

Complementary and Alternative Medicine in Chronic Liver Disease

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Chronic liver disease is a major cause of mortality and morbidity in the United States. Medical therapies for these diseases are often difficult to handle and limited in efficacy and, therefore, affected patients often seek other treatments, either to complement or to replace standard care. The types of complementary and alternative medical (CAM) therapies sought and used encompass a wide range of approaches, including prayer, meditation, hypnosis, biofeedback, herbal medicals, chiropractic, diet, and life style modification. Such approaches are often believed to be safer and better than standard medical practice because they are "natural" or are based on a religious, philosophical, or a strongly felt concept of "wellness" and health. Indeed, despite all the advances in conventional medical therapies in the last 20 years, there has been an escalation in the use of CAM by the American public as well as an increasing attention to the issue by the popular press and medical establishment; there is already a second edition of the Physicians Desk Reference for Herbal Preparations, and the U.S. Pharmacopoeia now describes several botanicals, and the number is expanding.

The expanded use of CAM by patients often occurs without the advice or knowledge of their medical practitioner. Most physicians know little about CAM and either actively disparage its use by focusing attention on potential toxicities, reluctantly accept it, or ignore its use altogether. These factors underscore the need to carefully and objectively assess the benefits and risks of CAM in liver disease to educate both physicians and patients. Accordingly, in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), the Office of Dietary Supplements (ODS), and the American Association of Naturopathic Physicians, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) organized a 3-day research workshop to:

- 1) Review the current use of herbal products and other CAM therapies among patients with chronic liver disease,
- 2) Examine the types of products used and their standardization and quality control,
- 3) Assess the current scientific evidence for their benefit,
- 4) Review their toxicities, and
- 5) Make recommendations regarding needs for future research.

THE NCCAM

The NCCAM was established in 1998 with the charge of providing the public with a reliable assessment of the safety and efficacy of CAM and of helping to integrate proven CAM interventions into conventional medical care. The budget in support of NCCAM has grown from \$2 million in 1993, to \$49 million in 1999, and to an estimated \$89 million for 2001. An initial activity of NCCAM was the rigorous assessment of the literature on the efficacy and safety of CAM, done with the Cochrane Collaboration (a database of over 4,000 randomized controlled trials) and the Agency for Healthcare Research and Quality (AHRQ). The Center now supports research through a variety of grant mechanisms, from training grants and career development awards to innovative developmental grants (R03 and R21), center grants (P50 and U24), and full- scale research project grants (R01) generally through a formal process of Requests for Applications (<http://nccam.nih.gov>).

NCCAM supports the general definition of CAM as "medical and health care practices not an integral part of

conventional (Western) medicine." A classification system of 5 categories of CAM was developed for review and funding of applications:

- 1) Mind-body medicine
- 2) Alternative medical systems
- 3) Biologically based therapies
- 4) Manipulative and body-based systems, and
- 5) Energy-based therapies.

Herbal medications, the major focus of this conference, falls into the category of biologically based therapies, which is further divided into

- 1) Phytotherapy or herbalism,
- 2) Special diet therapies,
- 3) Orthomolecular medicine, and
- 4) Pharmacologic, biological, and instrumental interventions.

EPIDEMIOLOGY OF CAM

The extent of CAM use by the general public was assessed by randomized household telephone surveys conducted in the United States in 1990 among 1,539 adults and again in 1997 among 2,055 adults. The proportion of respondents using CAM rose from 34% in 1990 to 42% in 1997, a highly significant increase ($P = 0.001$). Herbal medication use increased from 2.5% to 12%, a 5-fold rise that was matched only by folk medicine and homeopathy among the 16 therapies reviewed. Visits to alternative medicine practitioners increased from 36% to 46%. The major reasons given for CAM use were back problems, anxiety, depression, and headaches; few used CAM for liver disease. Almost 40% of respondents in both 1990 and 1997 failed to disclose the use of alternative therapies to their physician.

These findings, extrapolated to the general population, provide an estimate of the magnitude of CAM use in the United States. Thus, the number of visits to alternative care practitioners appears to have exceeded the total visits to all primary care physicians in both 1990 and 1997. Approximately 15 million adults in 1997 used both conventional and herbal remedies with or without high-dose vitamins. An estimated \$12.2 billion was paid out-of-pocket for alternative medicine professional services, an expenditure exceeding out-of-pocket costs for all U.S. hospitalizations, and an estimated \$27 billion was paid out-of-pocket for CAM therapies, comparable to the projected out-of-pocket expenditures for all U.S. physician services. This survey indicated that the rise in use and expenditures for CAM was caused by an increase in the number of individuals seeking alternative therapies and not to increased visits or costs per patient.

