

# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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## Herbal Products and the Liver: A Review of Adverse Effects and Mechanisms



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Herbal products have been used for centuries among indigenous people to treat symptoms and illnesses. Recently, their use in Western countries has grown significantly, rivaling that of prescription medications. Currently, herbal products are used mainly for weight loss and bodybuilding purposes but also to improve well-being and symptoms of chronic diseases. Many people believe that because they are natural, they must be effective and safe; however, these beliefs are erroneous. Few herbal products have been studied in well-designed controlled trials of patients with liver or other diseases, despite testimony to the contrary. Moreover, current highly effective antiviral drugs make efforts to treat hepatitis C with herbal products redundant. Herbal products are no safer than conventional drugs and have caused liver injury severe enough to require transplantation or cause death. Furthermore, their efficacy, safety, and claims are not assessed by regulatory agencies, and there is uncertainty about their reported and unreported contents. We review the history of commonly used herbal products, as well as their purported efficacies and mechanisms and their adverse effects.

**Keywords:** Dietary Supplement Health and Education Act; Contamination and Adulteration; Herbal Therapies; silymarin.

Pharmacological agents emerged in the 19th century, when work in the textile and synthetic dye industry produced organic chemicals distilled from coal tar.<sup>1</sup> Before that, indigenous people treated illnesses with herbal products; these practices date back more than 5000 years.<sup>2</sup> Supporting evidence comes from clay tablets by Sumerian people in Mesopotamia (Babylonia) as well as writings in a book from China titled *Pen Tsao*, describing >300 herbs for medical treatments that included ma huang containing ephedra. More than 3000 years ago, numerous herbs used in the Indian medical system called Ayurveda were listed in the Indian *Materia Medica*. Other early cultures that used herbal products as medicine included the ancient Greeks (Hippocrates was a herbalist), Romans, Egyptians, and

Arabs, as well as native people of Africa, Australia, New Zealand, the South Pacific Islands, and the Americas. Interestingly, early European immigrants to the United States learned much about herbal medicines from Native Americans as part of their healing tradition.

During the Middle Ages, monks preserved interest in medicinal herbs, aided by works compiled by Arab cultures. An Iranian physician, Ibn Sina, known as Avicenna, created *The Canon of Medicine*, an influential medical text based on herbal traditions. Interest in herbs grew during the Renaissance period, fueled by wealthy landowners who obtained spices from the East to flavor foods. In 1652, Nicholas Culpeper developed a systematic listing of all known herbs. In the early 18th century, because of confused nomenclature, the Swedish botanist Linnaeus catalogued all known plants, including medicinal plants, using Latin names.

### Sources and Production of Herbal Products

Herbal products used for medicinal purposes comprise 3 broad categories. First are individual crude herbal products derived from plants (stems, roots, leaves, berries, seeds, flowers) and barks of trees, used over centuries and selected generally by traditional healers. Their chemical constituents are often unknown or not fully characterized and may vary widely depending on weather conditions, geographic location, and elevation where grown. Most are given as a single product, although some, such as traditional Chinese medicines (TCMs) or Japanese Kampo medicines, may include several herbal products bundled together, selected by experienced herbalists based on traditional values and long use. Herbal products are administered as infusions, decoctions, syrups, poultices, lotions, or

**Abbreviations used in this paper:** ALT, alanine aminotransferase; CAM, complementary and alternative medicine; CHC, chronic hepatitis C; CYP, cytochrome P450; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; EGCG, epigallocatechin gallate; FDA, Food and Drug Administration; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; mRNA, messenger RNA; NAFLD, nonalcoholic fatty liver disease; SNMC, Stronger Neo-Minophagen C; TCM, traditional Chinese medicine.

compresses. Most have not been evaluated for efficacy (or safety) by scientific methods such as controlled trials, and effective doses have rarely been established.

The second category is botanicals, the chemical constituents of which were used to synthesize potent and effective conventional drugs and helped launch the pharmaceutical industry. Through the mid-1980s, more than 80% of drugs were derived from plants; this value is now approximately 15%. Examples are willow bark containing acetylsalicylic acid, the precursor of aspirin; china bark (cinchona), the original source for quinine; poppies that yielded opioids and morphine; purple foxglove, from which digitalis was extracted; deadly nightshades (jimson weed, mandrake), the source for atropine; and many others. Some anticancer drugs also originated from herbal products, including alkaloids derived from berberine and piperine and vincristine from Madagascar periwinkle<sup>3</sup>; efforts to seek botanicals that might yield new chemotherapeutic agents continue.

The third category encompasses the burgeoning commercial herbal industry that creates and markets products under trade names, now the predominant type used in Western countries, as much with the hope of improving well-being as for treating illnesses. Products generally contain multiple constituents, ranging in number from 2 to more than a dozen, and may include additional components such as vitamins. Constituents are selected for their purported individual benefits, not necessarily by an experienced herbalist and without evidence that the combination is complementary. Like traditional herbal products, few if any have been evaluated for true benefit using scientific methods. For some, there is concern about contamination and/or adulteration.

## Epidemiology and Expenditure

The use of complementary and alternative medicines (CAMs) is unquestionably increasing, especially in Western countries. In an extensive national telephone survey conducted in the United States in 1990, 34% of respondents reported using CAMs during the preceding year, with 2.5% using herbal products.<sup>4</sup> On further analysis, 67.6% admitted using an alternative therapy during their lifetime, a secular trend believed to have started half a century earlier.<sup>5</sup> When the investigators repeated the telephone survey in 1997, they found that use of CAMs had increased to 42%, with 12.1% of participants using herbal products.<sup>6</sup>

The same trend was reported in a series of National Health and Nutrition Examination Surveys. In the survey conducted from 1971 to 1974, 23% of the general population reported using vitamin supplements.<sup>7</sup> From 1976 to 1980, 35% of the population reported using supplements (predominantly older people with higher education and income levels).<sup>8</sup> From 1988 to 1994, 35% of men and 44% of women took supplements<sup>9</sup>; this value increased to 52% between 1990 and 2000.<sup>10</sup>

Similarly, a 1999 National Health Interview Survey of noninstitutionalized civilians found that 28.9% of adults used at least one CAM in the preceding year, with 9.8% using herbal products.<sup>11</sup> In a further analysis of the data,

38.2 million US adults were estimated to have used CAMs during 2002, with women using CAMs more frequently than men.<sup>12</sup> Also, a telephone health and dietary survey among noninstitutionalized US adults, sponsored by the US Food and Drug Administration (FDA), found that 73% of respondents used dietary supplements, with 4% attributing an adverse event to the supplement.<sup>13</sup>

These findings are similar in other Western countries. A survey from Europe involving 6 European countries (Finland, Germany, Italy, Romania, Spain, and the United Kingdom) found that among 2359 consumers, 18.8% admitted using one or more plant food supplements.<sup>14</sup>

Expenditures have paralleled use. Based on the telephone surveys, it was estimated that \$13.2 billion was spent on CAMs in 1990,<sup>4</sup> increasing to \$27 billion in 1997.<sup>6</sup> The National Center for Complementary and Alternative Medicine estimated an expenditure of \$33.9 billion in 2007, equivalent to approximately one-third of total out-of-pocket spending on prescription drugs.<sup>15</sup> Most informative are data from the American Botanical Council, who have tracked annual sales of herbal products in the United States since 1999. Except for 2002 and 2003, sales increased each year from \$4110 million in 1999 to \$5600 million in 2012.<sup>16</sup>

Practitioners must be aware of these trends and always query their patients regarding use of herbal products.

## Reasons for Using Herbal Products

Some people believe that pharmaceutical drugs are too costly, cause adverse effects, and conflict with their personal beliefs in natural healing.<sup>17</sup> Others regard general medical care as lacking compassion and time restricted. Most, however, believe that because medicinal herbal products have been used for centuries, they must be effective and safe; this view is bolstered by positive feedback from the Internet and testimonials. Unfortunately, many people who use herbal products are reluctant to inform their physicians of their use for fear of reprimand.

