Golgi apparatus. In an uncontrolled trial of 17 hepatitis B antigen-positive patients with chronic hepatitis B, a 4-week course of glycyrrhizin followed by 4 weeks of interferon-alfa produced loss of hepatitis B e antigen in 10 of 17 patients after 6 months. However, only 3 of the 10 patients underwent seroconversion to antibodies to e antigen, and virus titers were not reported. In a small randomized study of 28 patients with chronic hepatitis C who were nonresponders to interferon monotherapy, 13.3% became hepatitis C virus–RNA negative after interferon alone compared with 33.3% after a glycyrrhizin/interferon combination therapy over 3 months. However, this was not statistically significant. In a retrospective analysis of 84 patients with chronic hepatitis C virus infection who were treated with intravenous glycyrrhizin 2 to 7 times weekly for a median of 10.1 years, comparison with a matched group of 109 patients who remained untreated over 9.2 years revealed a 2.5-fold reduction of the relative risk of hepatocellular carcinoma. This could be due to an anti-inflammatory effect of the preparation rather than to its weak antiviral effect. Because of its aldosterone-like activities, use of the drug requires caution and monitoring for hypertension, hyperkalemia, and worsening ascites.

Phyllanthus amarus. This herb and related species are Indian plants that contain phyllantins, hypophyllantins, and polyphenols with antiviral properties. An aqueous extract inhibited

<table>
<thead>
<tr>
<th>Causative Plants</th>
<th>Toxic Agents</th>
<th>Symptoms</th>
<th>Mechanism/Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crotalaria</td>
<td>Pyrrolizidine alkaloids</td>
<td>Veno-occlusive disease</td>
<td>Endothelial cell glutathione depletion, central vein necrosis, thrombosis, and fibrosis</td>
</tr>
<tr>
<td>Senecio</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heliotropium</td>
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<td></td>
<td></td>
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<tr>
<td>Symphytum officinale (Comfrey)</td>
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<td></td>
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<tr>
<td>Atractylis gummifera</td>
<td>Atractylate, gummiferin</td>
<td>Hepatitis</td>
<td>Inhibition of oxidative phosphorylation, hepatic necrosis</td>
</tr>
<tr>
<td>Callitopsis laevoila</td>
<td>Atractylate</td>
<td>Hepatitis</td>
<td></td>
</tr>
<tr>
<td>Chelidonium majus (greater celandine)</td>
<td>Chelidonine, sanguinarine, berberine, coptisine?</td>
<td>Hepatitis (cholestatic)</td>
<td>Lymphocyte infiltration</td>
</tr>
<tr>
<td>Larrea tridentata (chaparral)</td>
<td>Guaiaretic acid derivatives</td>
<td>Hepatitis</td>
<td>?</td>
</tr>
<tr>
<td>Teucrium chamaedrys (germander)</td>
<td>Furano-diterpenoids</td>
<td>Hepatitis</td>
<td>Hepatocyte glutathione depletion and apoptosis</td>
</tr>
<tr>
<td>Chinese herbal mixtures (artemisia, hare's ear, chrysanthemum, plantago seed, gartimia, red peony root, etc.)</td>
<td>Largely undefined</td>
<td>Hepatitis</td>
<td>?</td>
</tr>
</tbody>
</table>

NOTE. Data are selected from Larrey and Pageaux, Kaplowitz, Benninger et al., and Yoshida et al.
woodchuck hepatitis virus DNA polymerase and surface antigen expression and several protein kinases such as cAMP-dependent protein kinase, protein kinase C, and myosin light-chain kinase in rat liver. A nonrandomized clinical study showed a remarkable 59% (22 of 37 patients) clearance of HBsAg in chronic carriers who were treated for 30 days compared with only 4% (1 of 23 patients) given placebo. However, these results await confirmation. There was no effect of P. amarus on duck hepatitis B virus.

Daphnoretin. This dicoumarin drug extracted from the Chinese herb Wilkstroemia indica was shown to suppress HBsAg in Hep3B cells, an effect mediated by activation of protein kinase C. The same investigators reported a powerful suppression of HBsAg by costunlate and dehydrocostus lactone, two alkaloids from Saussurea lappa Clarks root. However, no clinical studies with these compounds have been reported.