USE OF CAM BY PATIENTS IN LIVER DISEASE CLINICS

CAM use by patients with liver disease appears to parallel its use in the general population. To prepare for this workshop, a questionnaire survey on CAM use was developed and, during a 3-month period in 1999, was administered to all adult patients attending 6 geographically diverse liver disease outpatient clinics in the United States. The questionnaire gathered demographic, income, and educational information as well as data regarding the range and use of most forms of CAM. Among 809 patients who completed the questionnaire, 41 % (range 33% to 75% at the 6 institutions) indicated that they had used some form of CAM at least once during the preceding month. Herbal preparations were taken by 12% to 50% (median, 20%) of patients. The most common herbal taken for liver disease was milk thistle (silymarin), reported by 12% of respondents. A small proportion (< 1 %) used glycyrrhizin and other products for liver disease. Several herbal medications (ginseng, St. Johns wort) were taken for conditions other than liver disease—depression, memory loss, or general wellness. CAM use was more common among women, patients with college education, and those with a higher income level. Its use did not correlate with age, severity, or etiology of disease.

These and other survey data presented as posters at the workshop confirmed the beliefs of practicing hepatologists that CAM use among patients with chronic liver disease, particularly hepatitis C, is common.

The challenge will be to determine whether and how herbal products should be integrated into the medical management of chronic liver disease and particularly hepatitis C.

CONVENTIONAL MEDICAL MANAGEMENT VERSUS NATUROPATHIC MEDICINE FOR HEPATITIS C

Conventional, Western medicine uses a disease paradigm that focuses on therapeutics to eradicate the cause and reverse the disease process. Treatment strategies are typically disease specific and based on known biological factors. The introduction of new therapies is generally preceded by scientifically rigorous, prospective randomized controlled trials (RCTs) that compare the new treatment with standard therapy. Endpoints used to assess conventional therapies are either significant morbidity and mortality or, more commonly, objective surrogate markers that reflect the known cause and natural history of the disease. In contrast, naturopathy is based on a paradigm of natural health and healing, and treatments concentrate on reestablishing or re-enforcing natural healing processes and wellness. Naturopathy attempts to improve the patient's feelings of well being and to correct the disturbance in health that affects how the patient interacts with family and environment.

With regard to hepatitis C, conventional medical treatment involves the use of a combination of antivirals and biological response modifiers that have been shown to be efficacious in large RCTs using rigorously applied, surrogate end points. In the most recent multicenter RCT, long-acting pegylated interferon, in combination with ribavirin, induced a sustained virologic response (loss of HCV RNA for at least 6 months after stopping treatment) in 56% of treated patients. A sustained virologic response is considered to be a valuable and clinically important end point.

The naturopathic approach to managing hepatitis C would be to strengthen the liver, gastrointestinal, and immune systems. The small intestine is viewed as the first, the liver as the second, and the immune system as the third line of defense in dealing with antigenic substances believed capable of crossing the intestinal barrier. Thus, a therapeutic trial in naturopathic medicine would include efforts to:

- 1) "Enhance the terrain," using agents capable of improving gastrointestinal, liver, and immune functions;
- 2) Remove obstacles to cure by increasing excretion or chelation of pro-oxidant compounds (such as iron), and lowering the toxic burden (by eliminating alcohol, smoking, and drugs); and
- 3) Improve healing of the liver.

In addition, therapy would be individualized according to host characteristics, such as the degree of oxidative stress/imbalance. The holistic approach would be further maintained by guided imagery or support group therapy focusing on quality of life.

Distinctions between conventional and natural medicine are apparent in the methods of development and application of treatments for chronic hepatitis C. The conventional drug development model focuses on identification of an "active" component of the drug, its purification, quantitation, and manufacture with minimal variation from batch to batch. In contrast, drug development in natural medicine uses a long, sometimes ancient and oral tradition of herbal preparations that may have multiple components, some active, some that buffer, and some that dilute the active components. This approach takes into account the time of harvest of the herb, the soil and climate conditions, and the method of drying, processing, and extraction. An important adjunct to this therapeutic approach is the perceived value of the ritualistic and nonspecific effects of treatment. Conventional medicine practitioners using herbal products usually remove botanicals from their traditional context. In contrast, Chinese practitioners use herbs in the context of the Yin and the Yang, Ayurvedic practitioners in the context of the 4 Vedas, and Native Americans in the context of ceremony and prayer. Similarly, neighborhood herbalists in the United States typically recommend herbs in the context of personal advice and incantation. Thus, herbal therapies go beyond simply prescribing pills. Natural medicine stresses the psychosocial aspects of health as well as faith healing and the drug-placebo effect. Clearly, future clinical trials aimed at analyzing alternative forms of therapy must include these psychological and spiritual elements if they are to be anything more than pharmacologic studies of a drug that happens to be derived from a plant. This raises the question of whether the contrasting therapeutic styles can be coupled in