Herbal products are used to complement conventional medications or as an alternative to pharmaceuticals, hence the term CAM. Using unproven herbal products alone to treat serious diseases such as cancer, human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome, diabetes, and cardiovascular and liver diseases, among others, obviously carries great risk.<sup>18-20</sup> Those who use herbal products also have other objectives; in a recent questionnaire, their goals, in order of prevalence, were to influence the natural history of the disease, promote well-being, reduce adverse effects, take control of their lives, relieve symptoms, provide emotional support, improve quality of life, cope better with illness, and support natural healing.<sup>21</sup>

## Regulation of Herbal Products and Dietary Supplements in the United States

At the turn of the 20th century, the American Medical Association, concerned by the flood of patent medicines in

the United States, pushed unsuccessfully for federal evaluation of new medical products.<sup>22</sup> Later, mounting evidence of product adulteration or misbranding prompted the first federal food and drug statute, the 1906 Pure Food and Drugs Act. The Bureau of Chemistry, the predecessor of the FDA, now had the power to seize adulterated or misbranded medicinal products. Thereafter, a series of amendments evolved, often instigated by catastrophic events. In 1937, a liquid preparation of the antibiotic sulfanilamide, suspended in diethylene glycol, caused more than 100 deaths, prompting the 1938 Food, Drug, and Cosmetic Act, requiring premarket submission of safety data. In 1958, Senator Estes Kefauver from Tennessee held Congressional hearings, concerned by high markups on drugs and the poor quality of clinical research conducted by drug companies. In 1961, another medical crisis, the development of appalling birth defects from thalidomide, occurred mostly in Europe but also in the United States because American physicians received samples and gave patients the unapproved drug. This led to the 1962 Drug Amendments requiring premarketing controlled clinical trials to demonstrate the efficacy and safety of drugs. Other modifications have followed, aimed mostly at increasing the use and improving the quality of controlled clinical trials.

In the late 1980s to 1994, the FDA regulated herbal products as foodstuffs. Regulatory intervention was required for products claiming to treat, cure, mitigate, or prevent disease, directly affecting manufacturers who alleged their products could combat disease. Congress then considered bills to tighten product labeling regulations, with one titled the Nutrition Advertising Coordination Act of 1991. Incensed by these events, herbal companies lobbied Congress.

A new bill was introduced in 1994 titled the Dietary Supplement Health and Education Act.<sup>23</sup> It defined a dietary supplement as a vitamin, mineral, herb or other botanical, amino acid, or dietary substance to supplement the diet that may exist as a concentrate, metabolite, constituent, extract, or combination of ingredients. The Act permitted manufacturers to market such products without registering them or requiring FDA approval. Manufacturers of herbal products were now themselves responsible for ensuring the safety of their supplements and their ingredients. Whereas the FDA requires pharmaceutical companies to prove that their drugs are effective and safe before marketing, dietary supplements could now be marketed without these requirements, shifting the burden of proof to the FDA to prove lack of safety.

Manufacturers are required, however, to provide truthful labeling that complies with Current Good Manufacturing Practices. A new directive published later, titled the 2007 Final Rule for Supplement Current Good Manufacturing Practices, requires manufacturers to assure the absence of contamination and adulteration. More recently, the FDA drafted a new guidance, Draft Guidance for Industry Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: July 2012, requiring notification if any ingredient not listed in 1994 is now added.

## Regulation of Herbal Products in Other Countries

### *European Union*

Traditional medicines must be registered and products approved as established by the Traditional Herbals Medicine Products Directive 2004/24/EC. Acceptable products are those “plausible on the basis of long-standing use and experience” and deemed safe after 30 years of use, including at least 15 years in the European Union.

### *United Kingdom*

Beginning in 2005, the quality, efficacy, and safety of herbal products have been reviewed by the Herbal Medicines Advisory Committee, requiring adherence to the EU Directive. Previously, the 1968 Medicine Act covered herbal regulations.

### *Canada*

The Natural Health Products Act requires licensure of manufacturers, products, packages, and importers, evidence of safety and efficacy, and specific labeling.

### *Asia*

A subdivision of the State Food and Drug Administration governs registration of herbal products in China, whereas the Ministry of Health, Labor and Welfare does so in Japan. For additional information on regulation in other countries, see a review published elsewhere.<sup>24</sup>

## Issues of Concern

### *Standardization*

Herbal constituents vary with season, location, and altitude at which the herb was grown, so the same product can vary from batch to batch. The extraction process produces variable concentrations of chemicals, including fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, and others.<sup>25</sup> The actual effective constituent is rarely known, so some manufacturers base standardization on a presumed active ingredient. Labeling constituents are not always followed faithfully. Twenty-five commercial ginseng products obtained from a local health food store and analyzed for specific constituents were found to have different concentrations of ginseng than stated on the label and to have significant variation among products.<sup>26</sup>

### *Contamination and Adulteration*

Plants cultivated as sources for herbal medications are generally sprayed with pesticides or may be collected from the wild and then harvested, washed, dried, sorted, and their constituents extracted using several methods. Unfortunately, contamination by pesticides, microbial agents, mycotoxins, and even heavy metals such as lead, mercury, or arsenic has been reported, particularly in herbal products sold over the Internet.<sup>27–30</sup>

Furthermore, there have been numerous reports of the addition of unlabeled drugs to commercial herbal products.

Examples include benzodiazepines, chlordiazepoxide, chlormethiazole, chlorpheniramine, corticosteroids, diclofenac, diethylstilbestrol, diphenhydramine, indomethacin, promethazine, sildenafil citrate, triamterene, and warfarin.<sup>31–33</sup>

### Deceptive Marketing

Although regulations prohibit claims that herbal products can treat, prevent, or cure specific diseases, some have misleading labels, especially those sold via the Internet. There are similarly reports of deceptive marketing of products sold in retail stores and on web sites.<sup>34,35</sup> Daniel Fabricant, the former director of the Division of Dietary Supplement Programs, Center for Food Safety and Applied Nutrition, FDA, stated in a Natural Products Association webinar in April 2012 that he was “somewhat aghast” at the level of manufacturer noncompliance with dietary supplement Current Good Manufacturing Practices.<sup>36</sup> Moreover, when interviewed 1 year later at a show in Las Vegas, he noted that violations of Good Manufacturing Practices seemed to have remained at the same level as the previous year.<sup>37</sup>

### Herbal Products for Liver Diseases

Before the era of scientific discovery that facilitated the discovery and categorization of diseases, herbal products were not used to treat specific illnesses but rather their symptoms. For people with liver disease, jaundice was the primary symptom treated by herbal products. In ancient China, the therapeutic approach differed. Illness was considered a consequence of disordered body energies (imbalance between yin and yang), and botanicals were given as part of a holistic philosophy to rebalance the whole body by boosting the mind, body, and environmental equilibrium. People began using herbal products to treat specific diseases as their identification became possible; the liver diseases targeted have been cirrhosis (largely of alcohol origin), viral hepatitis, and fatty liver diseases. Also, because some botanicals appeared to be hepatoprotective, they have been used to treat or protect the liver against toxic insults.

Herbal products have shown modest effects in animal studies of liver injury, reducing increases in serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase, decreasing necroinflammatory scores, and reducing fibrosis on liver biopsy.<sup>38–40</sup> For humans with liver diseases, there are countless reports describing treatment with herbal products. Surveys show that 20% to 30% of patients with chronic liver disease use herbal products, often together with conventional medications.<sup>20,41</sup> However, few products have been adequately evaluated in well-designed, double-blind, controlled trials, so there is little meaningful evidence to support their benefits, despite claims of manufacturers, distributors, and testimonials. In an analysis of more than 1000 plants marketed in Western countries, only 156 clinical trials provided evidence to support their specific pharmacological activities and therapeutic applications. Only 9 plants had considerable evidence of therapeutic effect.<sup>42</sup>

A search of [ClinicalTrials.gov](http://ClinicalTrials.gov) lists 40 studies of herbal products to treat liver diseases (Table 1). Among these, 18

involve silymarin, 15 involve TCM, 4 involve glycyrrhizin, and 3 involve Sho-saiko-to. It is noteworthy that although 17 studies have been completed and recruiting continues in 8 studies, the remaining 15 studies are listed as terminated, suspended, active but not recruiting, or unknown. Also of note is that there are associated publications for only 4 of the 40 studies, none of which offer usable information on efficacy. Presented here are data on silymarin in particular but also on TCM, *Glycyrrhiza glabra*, and Sho-saiko-to. Less frequently used herbal products, none of which have been subjected to controlled trials, are curcumin (turmeric), *Picrorhiza kurroa*, and *Phyllanthus amarus* (see [Supplementary Material](#)).