Silymarin. A standardized extract from the milk thistle Silybum marianum contains as its main constituents the flavonoids silybinin, silydianin, and silychristin. Milk thistle extracts were used as early as the 4th century B.C., became a favored medicine for hepatobiliary diseases in the 16th century, and experienced a revival in central Europe in the late 1960s (Table 2). The flavonoid silibinin, which constitutes 60% to 70% of silymarin, has been identified as the major active ingredient. Its pharmacological profile is well defined, and studies in cell culture and animal models clearly show its hepatoprotective action with little or no toxicity. Silymarin enhances the activity of hepatocyte RNA-polymerase I, complexes toxic free iron, protects the cell membrane from radical-induced damage, and blocks the uptake of toxins such as Amanita phalloides toxin. A potent scavenger, it prevents lipid peroxidation and normalizes the lipid profile of hepatocyte membranes. Silymarin provided liver protection in rat models of liver damage induced by carbon tetrachloride and paracetamol. Four of 12 dogs fed lyophilized Amanita toxin and given supportive care died from hepatic failure and coma within 35 to 54 hours, whereas all 11 dogs receiving high-dose silymarin survived. In a retrospective analysis of 205 patients with Amanita intoxication, of whom 30 received treatment, the death rate of those given intravenous silymarin was reduced significantly (12.8% vs. 22.4%).

In recent in vitro studies, silymarin down-regulated the proinflammatory leukotriene B4 in Kupffer cells. In randomized clinical trials for acute viral hepatitis A or B, oral silymarin either exerted no benefit or accelerated clinical recovery, causing a significantly more rapid normalization of bilirubin and aspartate transaminase than did the control.

Similarly, in alcohol-related hepatitis treated with silymarin, transaminase levels dropped more rapidly than in the untreated disease. A 4-month course of silymarin in patients with moderately active alcohol-related liver disease led to a 41% reduction of alanine transaminase, compared with no change in controls. In a randomized trial, 170 biopsy-proven cirrhotic patients, 92 with alcohol-related and 78 with nonalcohol-related liver disease, were treated with silymarin or placebo for a mean of 41 months. Although serum biochemistry values did not differ between the 2 groups, the number of surviving cirrhotic patients with alcohol-related liver disease was significantly higher in the silymarin group, especially in those with Child-Pugh class C cirrhosis. Most of the latter patients continued to drink, which may have influenced the results. Also, the dropout rate was high, although dropouts were counted as therapy failures. A subsequent randomized, placebo-controlled study of 200 patients with alcohol-related cirrhosis, 75 of whom dropped out, could not confirm a survival benefit.

These data point up the difficulty of studying a heterogeneous group of patients and of using death as the endpoint for a condition that progresses over many years. An intermediate endpoint is progression of fibrosis to cirrhosis, which is the primary determinant of morbidity and mortality in patients with chronic liver diseases. In vitro, silymarin blocks proliferation of hepatic stellate cells, the main source of excess collagen in fibrosis. This is accompanied by down-regulation of the profibrogenic transforming growth factor β. In liver injury induced by complete occlusion of the biliary system in the rat, oral silymarin reduced collagen accumulation in a dose-dependent fashion. It was similarly antifibrotic when administered from weeks 4 to 6, i.e., starting at a time when liver collagen is already increased 4-fold, a situation encountered in most patients with chronic liver disease. The antifibrotic effect was accompanied by reduced numbers

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**Table 2. History of the Milk Thistle as a Liver Remedy**