a combined approach in the management of patients with hepatitis C, a tactic that needs consideration given the extent of use of CAM by patients with liver disease. One strategy might be to use CAM to ameliorate the side effects of conventional therapy. Alfa interferon, in particular, causes fatigue, irritability, and depression that can be dose limiting. Lessening of these symptoms might permit a higher rate of compliance and a better rate of response. In such studies, the end point of beneficial response to CAM would be measures of side effects, symptoms, and total dose of conventional therapy tolerated. Another possibility is that CAM therapy might ameliorate the chronic liver disease of hepatitis C even though it might not inhibit or eradicate the actual viral infection itself. Some CAM therapies appear to exert biological effects that include antioxidant, antifibrotic, or immune modulatory activities, that may help to ameliorate the disease. Proof of such an effect would probably require documentation by liver histology.

HERBAL PRODUCTS AND OTHER "NATURAL HEALTH" APPROACHES OF THERAPEUTIC INTEREST

There are numerous herbal products and mixtures believed to have therapeutic benefit. What follows is an appraisal of several products that have been considered helpful for treating liver disease, as well as mention of products of potential interest deriving from plants of diverse geographic origin and based on local cultural practices.

Silymarin (Milk Thistle)

Silymarin is an extract of *silybum marianum* (Milk Thistle) found commonly throughout Europe, Asia, and North America. Highly purified extracts were made available in the 1960s. Chemical analyses of extracts describe multiple biologically active compounds, including 4 flavinoids, the major one being silibinin, which accounts for 90% of the herb's components in most preparations. Silymarin has been used in Europe since the 16th century, and continues to be used there as a treatment of liver disease and jaundice.

Experimental data indicate that silymarin acts as an antioxidant and free-radical scavenger and prevents glutathione depletion and free-radical formation. It may also have antifibrotic activity through an as yet unknown mechanism. Silymarin extracts protect rats and mice from several forms of experimental liver injury, including *Amanita phalloides* poisoning, galactosamine toxicity, and thioacetamine-induced liver failure. Maximal efficacy occurs with pretreatment of animals, but some effect is noted when silymarin is given after exposure. Because of the impressive effect of silymarin in reducing phalloidin toxicity, an intravenous form was developed for therapy of mushroom poisoning.

The first large-scale clinical trial of silymarin began in 1971 as a long-term, double-blind RCT that compared silymarin (140 mg three times daily) with a placebo vitamin preparation in 170 patients with cirrhosis of diverse causes. The study had several shortcomings, designed before the discovery of hepatitis C and at a time when diagnosis of hepatitis B, management of cirrhosis complications, and use of liver transplantation were still limited. Moreover, the original investigator died before ending the study, which was completed by different investigators. Nevertheless, the study showed a significant difference in survival between patients treated with silymarin and the vitamin placebo (77% versus 67% at 2 years, and 58% versus 39% at 4 years; $P = .036$). Subgroup analyses showed that the major effects were in patients with Child's class A cirrhosis ($P = .03$) and with alcohol-induced liver disease a ($P < .01$). Importantly, silymarin had no significant side effects. The results of this trial were a major impetus to widespread use of silymarin in Europe for many forms of liver disease.

A second multicenter, RCT was initiated in 1985 and enrolled 200 patients with cirrhosis caused by alcohol-induced liver disease. Study subjects were given 150 mg of silymarin or a placebo 3 times daily for 2 years. Complications in this study included a high dropout rate, poor compliance, and limited outcome measures. Mortality rates in the silymarin and placebo groups were 17% and 12% at 2 years and 19% and 16% at 5 years, most deaths (76%) being caused by liver disease. Overall mortality was unexplainably low and concerns about compliance and dropouts complicated the interpretation of these negative results. Furthermore, neither this study nor the previous trial reported histologic data or follow-up liver chemistry results.

There have been no RCTs of silymarin therapy aimed at chronic hepatitis C or other specific forms of chronic liver disease. Pilot studies suggest that silymarin does not lower hepatitis C virus (HCV)-RNA levels, but it may decrease alanine aminotransferase (ALT) levels. The absence of appropriate controls and rigorously defined end points limits the significance of these studies. Clearly, properly controlled and adequately powered RCTs of silymarin are needed.

A major limitation in clinical research on silymarin is the lack of a reliable formulation for clinical studies. In Europe, pharmacokinetic studies of various preparations of silymarin have shown great variations in peak drug levels and concentration areas under the curve after administration of single and multiple doses. Indeed, the appropriate doses and treatment regimens have yet to be defined. Standardization of product and proper bioavailability and pharmacokinetic studies are needed before rigorous controlled trials can be initiated.