### Silybum marianum (Silymarin; Milk Thistle)

By far, the most popular and potentially effective herbal product used to treat liver disease is silymarin. The major components of silymarin are a related series of compounds with similar basic structure; these include polyphenolic flavonoids with quinone structures, some with alcohols, and *O*-methyl side chains (Figure 1).<sup>43</sup>

When a healthy person is given a single 600-mg oral dose of standardized silymarin, the major flavonolignans are rapidly conjugated (glucuronidated and sulfated) and eliminated with short half-lives (1–3 hours and 3–8 hours for free and conjugated species, respectively). The areas under the curves for plasma-conjugated flavonolignans are 4- to 30-fold higher than their free fractions. Thus, after oral administration, silymarin flavonolignans are metabolized rapidly to form glucuronides, and the conjugates are the principal components present in human plasma.<sup>44</sup>

Recent pharmacokinetic studies in subjects with nonalcoholic fatty liver disease (NAFLD) or chronic hepatitis C (CHC) have shown variable effects on silymarin parent drug and metabolite levels. Not surprisingly, areas under the curves (0–24 hours) were higher in subjects with CHC with cirrhosis and in those with NAFLD compared with controls.<sup>45</sup>

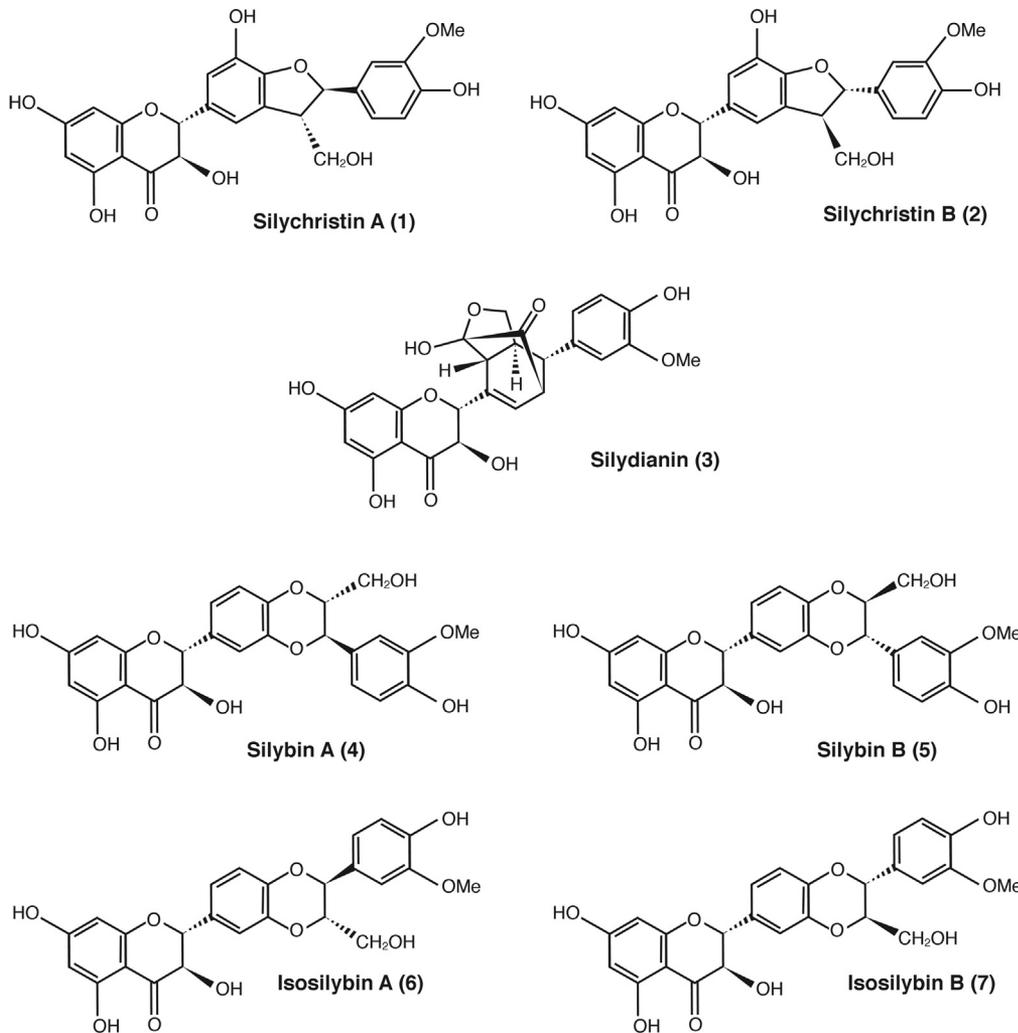
Silymarin is an established therapy for acute mushroom poisoning from *Amanita phalloides* in Europe, especially in Germany.  $\alpha$ -Amanitin and  $\beta$ -amanitin account for >90% of the total amatoxin content of *A phalloides*. The lethal dose for humans is  $\sim 0.1$  mg/kg body wt. Ingestion of 5 to 7 mg of amatoxins (an amount found in <50 g of fresh mushrooms) may be lethal.<sup>46</sup> Toxicity results from the avid binding of a subunit of DNA-dependent RNA polymerase, causing overall inhibition of new messenger RNA (mRNA) synthesis, inhibition of protein synthesis, and necrosis of hepatocytes and other cells. Enterocytes and tubular epithelium of the kidneys are also affected because they are exposed to relatively high concentrations of the toxin, along with cells undergoing large amounts of mRNA and protein synthesis.

In the United States, Legalon SIL (Rottapharm, Madaus, Cologne, Germany), a water-soluble form of silybinin, is the chief product used for treatment of *Amanita* poisoning. Treatment should begin promptly after ingestion, because survival correlates with rapidity of administration. Legalon