<table>
<thead>
<tr>
<th>Century/Year</th>
<th>Use/Indication</th>
<th>Characterization/First Clinical Studies</th>
<th>Source (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th Century B.C.</td>
<td>General medicinal herb</td>
<td>Characterization of active compounds</td>
<td>Wagner et al.29 and Sonnenbichler et al.30</td>
</tr>
<tr>
<td>1st Century A.D.</td>
<td>Emetic, general medicinal herb</td>
<td>First animal experimental studies on liver protection</td>
<td>Platt et al.32</td>
</tr>
<tr>
<td>11th Century A.D.</td>
<td>Ucers, shingles</td>
<td>Antidote for Amanita phalloides intoxication in the rat</td>
<td>Schriewer et al.36</td>
</tr>
<tr>
<td>1564</td>
<td>Stitch in the side, astringent</td>
<td>Elucidation of molecular actions of silybinin</td>
<td>Sonnenbichler et al.38</td>
</tr>
<tr>
<td>1626</td>
<td>Stitch in the side, paresthesia, renal calculi</td>
<td>First controlled clinical studies in acute viral hepatitis</td>
<td>Bode et al.39 and Maghul et al.40</td>
</tr>
<tr>
<td>1759</td>
<td>Liver disease, liver pain</td>
<td>First controlled study in alcoholic cirrhosis</td>
<td>Benda et al.31</td>
</tr>
<tr>
<td>1846/1951</td>
<td>Liver disease, icterus, biliary colic</td>
<td>Amanita phalloides antidote in clinical studies</td>
<td>Hruby et al.32</td>
</tr>
<tr>
<td>1938</td>
<td>Hepato-cholangiopaties, chronic leg ulcers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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of activated stellate cells and a greater than 50% reduction of both procollagen I and tissue inhibitor of metalloproteinase messenger RNA, both being major effectors of fibrogenesis. These data have spawned randomized, placebo-controlled studies of silymarin in patients with chronic viral hepatitis that include follow-up biopsies and a panel of serum markers of liver fibrosis.

Picroliv. Picroliv is an alcoholic extract from the root of *Picrorhiza kurroa* that contains the iridoid glycosides kutkoside and picroside. In the rat these glycosides act as antioxidants and ameliorate the hepatotoxic effects of carbon tetrachloride, thioacetamide, galactosamine, and paracetamol. Despite their wide oral usage in India, no reliable data for human liver disease exist.

TJ-9. TJ-9, commonly prescribed in China as shao-saiko-to, is an aqueous extract from the roots of scutellaria, glycyrrhiza, bupleurum, and ginseng; the pine needle; the jujube fruit; and the thew ginger rhizome. Two major alkaloids from scutellaria, baicalin and baicaicain, are strong inhibitors of lipid peroxidation. The extract prevented hepatocellular membrane damage and restored mitochondrial function in endotoxin-treated rats, increasing hepatic levels of superoxide dismutase and glutathione. Other *in vitro* effects that are related to the observed antitumour activity of shao-saiko-to include up-regulation of the inducible nitric oxide synthase in hepatocytes cultured in the presence of interferon-γ and inhibition of proliferation and induction of apoptosis in hepatoma cells. The extract modulated the *in vitro* cytokine production in peripheral blood mononuclear cells, stimulated release of tumor necrosis factor-α and granulocyte-colony-stimulating factor in patients with hepatocellular carcinoma and down-regulated synthesis of interleukin-4 and -5 in favor of interleukin-10 in patients with chronic hepatitis C.

Other *in vitro* effects include stimulation of inducible nitric oxide synthase and down-regulation of interleukin-4 and -5 in favor of interleukin-10 in patients with chronic hepatitis C. In the rat model of dimethylnitrosamine-induced liver injury, the extract shao-saiko-to protected liver synthetic function and restored hepatic retinoid levels. An extract of several plants prepared for ayurvedic medicine has been marketed in the West as LIV.52. Standardization, chemical characterization, functional, and pharmacological studies are not well documented. The extract was reported to improve serum biochemistry values in rats with toxic liver damage, and uncontrolled observations in patients with liver disease seemingly gave similar results. Furthermore, it lowered circulating levels of acetaldehyde in healthy adults consuming alcohol. Therefore, Fleig et al. performed a randomized, placebo-controlled, 2-year clinical trial in 188 patients with alcohol-related cirrhosis. LIV.52 did not affect the survival rate of Child class A and B patients but increased mortality among the 59 Child class C patients (81% in the treated group, compared with 40% in the placebo group). Twenty-two of 23 deaths in the LIV.52 group were related to bleeding or liver disease compared with only 3 of 11 deaths in the placebo group. This result led to immediate withdrawal of the drug. It highlights the danger of ill-defined herbal preparations and the necessity for in-depth preclinical testing.

**FUTURE DIRECTIONS**

There is no doubt that certain herbal products contain chemically defined components that can protect the liver from oxidative injury, promote virus elimination, block fibrogenesis, or inhibit tumor growth. Although additive effects may be lost, the active molecules must be isolated and tested in suitable culture and animal experiments and finally in randomized, placebo-controlled studies to enable rational clinical use of the agents. Biologically active molecules derived from herbal extracts can serve as suitable primary compounds for effective and targeted hepatotropic drugs.

**REFERENCES**

Silybum marianum