Glycyrrhizin (Licorice Root Extract)

Glycyrrhizin is an aqueous extract of the licorice root, *Glycyrrhiza glabra*, which is endogenous to southeastern Europe and western Asia. Licorice root (*liquiritiae radix*) has been used for centuries in traditional medicine to treat cough, bronchitis, gastritis, and liver inflammation. It is available over-the-counter in liquid, powder, and pill forms in the United States. Its major constituents are glycyrrhetic acid, multiple flavonoids, isoflavonoids, hydroxy-coumarins, and sterols, including beta-sitosteroid, which may have glucocorticoid and mineralocorticoid activities. Recommended daily doses are 5 to 15 g of the root, equivalent to 200 to 600 mg of glycyrrhizin. In Japan, a product referred to as Stronger Neominophagen C (SNMC), containing glycyrrhizin, cysteine, and glycine, is used to treat acute and chronic hepatitis.

Glycyrrhizin prevents several forms of experimental liver injury in animals. It appears to inhibit the activity of 11-beta-hydroxysteroid dehydrogenase, PGE₂ production by macrophages, and modifies arachidonic acid metabolism. It also has antioxidant activity, inducing glutathione-S-transferase and catalase activity and decreasing polymorphonuclear cell oxidative product formation. Glycyrrhizin treatment blunts ALT elevations and impedes fibrosis in animals, possibly through blocking the activation and action of nuclear factor κB in response to injury signals.

Glycyrrhizin has been reported to be beneficial in viral hepatitis; however, in one study, HCV-RNA levels did not change over time and the observed reduction in ALT levels may have been caused by the coadministration of ursodiol. In an often-cited Japanese study of SNMC in patients with hepatitis C, cirrhosis developed after 15 years in 21% of treated patients compared with 37% of untreated controls, whereas hepatocellular carcinoma arose in 12% of treated persons and 25% of controls. This trial, however, was not prospective or randomized, varying doses of SNMC were used, and some patients received other unknown herbal therapies. Moreover, neither HCV-RNA levels nor follow-up data on biochemical tests, liver histology, and quality of life were reported.

Treatment with glycyrrhizin is also not without side effects. Because of its mineralocorticoid activity, treatment can cause worsening of symptoms of cirrhosis, including fluid retention and hypokalemia. Nevertheless, glycyrrhizin is a common component of many herbal medications including Kampo, TJ-9, and Herbal Recipe 861 (see later). Clearly, the active ingredients of licorice root deserve better characterization, and development of a purified and reliable product is needed before clinical trials can proceed. For the present, this agent should be avoided in patients with cirrhosis.

Blended Herbal Formulations and Extracts

Many cultures have a tradition of using herbal formulations, based on the local horticulture, to treat chronic debilitating conditions. Addressed at this conference were herbal formulations in Chinese Traditional Medicine (CTM), Japanese Herbal Medicine (Hozai and Kampo), Ayurvedic Medicine (Indian Subcontinent), Traditional African Medicine, Traditional Medicines of the Amazonian Basin (South America), and Arab Traditional Medicine as potential candidate therapies for chronic liver diseases.

Chinese Traditional Medicine. CTM has been practiced for roughly 2 millennia, with comprehensive records of Chinese medical theories dating back to 221 BC. CTM comprises multiple forms of ritualistic healing practices. These include the relatively well-known practices of acupuncture and herbal therapy and the lesser-known moxibustion (dermal counter-irritation therapy), massage, and exercise therapy (Qi Gong). Chinese herbal therapy comprises over 100,000 recorded treatments, roughly 80% being combination or herbal mixtures. Most herbal mixtures comprise 4 to 5 herbs with 1 to 2 major pharmacologically active compounds (King herb), the remaining herbs playing a "helper function," such as reducing toxicity, promoting delivery to the target site, or working synergistically with the "King."

Regarding chronic liver disease, a limited number of mixtures (approximately 76) have been identified by screening a Traditional Oriental Medicine Database (Tradi/Med DB). A hepatoprotective extract with the highest potency and the lowest toxicity is the *Plantago asiatica* seed, the active component being aucubin. Aucubin appears to inhibit hepatitis B virus (HBV) replication in vitro and in animals (100 mg/kg daily for 1 month). Its use in a human trial, 10 mg/kg administered intravenously for 4 weeks, led to a 10% to 40% decrease in serum HBV-DNA levels that returned to pretreatment values after stopping therapy.