**Table 1.**List of Herbal Products Used to Treat Liver Diseases ([ClinicalTrials.gov](http://ClinicalTrials.gov))

Study	Clinical trial identifier	Status
Silymarin for treatment of non-alcoholic fatty liver disease (NAFLD)	NCT02006498	Recruiting
Phase II trial of silymarin for patients with chronic hepatitis C who failed conventional antiviral treatment	NCT00680342	Completed <sup>a</sup>
Phase II trial of silymarin for non-cirrhotic patients with NAFLD	NCT00680407	Active, not recruiting
Study to evaluate the effect of RGMA001 on NAFLD	NCT01511523	Invitation
Clinical research study to determine if treatment of HCV with milk thistle is more effective than no treatment in patients with HIV and hepatitis C	NCT00246363	Completed
Legalon SIL for treatment of HCV recurrence in liver transplanted patients	NCT01535092	Terminated
Randomized study for assessment of silibinin (Legalon® SIL) in treatment of naïve genotype 4 patients with chronic hepatitis C	NCT01871662	Not yet recruiting
Effect of Legalon SIL on HCV recurrence in stable liver transplant patients	NCT01518933	Terminated
THISTLE – the HIV-HCV silibinin trial	NCT01816490	Recruiting
Intravenous milk thistle (Silibinin-Legalon) for hepatic failure induced by amatoxin/amanita mushroom poisoning	NCT00915681	Recruiting
Efficacy of silymarin on the prevention of hepatotoxicity from antituberculosis drugs	NCT01800487	Completed
Efficacy of silymarin for acute hepatitis	NCT00412763	Completed
Effects of <i>Silybum marianum</i> on treatment of patients with chronic hepatitis C	NCT01292161	Completed
Randomized placebo-controlled trial evaluating the safety and efficacy of silymarin treatment in patients with acute viral hepatitis	NCT00755950	Terminated
To study the efficacy and safety of Renessans in chronic HCV infection	NCT01463592	Unknown
Safety, metabolism, and antioxidant activity of silymarin and green tea extract in patients with chronic hepatitis C	NCT01018615	Completed
Clinical study with silymarin in patients with chronic hepatitis C infection who failed conventional antiviral therapy	NCT 01258685	Completed
Intravenous silibinin in combination with peg-interferon and ribavirin in nonresponders	NCT00684268	Completed <sup>a</sup>
Clinical trial of NAFLD treated by Traditional Chinese Medicine	NCT01677325	Completed
Role of pioglitazone and berberine in treatment of NAFLD	NCT00633282	Completed
Traditional Chinese Medicine combined with entecavir to treat refractory liver fibrosis in liver cirrhosis due to HBV liver cirrhosis	NCT07241616	Recruiting
A clinical evaluation on Traditional Chinese Medicine diagnosis and treatment program blocking and reversing hepatitis B-related liver fibrosis: a randomized, controlled, double-blind, multicenter clinical trial	NCT02965418	Recruiting
Assess the antifibrotic activity of Fuzheng Huaya in chronic hepatitis C patients with hepatic fibrosis	NCT00854187	Completed
Treatment of liver cirrhosis due to hepatitis B virus with Fuzheng Huaya and entecavir	NCT02241690	Recruiting
Urinary metabonomics of two major patterns of NAFLD	NCT02077283	Recruiting
Study of botanical PHY906 plus capecitabine for advanced unresectable hepatocellular carcinoma	NCT00076609	Completed
Effects of Acupoint electrostimulation on preventing nausea and vomiting induced by cisplatin and oxaliplatin	NCT00430313	Active, not recruiting
Safety and efficacy of stem cell transplantation for treatment of liver cirrhosis	NCT01491165	Unknown
Huaier granules for prevention of recurrence and metastasis of hepatocarcinoma after radical hepatectomy	NCT01770431	Active, not recruiting
A prospective control study of cidan capsule combined with TACE in hepatocellular carcinoma	NCT 02253511	Recruiting
TCM etiological study on the theory of Xu Sun Sheng Ji in liver cirrhosis	NCT00540397	Unknown
Fuzheng Huaya tablets against posthepatic cirrhosis	NCT00543426	Completed <sup>a</sup>
Safety and efficacy study in hepatitis C patients with PHN121	NCT01052090	Terminated <sup>a</sup>
Efficacy of peginterferon alfa-2b (SCH 054031) vs glycyrrhizin in interferon (IFN)-treated patients with chronic hepatitis C and F2/F3 liver fibrosis (PO4773)	NCT00686811	Terminated
Efficacy of medical ozone therapy in patients with chronic hepatitis	NCT01342189	Invitation
Therapeutic effects of liver failure patients caused by chronic hepatitis B after autologous MSCs	NCT00956891	Completed
Ulinastatin preventing postoperative liver failure in hepatocellular carcinoma (HCC)	NCT01643447	Recruiting
SHO-SAIKO-TO for patients with chronic hepatitis C: A phase II study	NCT00590564	Recruiting
Sho-saiko-to following removal of liver cancer by embolization in treating patients with liver cancer that cannot be removed surgically	NCT00040898	Completed
Effects of sho-saiko-to, a herbal formula, in reducing viral load in hepatitis C	NCT00633230	Suspended

<sup>a</sup>Publications reported to [ClinicalTrials.gov](http://ClinicalTrials.gov).



**Figure 1.** Structures of the main components of silymarin.

SIL inhibits uptake of amatoxin through competitive inhibition of OATP1B3; interrupts biliary secretion, decreasing enterohepatic circulation of the toxin; inhibits release of tumor necrosis factor by damaged hepatocytes or effector cells; stimulates protein synthesis in damaged hepatocytes; and decreases reactive oxygen species and lipid peroxidation as well as other late effects of hepatocyte damage and necrosis.

There are no well-designed controlled trials of Legalon SIL for acute *A phalloides* poisoning (one is in progress), but data from 1491 patients treated worldwide showed that 93% treated with Legalon SIL survived.<sup>47</sup> There are claims that early aggressive use of Legalon SIL has reduced mortality from *A phalloides* poisoning from approximately 20% to 10%. No serious adverse drug effects have been reported, although mild flushing occurs during intravenous administration. The manufacturer estimates that >9000 patients have been treated with Legalon SIL.<sup>47</sup>

Early studies in Europe of orally administered silymarin to treat patients with alcoholic liver disease provided conflicting results. The first randomized controlled study was conducted in Vienna, and among 170 patients with alcohol-

associated cirrhosis treated with silymarin, survival after 41 months was significantly higher in the silymarin-treated group (58% vs 39% of controls).<sup>48</sup> In contrast, studies of subjects with alcohol-associated hepatitis or cirrhosis in France<sup>49</sup> and Spain<sup>50</sup> did not report any benefits from oral silymarin.

The continuing popularity of silymarin for treating patients with liver diseases then prompted several systematic reviews.<sup>51-53</sup> These reviews generally concluded that the moderate oral doses typically used are safe and well tolerated but that silymarin has no clinically meaningful effect on liver disease. One review stated that "The only statistically significant difference was a greater reduction in alanine aminotransferase levels among patients with chronic liver disease assigned to milk thistle (−9 IU/L), but this reduction was of negligible clinical importance."<sup>53</sup> Moreover, statistically significant differences were not observed in studies of longer duration and higher quality.

Subsequently, another groundbreaking study in Vienna showed that high doses of silibinin (10–20 mg · kg<sup>−1</sup> · day<sup>−1</sup>) administered intravenously to patients with CHC dramatically reduced levels of hepatitis C virus (HCV)

RNA.<sup>54</sup> Unfortunately, viral suppression persisted only as long as treatment continued, which is obviously not an option with intravenous therapy. Other compelling studies followed. In one case report, treatment with intravenous silibinin prevented HCV reinfection of the graft after liver transplantation.<sup>55</sup> In another study, Legalon SIL was effective in patients with severe HCV-related fibrosing cholestatic hepatitis.<sup>56</sup> Four patients with graft reinfection had significant reductions in serum levels of HCV RNA (mean  $-2.8 \log_{10}$ ) after 120 days of intravenous silibinin monotherapy, which was well tolerated.<sup>57</sup>

Silymarin significantly affects the levels and replication of HCV in human liver cell culture models.<sup>58,59</sup> It also up-regulates heme oxygenase 1, a cytoprotective and antioxidant enzyme, by 60% to 400% without affecting levels of *BTB and CNC homology 1 basic leucine zipper transcription factor 2* (Nrf2) mRNA or *nuclear factor erythroid related factor 2* (Bach 1) mRNA. A standardized silymarin extract called MK-001 inhibited infection of Huh-7 and Huh-7.5.1 cells by the HCV2a strain (JFH-1) and had prophylactic and therapeutic effects against HCV infection.<sup>60</sup> Combined with interferon (IFN)- $\alpha$ , silymarin inhibited HCV replication more than did IFN- $\alpha$  alone. The MK-001 extract also inhibited expression of tumor necrosis factor in stimulated human peripheral blood mononuclear cells and nuclear factor  $\kappa$ B-dependent transcription in Huh-7 cells. Silibinin A and B and Legalon SIL inhibited HCV RNA-dependent polymerase with 50% inhibitory concentrations of approximately 75 to 100  $\mu$ mol/L.<sup>61</sup> Silibinin A and B also inhibited HCV genotype 1b replicon replication and JFH-1 replication in cell cultures. None of the compounds tested inhibited HCV protease.

Together, these data indicate that silymarin has direct antiviral and anti-inflammatory effects in patients with CHC.<sup>62</sup> Modest anti-HIV effects have also been described, and silymarin has been proposed for treatment of patients coinfecting with HCV and HIV.

In view of these compelling data indicating that intravenous silymarin markedly suppresses HCV RNA and is safe, the National Institutes of Health supported a controlled trial in the United States of orally administered, high-dose silymarin.<sup>63</sup> A total of 154 patients with CHC who had not previously responded to IFN-based therapies were assigned randomly to receive 420 mg or 700 mg silymarin or a matching placebo 3 times daily for 24 weeks. For all outcomes (serum levels of ALT and HCV RNA as well as quality of life), the results were convincingly negative, although silymarin was well tolerated. The investigators concluded that, even at these high doses, orally administered silymarin was ineffective in patients with chronic HCV infection.

Although oral silymarin is ineffective against CHC, the antiviral effect of intravenous silymarin is compelling, and further research is warranted and ongoing.<sup>62</sup> However, with the recent approval of sofosbuvir and simeprevir, and more such therapies to come, silymarin has no role in treating patients with CHC who can afford the cost of antiviral drugs. For those who cannot, adjunctive treatment with silymarin may have some value, but high-dose oral administration must first be improved. The value of silymarin in treating

other forms of chronic liver disease is uncertain because of the lack of well-controlled trials. However, it remains the best treatment for *A phalloides* poisoning.

