Is There Any Use for Nontraditional or Alternative Therapies in Patients with Chronic Liver Disease?

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There has been a substantial increase in **the use** of so-called **complementary and alternative** therapies by **patients** with liver disease. Although **many** such **modalities are** available. **herbal therapies are the most popular, and of these remedies, silymarin** extracted **from the** milk thistle is most **widely** subscribed to **as a remedy** for **liver diseases.** Available evidence points **to a** potential. but unproven. benefit **for this as well as** other **therapies** based on **free radical** scavenger or antioxidant principles in **treating** patients with liver disease. These **therapies** deserve **further investigation** through **experimental** studier and **well-controlled** clinical **trials. Benefits to patients from these** therapies. **especially** to patients with established cirrhosis. **are most likely to** be modest and insignificant. Conversely, **the hepatotoxic** potential of **some alternative treatments is well recognized. As practitioners** educating and **treating patients with liver disease, we are** obliged **to** be Informed about **popular alternative therapies, understanding** of our **patients' need** to **be partners** in **their care, and open-minded to the possibility** that some benefit may **come** from **some therapies currently** regarded **as alternative. We need** to **be effective and tolerant** in **learning about which alternative treatments our** patients **are taking, so that we can** monitor **their effects** if any and counsel **appropriately against those** that **may** cause harm.

lnrroduction

Alternative therapies, now commonly referred to as cornplementary and alternative medicine (CAM) [1], have been variously defined as therapies not **widely taught** in medical schools, not generally used in hospitals, and not typically reimbursed by medical insurance companies [2]. This situation is rapidly **changing**. It is now estimated that more than 30 medical schools in the United States offer courses in CAM, with some acknowledging the huge popularity of these therapies **through establishing** centers for integrative medicine. In a landmark **paper, Eisenberg** *et* al [2] estimated the use of CAM to be 34% in the general population, close to the estimates for the use of these approaches among patients with cancer [3], and the self-medication with alternative therapies to be from 30% to 80% among people with HIV or AIDS [4] Based on questionnaires administered to patients **attending** the University of California, San Francisco Liver **Transplant** Clinic, **my** own estimate of the **prevalence** of CAM use among patients with chronic liver disease across **the board** is closer to 80%. The growing demand for CAM and its impact in the marketplace led the US Congress to **nstruct** the National Institutes of Health **(NIH/OAM)** to establish an Office of Alternative Medicine in 1992 to support studies of **alternative** therapies (their **informative website** is at http://altmed.od.nih.gov/oam/resources/bibs/). Consumer demand is now motivating more **insurers** and hospitals to incorporate CAM into the services they **cover** and provide [5,6••]. From an economic **perspective**, this is a major market force with an estimated **$13 billion per** year in 1990 [2]. Recent data certainly suggest at **least** a threefold growth in this **amount [7]**.

A more recent **definition for** CAM proposed by NIH/OAM takes into **consideration** he changes in acceptance of these therapies by the public **and**, in many **cases**, providers. but the definition is still **not entirely** satisfactory. CAM is thus defined as "**a** broad **domain** of healing resources that encompass all health **systems, modalities** and practices and their accompanying **theories and** beliefs, other than those intrinsic to the politically **dominant** health system of a particular society or **culture** in **a** given historical **period...boundaries** within CAM and between the CAM domain and the domain **of the** dominant system are nor always sharp or fixed' [8]. Although it emphasizes the sociopolitical aspects of CAM, this definition. in the eyes of the physician and scientist, **must** be seen as **deemphasizing** the scientific basis for **what we advocate** and practice **as** conventional medicine. **This** system is not perfect. **certainly,** but is has been **advanced and tested by a process** that has evolved through the **application of the** most disinterested, logical, and **honest** principles available to **us.** Although the **dangers inherent in the uncritical acceptance**

and widespread use of CAM have led to strong opinion focused against this growing practice [9••], CAM represents a means of empowerment to patients. and it is deadedly here to stay. Perhaps its growth is part of the millennial phenomenon: perhaps it is a means of empowerment for patients frustrated with the diminished time their physicians spend explaining the mysteries of their ailments to them as we rush to meet the demands of the new medical marketplace. In hepatology, where we often must confront diseases that are physically and emotionally devastating, with demoralizing symptoms such as pruritus, fatigue, and pain, perhaps it should come as no surprise that patients often seek alternatives.