A second combination of 10 herbs, termed "Herbal Medicine 861 (H;M861)," was tested for antifibrotic activity in 3 controlled clinical trials encompassing 107 patients with hepatitis B. ALT levels fell into the normal range in 73% of patients, while spleen size, portal pressure, and serum procollagen peptide and laminin levels decreased in 53%. Liver biopsies, 6 months posttreatment, showed reductions in fibrosis and inflammatory infiltrates and quantitative decreases in tissue hydroxyproline. All patients remained hepatitis B surface antigen (HBsAg) positive. In vitro studies using human stellate cells and in vivo studies using animal models of fibrosis (CCI+ and albumin induced) showed that HM861 inhibited stellate cell activation by blocking cyclin/cyclin-dependent kinase activity in the cell cycle, and that fibrotic tissues were remodeled, with revascularization of liver sinusoids. Transforming growth factor β and collagen type I, III, and IV gene transcripts were reduced while matrix metalloproteinase I was increased, suggesting a reversal of early stages of cirrhosis through the correction of imbalance in the dynamics of synthesis and degradation of the extracellular matrix.

CH-100 is a formulation of 19 different herbs developed for treatment of liver disease. In a double-blind, placebo-controlled trial involving patients with hepatitis C, treatment with the product was associated with a significant reduction in ALT levels, although no treated person cleared the virus. NCCAM is currently supporting a study of a 10-herb combination, referred to as 3AR. The trial will assess safety and adverse events, as well as symptoms of fatigue, quality of life, liver function, and HCV-RNA levels in patients who do not qualify for standard therapy of hepatitis C. Thus, there is increasing interest in conducting rigorous testing of candidate CTM compounds (1) as alternatives to standard treatment, (2) to augment conventional treatments, or (3) to ameliorate the side effects of current therapies.

Japanese Traditional Medicine. The medical system in Japan mixes Western and Kampo traditions. In 1976, Kampo medicines were approved for use by the National Health Insurance System. By 1993, 77% of Japanese doctors were using Kampo medicine. Presently, 148 Kampo extracts are officially approved for use. TJ-9 (Shosaiko-to) is recommended for treatment of hepatitis B. Several animal studies have shown a reduction in hepatic fibrosis. In a long-term (5 years), prospective, randomized, nonblinded, controlled study of HBsAg-positive patients given conventional drugs together with the herb, in a dose of 7.5 g daily, the cumulative development of hepatocellular carcinoma was significantly lower in those given TJ-9 than in the controls. Studies of TJ-9 in patients with liver cancer have shown a dose-dependent increase in tumor necrosis factor α (TNF- α) and granulocyte colony-stimulating factor.

Another class of herbal medicines, termed "supplemental medicines" or Hozai, are thought to have immunologic activities, such as activating macrophages or stimulating cytokines. TJ-108 (Ninjin-yomei-to), TJ-41 (Hochu-ekki-to), and TJ-48 (Juzen-daiho-to) have been used extensively in Japan, having been tested in vitro for cytostatic properties. TJ-108 may have antiviral properties, because it contains *Shisandrae Fructus*, the active component being Gomisin A. In a study of 37 patients with hepatitis C, Gomisin A reduced the HCV-RNA levels in 21% of patients. Accordingly, TJ-108 is being evaluated in Japan as a complement to Western treatments.

Ayurvedic Medicine. Ayurvedic (ayu-life and veda- knowledge or science) medicine is the traditional medicine of India, a practice dating back 5,000 years. Treatment is mainly dietary and herbal, but may also include aspects of meditation.

Ayurvedic medicine classifies patients by body types or prakriti, determined by proportions of the three doshas, which regulate mind-body harmony. Illness and disease are considered an imbalance in the doshas and treatment is aimed at restoring innate harmony or balance to the mind-body system.

Ayurvedic medicine targets the liver as part of maintaining whole body harmony. Specific herbal formulations and herbal extracts have been studied for the treatment of chronic liver disease, including Liv-52, HD-03, AO-8 herbal formulations, and extracts of *Eclipta alba* and *Phyllanthus amarus*. Liv-52, marketed in India as an Ayurvedic hepatoprotective agent, is an herbal formulation that comprises *Capparis spinosa* (capers), *Cichorium intybus* (wild chicory), *Terminalia arjuna* (arjuna), *Solanum nigrum* (black nightshade), *Achillea mille folium* (yarrow), and *Tamarix gallica* (tararisk). It was originally thought useful for treating alcohol-induced liver disease, but a recent RCT from Europe showed a detrimental effect on the course of advanced alcohol-induced cirrhosis. AO-8 and HD-03 are herbal formulations that may be useful as an antioxidant and antitoxin, respectively. Perhaps the most promising agent for liver disease, principally chronic hepatitis B, is *Phyllanthus amarus*. In an initial study, 59% of individuals treated with a plant extract of *Phyllanthus* for 30 days became HBsAg negative, compared with 4% in the placebo control group. In animal studies, *Phyllanthus amarus* extract reduced or eliminated woodchuck hepatitis virus in woodchucks but not duck HBV in ducks. Recent studies show that an extract of *Phyllanthus amarus* down-regulates HBV in vitro by inhibiting the viral polymerase, decreasing episomal HBV-DNA content, and suppressing virus release through specifically inhibiting HBV enhancer I activity by complexing with the C/EBP α and β transcription factors. Although the active compound remains to be identified in these studies, screening studies of specific compounds derived from Ayurvedic medicines are being performed in an effort to further drug development.