### TCMs

TCMs have been used to treat viral hepatitis for many centuries. There are also numerous contemporary basic and clinical research studies of TCMs (>80% of Chinese publications on treatment of hepatitis and hepatic fibrosis). Many are clinical trials, some with TCM alone and others in combination with Western medicines.

TCM as an art views the entire human body as a unit, using a formula of several herbs selected for their individual properties and alleged ability to work in a complementary fashion to treat a disease in numerous domains. From a modern molecular perspective, it is difficult to determine which ingredients account for which particular physiological effects. Moreover, the unique theoretical system and protocols of TCMs limit the use of biostatistics in clinical research to interpret the results and to communicate with Western medical investigators.

We reviewed and analyzed all Chinese publications between 1998 and 2008 of TCMs (randomized and non-randomized controlled trials and summaries of clinical experience) for treatment of hepatitis B and hepatitis C.<sup>64</sup> Overall, in patients with hepatitis B, TCMs surpassed IFN or lamivudine in reducing serum levels of hepatitis B e antigen (HBeAg) and normalizing serum levels of ALT and were equivalent to IFN and lamivudine in clearing serum hepatitis B virus (HBV) DNA. TCMs, together with IFN or lamivudine, significantly reduced serum levels of HBeAg, increased serum clearance of HBV DNA, and improved normalization of serum ALT levels compared with either IFN or lamivudine alone. No serious adverse effects of TCMs were reported. Although the composition of agents included in the TCMs differed among the trials, approximately 60% of the herbs were homologous.

Thirteen nonblinded, randomized, controlled trials of the effects of TCMs in patients with HCV infection were reported during the same period.<sup>64</sup> These TCMs comprised different traditional medicines, but herbs were approximately 50% homologous. TCMs rivaled IFN in clearing serum HCV RNA and in normalizing serum levels of ALT at the end of treatment and during 6 to 12 months of follow-up. TCMs with IFN were more effective than IFN alone in normalizing serum levels of ALT, but without significant improvement in clearing serum HCV RNA.

We statistically analyzed which individual herbs were included most frequently in TCM formulations. In 235 trials of patients with hepatitis B, 235 TCM formulas were used, comprising 203 herbs. Thirty-two TCM formulas used in 32 HCV clinical trials included 103 herbs. Similar herbs were used for hepatitis B and hepatitis C treatments. However, milk thistle (Shui fei ji), which is commonly used in Western countries for treatment of liver disease, is not ranked in the top 10 in China. This suggests that Chinese practitioners of TCM choose herbs for treating hepatitis based mainly on TCM theory. The most commonly used

herbs are Huang Qi, Dan Shen, Hu Zhang, Chai Hu, and Bai Hua She She Cao.

Although TCMs seem to be effective as alternative remedies for patients with HBV or HCV and are affordable and well tolerated, there are no convincing well-controlled trials to determine whether they have real value. Clearly, despite reported successes in treating patients with hepatitis B and hepatitis C with Chinese herbs, many studies were poorly designed and therefore require replication in higher-quality clinical trials. Of importance is whether and how frequently Chinese Western medicine practitioners use TCMs to treat viral hepatitis. Because of the multiple TCM formulations used, we also need to learn what criteria are applied in selecting formulations for clinical studies. Is there quality assurance and control of the TCM products used in clinics? More data are needed regarding the safety of the TCM formulations, particularly in long-term use.

### *Glycyrrhizin (G glabra [licorice])*

The word *licorice* comes via medieval French from the Greek, meaning “sweet root.” Licorice derives from the roots of the legume *G glabra*, which is native to southern Europe and parts of Asia. Most of the sweetness is from glycyrrhizin, a triterpene, which is 30-fold to 50-fold sweeter than sugar. The isoflavones glabrene and glabridin, also found in the roots of *G glabra*, are phytoestrogens. Most of the world’s production of licorice is used for flavoring tobacco.

Traditional medicinal uses of licorice include the treatment of abdominal pain, asthma, diverse infections, malaria, peptic ulcer, and pharyngitis. Glycyrrhizin has been shown to protect hepatocytes exposed to carbon tetrachloride or galactosamine and to increase phase I and II metabolism of drugs and chemicals in mice.<sup>65</sup> In vitro studies have shown that glycyrrhizin has antiviral activity against hepatitis A, varicella zoster, HIV, herpes simplex type 1, Newcastle disease, and vesicular stomatitis.<sup>65</sup> Also, it inhibits a nuclear component, high-mobility group box 1 protein, a signaling molecule involved in acute and chronic inflammation.<sup>66</sup> Glycyrrhizin is used commonly in Japan to treat chronic hepatitis, where it is called Stronger Neo-Minophagen C (SNMC) (Eisai Co, Ltd, Tokyo, Japan), a parenteral preparation that contains 2% glycyrrhizin, 0.1% cysteine, and 2% glycine.<sup>67,68</sup>

There have been several clinical trials evaluating glycyrrhizin for the treatment of patients with CHC and hepatocellular carcinoma; most were open-label, uncontrolled studies. A European randomized, double-blind, controlled trial found that glycyrrhizin, given intravenously at a dosage of 240 mg thrice weekly, lowered serum levels of ALT during treatment without affecting HCV RNA levels.<sup>69</sup> In a study of patients with hepatitis-related hepatic failure, 72% of those treated with SNMC for 12 weeks survived versus 31% who received standard supportive therapy.<sup>70</sup> The antiviral action was believed to derive from stimulation of endogenous IFN- $\alpha$  production.<sup>69</sup> A recent phase 3 randomized, double-blind, placebo-controlled study

produced reliable data.<sup>71</sup> Prior nonresponders to IFN-based therapies were randomly assigned to receive intravenous glycyrrhizin 3 times per week or 5 times per week or placebo 5 times per week for 12 weeks. Thereafter, patients were randomly assigned to groups given glycyrrhizin 3 times per week or 5 times per week for an additional 40 weeks. At 12 weeks, a significantly higher proportion of patients treated with glycyrrhizin had a >50% reduction in ALT levels than those given placebo. At week 52, 44.9% of those treated with glycyrrhizin 5 times per week and 46.0% of those treated with glycyrrhizin 3 times per week had reduced necroinflammation in liver biopsy specimens. No changes were seen in levels of HCV RNA, but glycyrrhizin was well tolerated. The major dose-limiting toxicity of glycyrrhizin, however, is a mineralocorticoid aldosterone-like effect, with development of fluid retention, edema, hypertension, and hypokalemia.

Thus, there is cumulative evidence that glycyrrhizin lowers levels of ALT and has modest anti-inflammatory effects but has no effect on levels of HCV RNA. Accordingly, although there are medicinal effects of licorice for patients with CHC, its benefits are minor and are wholly surpassed by potent hepatitis-related antiviral drugs. Moreover, glycyrrhizin must be given intravenously and has mineralocorticoid adverse effects.

### *TJ-9 (Xiao Chai Hu Tang in China and Sho-saikoto in Japan)*

TJ-9 consists of 7 herbs (bupleurum root, Pinellia tuber, baical skullcap root, ginseng root, licorice root, ginger rhizome, and jujube fruit). It is manufactured with uniform quality and quantity of active constituents and is widely used to treat chronic hepatitis and cirrhosis. Its major compounds are baicalin, baicalein, glycyrrhizin, saikosaponins, ginsenosides, wogonin, and gingerol, but it is uncertain which of these, or which combination, has major effects. Saikosaponins are the main active components of bupleurum root; these have antihepatitis, antinephritis, antihepatoma, anti-inflammatory, immunomodulatory, and antibacterial effects. Saikosaponin-d induces lymphocyte apoptosis, partly by increasing levels of *MYC* and *TP53* mRNA and reducing levels of *BCL2* mRNA. At a higher concentration, saikosaponin-d induces necrosis.<sup>72</sup> Saikosaponin-c has a significant inhibitory effect on secretion of hepatitis B surface antigen and HBV DNA synthesis.<sup>73</sup>

Baicalin and baicalein, isolated from baical skullcap, are chemically very similar to silibinin and protect the liver against fibrosis and carcinogenesis by inhibiting oxidative stress in hepatocytes. They also inhibit activation of hepatic stellate cells.<sup>74</sup>

TJ-9 has been studied for treatment of patients with hepatitis B,<sup>75,76</sup> showing some unconvincing positive effects; studies are under way to evaluate TJ-9 for treatment of patients with CHC.<sup>77</sup> There are also studies to evaluate TJ-9 as treatment for patients with hepatocellular carcinoma.<sup>78,79</sup> Clinical trials of TJ-9 are being performed at Memorial Sloan-Kettering Cancer Center in New York to determine its effect as an anticancer agent. A number of

adverse effects of Sho-saiko-to, including thrombocytopenic purpura, induction of autoimmune hepatitis, and interstitial pneumonia with acute respiratory failure, have been reported.

### Adverse Effects of Herbal Products on the Liver

The prevailing belief that herbal products are safe is erroneous; indeed, herbal-related hepatotoxicity is well described. The earliest reports, mainly from non-Western countries, implicated single traditional botanicals. Currently, in the United States, multi-ingredient commercial products are the predominant offenders,<sup>80</sup> as identified in the ongoing National Institutes of Health-supported Drug-Induced Liver Injury Network (DILIN) study.<sup>81</sup> Among 839 patients enrolled by March 2013 with confirmed drug-induced liver injury (DILI), 130 (15.5%) had taken herbal products, which was the second highest implicated category.<sup>82</sup> Virtually all were commercial, multi-ingredient products, most of which were bodybuilding supplements, followed by weight loss products (Figure 2). Although DILIN is not a population-based study, it is noteworthy that, relative to the identified conventional drug cases of DILI, the proportion of cases of DILI from herbal products has been steadily increasing over the past 10 years, perhaps representing a trend (Figure 3).<sup>82</sup> Most, although not all, cases present with a pattern of acute hepatocellular liver injury, similar to that of acute viral hepatitis.<sup>80</sup>

#### Traditional and Single-Ingredient Products

Reports of DILI from traditional botanicals (Table 2) are dwindling partly because their toxicities have been recognized, they have been withdrawn, or commercial products are now preferred.

**Black cohosh (*Cimicifuga racemosa*).** Reports of liver injury from black cohosh,<sup>83–85</sup> which is used to relieve menopausal symptoms, prompted the US Pharmacopoeia to publish a cautionary monograph.<sup>86</sup> However, concerns about DILI were not corroborated by a later meta-analysis of 5 small randomized trials.<sup>87</sup> These conflicting views

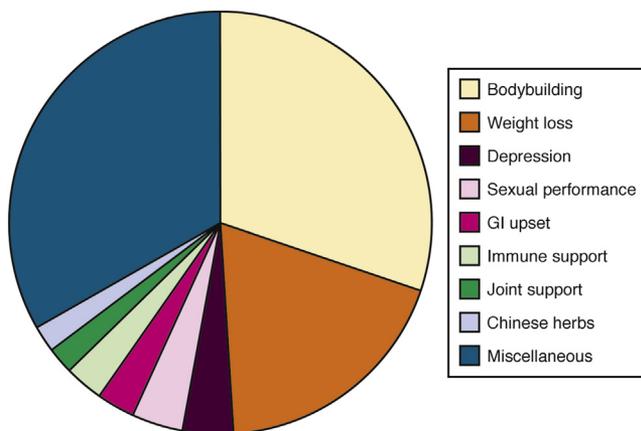


Figure 2. Types of herbal products implicated in DILI.<sup>82</sup>

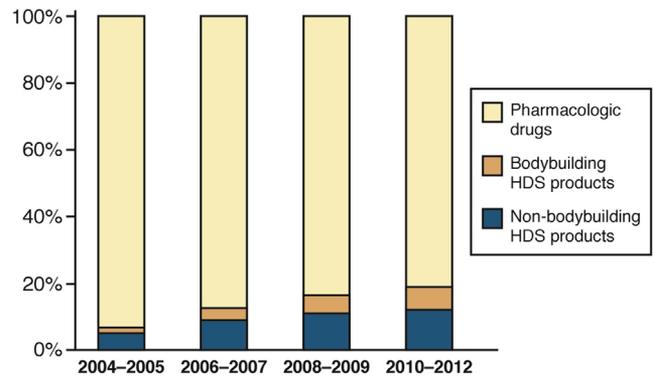


Figure 3. Trends in liver injury from herbal products in the DILIN study.<sup>82</sup>

require resolution. The basis for injury may be through mitochondrial damage.

**Catechins/green tea.** Green, black, and oolong teas come from leaves of *Camellia sinensis*, which is cultivated widely in the Far East. Green tea contains 30% to 40% polyphenols (by weight), whereas black tea contains approximately 3% to 10% polyphenols. The average cup of green tea contains 50 to 150 mg of polyphenols. Its major catechins are (+)-catechin, gallic acid, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate (EGCG). EGCG is believed to be the most active and most potentially hepatotoxic component.<sup>88</sup>

High doses of green tea extract, found in herbal products widely promoted for weight loss, may cause severe acute liver injury.<sup>89,90</sup> Studies in mice have shown that EGCG is a dose-dependent hepatotoxin.<sup>91</sup> A polymorphic variation in the gene encoding mitofusin 2 was identified as a risk allele for EGCG-induced liver injury.<sup>92</sup> Modest daily doses of green tea (1–3 cups/day) appear to be very safe. However, in susceptible hosts, more concentrated extracts of green tea, such as those found in numerous products marketed widely, can lead to serious and even fatal liver injury.

**Chaparral (*Larrea tridentata*).** Used for weight reduction and other diverse conditions, there are numerous reports of liver injury from chaparral.<sup>93–95</sup> An FDA article described liver dysfunction ranging from elevated enzyme levels alone to fulminant hepatitis, presenting mostly as cholestatic injury. The injury is believed to result from inhibition of prostaglandin G/H synthases and cytochrome P450 (CYP) by nordihydroguaiaretic acid.

**Comfrey (*Symphytum officinale*).** Comfrey, which is used as a tea but can also contaminate food, contains pyrrolizidine alkaloids that cause the sinusoidal obstruction syndrome.<sup>96–99</sup> In 2009, the FDA advised against its use as a dietary ingredient. Clinical manifestations are hepatomegaly, ascites, and eventually cirrhosis. Injury is due to transformation of pyrrolizidine alkaloids by CYPs into toxic adducts.

**Germander (*Teucrium chamaedrys*).** Reports of liver injury (acute, fulminant, chronic) have come from France, where germander was used as a weight loss product.<sup>100</sup> An inadvertent positive rechallenge proved that it

**Table 2.** Single-Ingredient and Multi-ingredient Herbal Agents Associated With Hepatotoxicity

Agent	Botanical name	Most common use	Most common presentation of hepatotoxicity	Suspected mechanism of injury
Black cohosh	<i>Cimicifuga racemosa</i>	Menopausal symptoms	Severe acute hepatitis, acute liver failure, autoimmune features	Mitochondrial injury
Chaparral	<i>Larrea tridentate</i>	Weight loss, rheumatic pain, antibiotic	Cholestatic hepatitis, acute liver failure	Prostaglandin, CYP inhibition
Comfrey	<i>Symphytum officinale</i>	Wound healing	Sinusoidal obstruction syndrome	Toxic adduct formation
Germander	<i>Teucrium chamaedrys</i>	Weight loss	Acute and chronic hepatitis with jaundice	Toxic epoxide formation
Greater celandine	<i>Chelidonium majus</i>	Liver and biliary tract disease	Cholestatic hepatitis	Immune activation
Green tea extract	<i>Camellia sinensis</i>	General health, weight loss	Acute hepatitis	Oxidative stress
Herbalife product line	Multi-ingredient	General health, weight loss	Acute hepatitis	Unknown
Kava kava	<i>Piper methysticum</i>	Mental health and well-being	Acute hepatitis with jaundice; acute liver failure	Toxic compounds derived from extraction process
Hydroxycut	Multi-ingredient	Weight loss	Acute hepatitis, acute liver failure	Unknown
Oxy-Elite Pro	Multi-ingredient	Performance-enhancement weight loss	Severe hepatitis, acute liver failure	Unknown
Saw palmetto	<i>Serenoa repens</i>	Prostate disease	Cholestatic hepatitis	Steroid-associated injury

could cause DILI. Liver injury results from toxic epoxides derived from one of its constituents: diphteroids.<sup>101</sup>