Other Traditions. Treatment of liver diseases in traditional African medicine involves the use of several dietary plants, spices, and common herbs. Unique to traditional African medicine is that spices and herbs are determined to be food or to be medicinal based on distinct preparatory practices. Approximately 89% of the rural African population uses traditional medicines. The seeds of *Garcinia kola* (Fam. Guttiferae) have shown antiviral and anti-inflammatory properties. A herbal formulation of bitter-kola (*G. kola*) and the leaves of *Kinkeliba* (*Combretum micranthum*) enjoys a folk reputation as an effective treatment for the management of liver diseases of unknown etiology. Extracts of *Combretum* have been shown to prevent chemical-induced damage to the liver and to exhibit in vitro antiviral activity. Teas containing *Utazi* (*Gongronema latifolia*), bitter-leaf (*Vernonia amygdalina*), or *Nimbima* (*Cryptolepis sanguinolenta*) are also used throughout West Africa for the management of diabetes and other metabolic diseases associated with the liver.

Tropical rain forests offer enormous prospects for the discovery of new drugs for use in Western medicine. The Amazon supports 80,000 species of higher plants. Focusing attention on plants used as medicines by indigenous peoples may help identify those with beneficial bioactive effects; this process is termed ethnobotany. Basic ethnobotany includes compiling and organizing plant information in the context of the entire environment (biota) obtained from indigenous peoples and understanding how local cultures manage their environments and generate lexicons and classifications. Regarding the search for experimental therapies for chronic liver diseases, several plants have been targeted for antiviral screening. With the assistance of a traditional herbal healer, plants high in tannins, polysaccharides, and flavinoids were identified as most promising for antiviral activity.

The healing systems of the ancient Egyptians include a blend of spiritual, allopathic, and herbal remedies. Medicinal plants and herbs have been used in Egypt, at least since the Pharaonic Period, with the treatment of liver diseases being part of these traditions. Current Arabic culture encompasses 3 main classes of medicinal plant and herbal use that include folk remedies, unlicensed herbalists, and herbal pharmacy. Folk remedies, widely used in homes, comprise teas of many kinds like "karkadeh" (hibiscus flower) for lowering hypertension, anise tea for indigestion, and "erkouse" a liquorice drink, for quenching thirst. Unlicensed, unregulated herbalists practice in shops in bazaars and through informal street displays. Some spice and

herb shopkeepers use herbal medicine reference books to prescribe individual herbs or create mixtures for specific ailments. Nubians and Bedouins, two minority groups, have the deepest traditions in herbal medicine, perhaps because of their relatively isolated lifestyle. Teas of various kinds predominate and are used for a wide variety of complaints, primarily indigestion, constipation, colds, and kidney disease. Remedies for liver diseases are available, with rosemary and turmeric being the most common ingredients. Also, parsley and lettuce oil are used for treatment of liver disease. The formal sector pharmacies and Sekem organic shops comprise Arabic herbal pharmacy. Medicinal plants are part of the standard pharmacy curriculum and pharmacists sell herbal products, most notably silymarin, for treatment of liver disease. Five herbal remedies (aqueous extracts of *Teucrium polium*, *Mercurialis annua*, *Pistacia lentiscus*, and *Urtica pilulifera*) were shown to inhibit iron-induced lipid peroxidation in vitro, comparable with vitamin E in antioxidant function. Sekem shops also sell a wide variety of teas made from herbs including the "Hepatic" tea. The labels include the ingredients in the teas, and the instructions for use. An antioxidant/silymarin formulation is often prescribed for treatment of hepatitis C.

In summary, numerous candidate compounds available on the open market have been used in the treatment of liver diseases (Table 1), but efficacy data still remain to be generated through clinical trials before any of these products can be integrated into the practice of Western medicine for the treatment of liver diseases.