**Kava kava (*Piper methysticum*).** Used to treat anxiety and depression, more than 100 cases of hepatocellular, fulminant, and cholestatic hepatotoxicity worldwide led to revocation of the license to distribute kava kava in the United States, Europe, and Australia.<sup>102–104</sup> Hepatotoxicity has been linked to the method of extraction of the pharmacologically active lactone ingredients.<sup>105</sup>

**Saw palmetto.** There are rare instances of liver injury from saw palmetto used to treat prostatic hypertrophy. Both cholestatic and hepatocellular injury have been reported.<sup>106,107</sup> The cholestatic injury may result from steroidal compounds within the plant structure.<sup>108</sup>

**TCM.** TCM accounts for approximately 40% of cases of DILI in China.<sup>109,110</sup> Xiao Chai Hu Tang (Sho-saiko-to in Japan), an ancient formula regarded as a classic TCM (Shang Han Lun) and comprising 7 herbs, has been reported to induce hepatotoxicity and cause medical problems.<sup>111–113</sup> Its toxic constituents (baicalin, glycyrrhizin, and saikosaponin-b) have a dose-response relationship with hepatotoxicity. TCM products containing more than 19 g of Chai Hu may increase the risk of liver injury.<sup>114</sup>

### Multi-ingredient Proprietary Mixtures

Multi-ingredient products, which constitute the bulk of cases of herbal hepatotoxicity in the DILIN study, are generally sold under a product line name. Examples in the DILIN study are M-One-T, Warrior Pro-Hormone, Lionheart VNS Xtreme, Incredible Hulk, N.O.-Xplode, Blue Dragon, Up Your Gas, Gaia's delights kroton, and many more.<sup>82</sup> Diagnosing the hepatotoxicity of these products is challenging; the ability to assign causality of the marketed product is similar to that of conventional drugs, but identifying the specific component among the bundled ingredients can be daunting or impossible.

An example is Herbalife, which is marketed globally for varying purposes through outlets other than retail stores.

Several items in this product line have been implicated in liver injury.<sup>30,115–117</sup> A recent effort of international investigators to confirm this evidence, however, was only partially successful, due in part to the fact that the analysis was retrospective and there were missing data.<sup>118</sup> Because of multiple differing constituents, the mechanism of injury remains unclear.

**Products used for weight loss.** Countless herbal products are sold in retail stores or advertised on the Internet to promote weight loss. Some of them, mostly proprietary mixtures, have caused liver injury (Figure 2). Among them are green tea extracts (see the preceding text) and Hydroxycut.

Marketed for weight loss and muscle building, Hydroxycut has been associated with acute hepatic failure, in some instances even requiring liver transplantation.<sup>119–122</sup> Certain formulations contain caffeine, chromium polynicotinate, *Gymnema sylvestre*, and green tea. These items received an FDA warning and were removed from the market.<sup>123</sup>

In 2013, the FDA issued a warning regarding severe hepatotoxicity from OxyELITE Pro; several cases resulted in liver transplantation or death.<sup>124</sup> The responsible ingredient has not been identified, but because a cluster of cases occurred in Hawaii among Pacific Islander and Asian people, genetic susceptibility or some behavior pattern might mediate susceptibility.

**Bodybuilding and performance-enhancing products.** There is a characteristic pattern of liver injury that is virtually diagnostic of the hepatotoxicity of bodybuilding and performance-enhancing products containing steroid-like ingredients.<sup>125–127</sup> Typically, subjects are young men with prolonged jaundice and intense pruritus that improves with product withdrawal. Most develop bland cholestasis, but some show increased serum enzyme levels consistent with hepatocellular injury.<sup>128</sup> Genetic factors might contribute to susceptibility.<sup>129</sup>

Legislation passed in 2004 made it illegal to include steroids or steroid-like substances related to testosterone in over-the-counter products.<sup>130</sup> The legislation identified numerous compounds as anabolic steroids. Yet, currently available products often identify steroid ingredients, possibly synthetic in nature, on the label. Whether ingredients in bodybuilding and performance-enhancing products are true anabolic steroids or steroid derivatives is unclear and presumably warrants investigation. The development of designer steroids is especially problematic, because these have evaded regulation and made their way to market.<sup>131</sup> However, although many bodybuilding and performance-enhancing products are not actual dietary supplements, they fall under the purview of the Dietary Supplement Health and Education Act legislation and the same regulatory body that oversees herbal products (Center for Food Safety and Applied Nutrition in the FDA).

**Herb-drug interactions.** There are several well-described and potentially dangerous interactions between drugs and herbal products (Table 3).<sup>132</sup> Health care providers must always question patients about use of herbal products; patients are often reluctant to spontaneously disclose their use because of embarrassment or concern of reproof.

### Assessment of Causality for Potential Herbal Hepatotoxicity

Proving that herbs cause DILI requires a disciplined, stepwise assembly of historical and clinical information to exclude competing causes of liver injury.<sup>133</sup> The amassed data are then graded for the likelihood of DILI using either

expert analysis or a recognized instrument such as the Roussel Uclaf Causality Assessment Method.<sup>134-136</sup> Although neither approach is flawless, the Roussel Uclaf Causality Assessment Method in particular has limitations.<sup>137</sup> Indeed, making a case for hepatotoxicity of conventional drugs is difficult enough but is especially challenging for herbal hepatotoxicity. The problem is not so much overall assessment of liver injury but rather identifying which of the many possible implicated botanicals used, or the ingredients within each botanical, caused the injury. Efforts are under way to improve assessment of causality for herb-related hepatotoxicity.

### Summary

Herbal products are used extensively and now rival prescription medications for treatment of various disorders. Herbal products are currently used mainly for weight loss and bodybuilding purposes but also to improve well-being and reduce symptoms of chronic diseases. Many believe that because they are natural, they must be effective and safe, but both beliefs are erroneous. Few herbal products have been studied using well-designed controlled trials to corroborate beneficial effects in liver disease despite anecdotes and testimonials to the contrary. Also, they are no safer than conventional drugs and have caused liver injury severe enough to require liver transplantation or cause death. Their safety is compromised in part by the fact that they are not FDA regulated, causing uncertainty about their reported and unreported contents.

**Table 3.** Interactions Between Herbs and Drugs

Medications	Herbs	Interactions and potential consequences
Warfarin and aspirin	Danshen ( <i>Salvia miltiorrhiza</i> )	Increased INR; bleeding risk
	Dong qua	Increased INR; bleeding risk
	Garlic	Increased INR; bleeding risk
	Papaya	Increased INR; bleeding risk
	Tamarind	Increased aspirin level; bleeding risk
	Feverfew	Platelet dysfunction: bleeding risk
	Ginkgo biloba	Platelet dysfunction; bleeding risk
	Ginseng	Decreased INR; clotting risk
	St. John's wort	Decreased INR; clotting risk
	Devil's claw ( <i>Harpagophytum cumbens</i> )	Purpura
	CYP3A4 drugs	Pyrolizidines
Germander		CYP34A induction; hepatotoxicity
Cyclosporine	St John's wort	CYP34A induction; rejection risk
	Grape fruit juice	CYP34A induction; rejection risk
Methotrexate	St. John's wort	Increased methotrexate level /toxicity
	Echinacea	Increased hepatotoxicity
Prednisolone	Ginseng	Possible additive effect
	Glycyrrhizin	Reduced clearance; hypokalemia
	Sho-saiko-to	Altered clearance; low prednisolone level
Protease inhibitors	St. John's wort	CYP34A induction; low viral activity
	Garlic	CYP34A induction; low viral activity
Spirolactone	Glycyrrhizin	Mineralocorticoid low spironolactone level
Benzodiazepines	Kava	Increased sedative effects

INR, international normalized ratio.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org) and at <http://dx.doi.org/10.1053/j.gastro.2014.12.004>.