Table 1. Candidate Compounds With Possible Efficacy in Liver Disease

Compound	Putative Biological Mechanism*	Targeted Liver Disease**
Silymarin (milk thistle)	Biologically active compound – silibinin Acts as an antioxidant and free radical scavenger In animals prevents glutathione depletion free radical formation in the liver May also be antifibrotic through undetermined mechanism(s)	Cirrhosis In Europe – chronic liver disease, digestive disorders, and gallbladder disease
Glycyrrhizin	Licorice root – multiple constituents appears to inhibit enzyme 11-beta-hydroxysteroid dehydrogenase, thus anti-inflammatory in inhibiting prostaglandin production and modifies arachidonic acid metabolism Also antioxidant properties – induces glutathione-S-transferase and catalase Aucubin – active ingredient, iridoid glycoside Transient inhibition of viral replication Herbal mixture, blocks stellate cell activation through inhibiting cell cycle progression	Used traditionally for cough, bronchitis, gastritis, liver inflammation Fibrosis
Plantago asiatica seed	Extract inhibits hepatitis B viral polymerase by inhibiting the virus enhancer I activity – complexes transcription factors	Hepatitis B Virus
Herbal Medicine		Fibrotic liver disease
TJ-09 (Sho-saiko-to)		Fibrotic liver disease In Japan, recommended for hepatitis B virus
TJ-41		Hepatocellular carcinoma
TJ-108		Hepatitis C
Liv-52		In India, alcohol-induced liver disease
Phyllanthus amarus		Hepatitis B

*Putative biological mechanism determined in animal models or by in vitro assays. Mechanisms in humans not identified

**As noted in text, herbal preparations are not prescribed as is conventional treatment. Targeted disease based on putative biological mechanism. Country designation indicates government-sanctioned use

VITAMINS, ANTIOXIDANTS, AND IMMUNE MODULATORS

Immune dysregulation is a component of the pathogenesis of liver disease so that drugs that affect immune function may be beneficial in treating these diseases. In alcohol-induced liver disease, for instance, there is an overproduction of proinflammatory cytokines such as TNF by peripheral blood monocytes and resident hepatic Kupffer cells. Antioxidants, like vitamin E, and glutathione prodrugs, such as N-acetylcysteine and procysteine, inhibit cytokine production by peripheral blood mononuclear cells and Kupffer cells in vitro. A trial of intravenous pro cysteine given to individuals with stable cirrhosis led to increases in blood glutathione levels and a decline in monocyte production of TNF, interleukin 8, and interleukin 6. Such results suggest that antioxidants and glutathione prodrugs may be beneficial in chronic liver diseases in which immune dysregulation appears to play a role.

Extending the use of antioxidant-anticytokine therapy to CAM, polyphenols derived from green tea were shown to block endotoxin-induced lethality in rats by inactivating nuclear factor KB transcription factor with subsequent reduction in TNF levels. Thus, polyphenols of green tea induce immune modulation through well-defined molecular mechanisms and may be useful for autoimmune liver diseases. S-adenosyl-methionine is a principal methyl donor important in polyamine biosynthesis. Polyamine synthesis appears to be important for the fidelity of enhanced DNA transcription and RNA translation in response to infection and during tissue repair after injury, in gut growth after surgery, and in gut barrier functions. Diet supplementation by polyamines or by the recently marketed S-adenosyl-methionine (SAME), has been termed "immunonutrition" and has been postulated to improve gut or systemic defenses to infection and injury. SAME therapy has been shown to protect against TNF hepatotoxicity in vitro and in animal models of liver injury. Patients with alcohol-induced liver disease have decreased SAME levels, which may predispose to mitochondrial glutathione depletion and dysfunction. Intravenous SAME administered to individuals with alcohol-induced liver disease was reported to improve methionine clearance and liver function in 4 patients studied to date.

TOXICITY OF HERBAL PRODUCTS, REPORTING OF ADVERSE EFFECTS

Although physicians recognize that many conventional drugs cause liver damage, they are less likely to consider the hepatotoxic potential of herbal remedies. Identification of toxicity from herbal preparations is often difficult, because patients generally self medicate with these products and may withhold this information. Patients may not even consider herbals as medications in the belief that "natural" products are safe. Because patients who attend conventional liver clinics commonly use CAM, it is incumbent on health care providers to inquire about CAM in as nonthreatening and nonpejorative a manner as possible.

Herbal preparations that have been reported to cause hepatotoxicity are shown in Table 2. A wide spectrum of liver injury can occur. Veno-occlusive disease may be caused by pyrrolizidine alkaloids, such as senecio, heliotropium, crotalaria, and symphytum (Comfrey). These compounds are generally ingested as soluble extracts in teas. Chapparal leaf ingestion can lead to the development of either fulminant hepatic failure or cirrhosis. Germander has been reported to cause severe hepatotoxicity and has been banned in some European countries. Pennyroyal (squawmint Oil), kava, margosa oil, and callilepis laureola have all been identified as causing an acute hepatitis. Many traditional Chinese herbal preparations have also been described to cause hepatotoxicity and rarely liver failure.