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**Conflicts of interest**

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## Supplementary Material

### *Herbal Products Used to Treat Liver Disease*

**Green tea.** Claims of medicinal and beneficial effects of green tea are many and varied. Unquestionably, when taken in modest quantities, green tea is safe and, for many, satisfying. Indeed, a great deal of tradition and custom surrounds the preparation and consumption of green tea in China and Japan, now including countries outside of East Asia.

Green tea also contains a variety of other components, including amino acids, peptides, carbohydrates, lipids, sterols, other phytochemicals, and minerals. The numerous claims of health benefits of green tea are based on its chemical composition and studies in animal models and cell cultures. The Internet is replete with claims that green tea can prevent cancer, boost the basal metabolism rate (enhancing weight loss), and reduce the risk of coronary artery disease and other vascular disorders. Support for such claims from well-designed and well-conducted clinical studies, however, is woefully lacking.

There is limited evidence for benefits of (+)-catechin ([+]-cyanidanol-3 [catergen]) in the treatment of patients with viral hepatitis. In one prospective, randomized, double-blind study involving 338 Japanese patients, a significant decrease in HBeAg levels was noted in 44 of 144 patients treated with cyanidanol versus 21 of 140 patients receiving placebo ( $P < .01$ ).<sup>1</sup> HBeAg levels decreased by at least 50% in 31% of patients ( $P < .01$  vs placebo control) and became undetectable in 16 (11%) vs 4 patients receiving placebo ( $P < .05$ ). Factors associated with a favorable response were higher levels of serum aminotransferases and immunoglobulin G at baseline. The cyanidanol was well tolerated; the only notable adverse effect was transient febrile response in 13 subjects. Thus, cyanidanol appears to have increased host anti-HBV responses and to have improved host clearing of infected hepatocytes.

***Curcuma longa* (turmeric).** This tropical plant is a member of the ginger family and is cultivated extensively in tropical Asia and Africa. Turmeric is a widely used spice in Indian cuisine, derived from the dried, ground rhizomes of *C longa*. It has long been used in Ayurvedic and Chinese traditional medicines and practices for a variety of gastrointestinal and hepatobiliary symptoms, including colic, flatulence, hepatitis, and jaundice. It has also been recommended for hematuria, menstrual difficulties, and states of inflammation.

The major active ingredient is believed to be curcumin (diferuloylmethane), a natural phenol with a bright yellow color, which is often used in foods for increasing color and the characteristic flavor of curry. It is poorly absorbed after oral administration; piperine (from black pepper) was shown to increase bioavailability of curcumin by 2000%.<sup>2</sup>

Like milk thistle, curcumin is reported to have hepatoprotective effects in cell cultures and in animal models of liver injury, including injury due to carbon tetrachloride, galactosamine, 1-chloro-2,4-dinitrobenzene, 4-hydroxynonenal, and acetaminophen.<sup>3</sup> Curcumin has

appreciable antioxidant effects and protects against lipid peroxidation. It was found to protect against liver damage caused by aflatoxin B1, a well-known toxin and carcinogen found widely in peanuts and other fungally contaminated ground crops.<sup>4,5</sup> It also has been shown to have choleric effects in rats.<sup>6</sup>

Curcumin taken orally appears to be relatively safe, perhaps in part because of its low absorption from the gastrointestinal tract. Patients taking up to 12 g have reported nausea and diarrhea. It has been found to bind iron and decrease its absorption, which may be of benefit in hemochromatosis, but it may also be a risk for development of iron deficiency.<sup>7</sup>

***Picrorhiza kurroa* (katki, kutkin, katuko, kuru).** *P kurroa* is a plant that grows at altitudes of 3000 to 5000 m in the Himalayas and has been used for centuries in traditional Indian (Ayurvedic) medicine, especially for gastrointestinal and hepatobiliary disorders. The plant has been harvested excessively, almost to extinction. The roots and rhizomes are the parts used for medicinal therapy. The major active constituents are 3 iridoid picrosides and kutkoside, collectively called katki, kutkin, and other names. Extracts have been found to protect hepatocytes from a variety of insults, including those due to amanitin, phalloidin, carbon tetrachloride, galactosamine ethanol, aflatoxin B1, oxytetracyclines, and monocrotaline.<sup>3</sup> Indeed, in one study in rodents, kutkin was slightly superior to milk thistle in decreasing injury and death due to *Amanita* poisoning.<sup>8</sup>

In a prospective, randomized, controlled study performed in India involving 32 patients with acute hepatitis not due to HBV (all were hepatitis B surface antigen negative), the 15 who received a powder derived from the roots of *P kurroa* (375 mg thrice daily for 2 weeks) showed lower levels of serum aminotransferases and total bilirubin than did those who received placebo.<sup>9</sup> The mean number of days for the serum total bilirubin values to decrease to  $<2.5$  mg/dL was 27.4 in the kutkin-treated group vs 75.9 in the group receiving placebo.

The mechanisms of action of kutkin are not fully known, but there is evidence of antioxidant, antilipid peroxidation, and anti-inflammatory effects. It also has choleric effects that surpass those of silymarin in potency.<sup>3</sup> Kutkin also appears to be quite nontoxic; in rats, the median lethal dose for the extract administered by mouth is  $>2600$  mg/kg body wt. There have not been reports of hepatotoxicity ascribed to kutkin.

In summary, the compounds found in the roots and rhizomes of *P kurroa* have been used for centuries in Ayurvedic medicine. It has apparent beneficial effects, with convincing studies in cell cultures and animal models as well as a few positive clinical studies. There is dwindling supply of the plant source due to its limited geographical range and overharvesting.

***Phyllanthus amarus*.** Used in China and India to treat diabetes, diarrhea, urinary tract problems, and hepatitis B,<sup>10</sup> this plant is found in tropical countries. It contains alkaloids, flavonoids, lignans, and terpenes. Studies using cell lines infected with hepatitis B and the woodchuck hepatitis virus have shown an inhibitory effect on HBV polymerase

activity as well as decreased activity of mRNA transcription in hepatitis B transgenic mice.<sup>11-13</sup> Its benefit in clinical trials of patients with HBV infection has been conflicting, with the most positive results occurring when used together with IFN.<sup>14-16</sup> Thus, in accord with other herbal products that have been used to treat liver disease, *Phyllanthus* displays interesting in vitro activity, in this instance against hepatitis B, but without compelling evidence of a beneficial effect in humans infected with HBV.

### Herbal Products That Cause Hepatotoxicity

In addition to the herbal products that cause liver injury described in the main text, there are numerous other herbal products that have been identified to cause hepatotoxicity. As has been noted, this includes both single-ingredient and multi-ingredient herbal products. A list of those implicated as causing liver injury is shown in [Supplementary Table 1](#).

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**Supplementary Table 1.** Herbal Agents Implicated in Liver Injury

Agent	Botanical name	Most common use	Most common presentation of hepatotoxicity	Suspected mechanism of injury
Camphor	<i>Cinnamomum camphora</i>	Arthralgia, myalgia	Severe acute hepatitis	Terpene-induced injury
Glucosamine chondroitin		Arthritis	Acute hepatitis with autoimmune features or hypersensitivity	Unknown
Greater celandine	<i>Chelidonium majus</i>	Liver and biliary tract disease	Cholestatic hepatitis	Immune activation
Kombucha tea	<i>Kombucha</i> fungus	Youthfulness, general health	Elevated liver test results	Microbial contamination
Margosa oil	<i>Azadirachta indica</i>		Acute liver failure, fatty liver; Reye syndrome-like illness	Mitochondrial injury
Noni Juice	<i>Morinda citrifolia</i>	Well-being, various uses	Severe hepatitis, acute liver failure	Anthraquinone injury
Pennyroyal oil	<i>Hedeoma pulegioides</i> , <i>Mentha pulegium</i>	Abortifacient, various uses	Acute liver failure	Glutathione depletion, oxidative stress
Senna	<i>Cassia angustifolia</i>	Laxative	Acute liver failure, cholestatic hepatitis	Anthraquinone, sennoside injury
Skullcap	<i>Scutellaria baicalensis</i>	Sedative, anti-inflammatory	Cholestasis, acute liver failure	Diterpenoid reactive metabolites
Usnic acid		Weight loss	Severe acute hepatitis, acute liver failure	Mitochondrial injury
Valerian	<i>Valeriana officinalis</i>	Insomnia, general health and well-being	Hepatitis	CYP inhibition