Table 2. Herbal Products That May Induce Liver Injury

Herb	Type of Injury
Pyrrolizidine alkaloids	
Crotalaria	veno-occlusive disease
Gordolobo herbal tea	veno-occlusive disease
Heliotropium	veno-occlusive disease
Maté (Paraguay) tea	veno-occlusive disease
Senecio aureus	veno-occlusive disease
Symphytum officinale (Comfrey)	veno-occlusive disease
Chaparral leaf	Zonal (zone 3) necrosis, cirrhosis
Germander	Zonal (zone 3) necrosis, cirrhosis
Pennyroyal (squawmit oil)	Zonal (zone 3) necrosis, microvesicular steatosis
Jin Bu Huan	Acute hepatitis, microvesicular steatosis
Traditional Chinese herbs	Acute hepatitis
Kava (rhizome of pepper plant)	Acute hepatitis
Kombucha mushroom (tea)	Acute hepatocellular injury
Valerian root and skullcap	"Hepatitis"
Mistletoe	Chronic hepatitis
Margosa oil	Microvesicular steatosis

Adapted from Schaino, Strader and Zimmerman, and Bass.

Patients must be made aware that the herbal products are not manufactured to the same standards as prescription or over-the-counter drugs. Indeed, they should recognize that any over-the-counter product, whether natural or synthetic, has the potential for harm. Plant products that can produce severe liver disease include certain strains of mushroom (*amanita phalloides*). Physicians and health care providers should become familiar with the natural or alternative products that are available and recognize which can be harmful.

They should also recognize that there may be interactions between conventional drugs and herbals, an issue that must be considered when unexplained abnormalities are detected.

Regulation of herbal products is still relatively scant. If a product claims to treat, cure, prevent, mitigate, or diagnose a disease, it must then be regulated by the FDA as a drug. In contrast, dietary supplements are considered to be foods, and products are not evaluated formally for safety and efficacy. Postmarketing surveillance is the only method of establishing safety, but no equivalent exists for determining efficacy. MEDWatch is an FDA-sponsored program available for physicians to report adverse events associated with products monitored by the FDA, including special nutritional products (telephone 1-800-FDA-1088; internet at www.fda.gov/medwatch/index.html). Consumers (patients) can report adverse events through the FDA Office of Consumer Affairs at 1-800-532-4440. In addition, CDC staff investigate instances of hepatotoxicity attributable to CAM products, but such toxicity usually goes unreported.

Finally, botanical products cannot, at present, be regulated or substantiated in the same way as pharmaceutical products. Botanicals are typically prepared from plants by simple processes such as pulverization, decoction, and aqueous or alcohol extraction, methods without extensive purification steps. Consequently, botanicals are often crude mixtures containing many chemical compounds. The chemical constituents may not be well characterized, the active ingredient may be unknown, or there may be multiple active ingredients. The quality and consistency of the botanical product often relies on the quality of the botanical plant, a consequence of where it is grown, at what elevation, and the time of harvest. In addition, the initial treatment and subsequent storage may affect quality. The validation and control of the manufacturing process are also important. As these products become more main-stream, methods will be developed that will permit needed initial safety and efficacy testing. Once appropriate regulations are developed to handle these issues and products are developed that conform to Good Manufacturing Practices, it will become possible to design appropriate RCTs that will permit the appropriate safety and efficacy studies of herbal products.

SUMMARY CONCLUSIONS AND RECOMMENDATIONS

CAM represents medical and health care practices that are not an integral part of conventional (Western) medicine. At least 42% of the general population and a similar proportion of liver disease patients use some form of CAM on a regular basis. Herbal preparations are used by 20% of liver disease patients, typically without the advice or even knowledge of their physician, the most common herb used being milk thistle or silymarin. Other candidate herbals for liver disease are glycyrrhizin, HM861, TJ-9, and Phyllanthus amarus. Many of these have been shown to protect against experimental liver injury in vivo, and most possess one or a combination of antioxidant, antifibrogenic, immune modulatory, or antiviral activities. None, however, have been shown to be effective in ameliorating the course of chronic liver disease in properly conducted RCTs. Current impediments to progress in developing reliable information on the safety and efficacy of botanicals are the incomplete understanding of their modes of action, the lack of standardization in their manufacture, and the complexity of the chemical ingredients in the average herbal extract.

Recommendations

- 1) physicians should routinely and non-confrontationally ask patients about use of CAM, and should become knowledgeable about CAM products, their traditional indications, and potential toxicities
- 2) research support is needed for both laboratory and clinical studies on CAM therapies for chronic liver disease
- 3) there is a specific need for reliable, standardized preparations of the active ingredients of candidate herbals for liver disease, produced using good manufacturing practices, and made available for pharmacokinetic, pilot safety and efficacy, and full-scale efficacy trials; and
- 4) there needs to be better communication and understanding between the academic and research medical community and practitioners of traditional or natural medicine to facilitate adoption of proven CAM therapies into conventional Western medicine.

Finally, it is appropriate to ponder the comment expressed in a recent editorial: "There cannot be two kinds of medicine-conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset."

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