We have an even larger challenge to contend with following the recent wave of publicity regarding hepatitis C infection. The ominous overtones of articles such as Groopman's [IO] dramatic report on the "shadow epidemic" have produced awareness and also much anxiety in the affected population. As noted in one alternative self-help newsletter [11•], it is not surprising that patients faced with the recommendation of a conventional treatment that entails months of injecting a substance that produces flu-like symptoms, or worse, and a response rate of at best about 50%, would seek alternative treatment. The increased awareness of hepatitis C, coupled with blood bank look-back programs, is predicted to uncover a population estimated at 4 million individuals infected with a virus the natural history of which we are learning a great deal about-but not fast enough for the needs of most patients.

Parallels have been drawn between the AIDS epidemic and the explosion of public awareness regarding hepatitis C infection. The huge difference is that, as opposed to the devastating diseases that affected the majority of patients with AIDS in the early days. in most cases of newly discovered hepatitis C infection. individuals will be faced with a lifetime of anxiety over the potential outcome of their infection, and decades in which to seek the broad array of services offered by the CAM Industry.

Types of Alternative Therapies

Many therapies fall under the general heading of CAM, more than could be listed in specific detail in this review. NIH/OAM classifies these into six broad fields of alternative medicine: diet-nutrition-lifestyle changes, mind-body interventions. bioelectromagnetic applications, alternative systems of medical practice, manual healing, pharmacologic and biologic treatments, and herbal medicine. Table 1 lists some of the more commonly practiced and sought-after specific therapies. Information about these therapies is disseminated via a variety of books, newsletters, and, more recently, through the Internet. The power of this colorful. enticing, and unregulated medium in providing information and boldly advertising both conventional and alternative therapies is tremendous. Of all the therapies aimed at the patient with liver disease. nutritional counseling and herbal remedies are by far the most popular

Table I. Examples of Complementary and Alternative Medical Therapies

Acupuncture
Aromatherapy
Chelation therapy
Chiropractic
Ethnomedicine (includes Chinese herbal medicine)
Herbal therapy
Homeopathy
Megavitamin treatment
Naturopathy
Nutritional therapy
Osteopathy
Psychosocial therapies (guided imagery, biofeedback, massage)

Nutritional therapies

Alternative therapy and self-help newsletters can provide an excellent source of education to patients, including advice on testing for hepatitis and recommendations that current conventional understanding would endorse strongly: avoidance of alcohol, overuse of acetaminophen, and illegal drug use [11•] These same publications. however, are also the purveyors of advice that often seems to be based on a little learning, borrowed from the mainstream of medicine and then rehashed in misinterpreted form. For example, newsletters [11•] and websites (such as http://www.liverdoctor.com/) often advise patients to eat a very low-protein (and often avery low-fat) diet, presumably on the basis of knowledge that protein is a source of ammonia or that fat digestion and absorption are impaired in cholestasis. When this advice is applied to patients with early disease or well-compensated cirrhosis, however, it goes against current recommendations regarding appropriate nutritional management of all but the most severe end-stage liver disease [12.13•]. Other dietary avoidances that I have seen advocated include chocolate and caffeine. Often emphasized as the basis for dietary therapies is the need for liver "cleansing," a quaint and appealing concept that at least recognizes the central role played by the liver in nutrient processing and drug and toxin elimination.

Our task as physicians is to pay attention to the fact that the two most common questions that our patients with liver disease wish us to address today (apart from how long they are going to live) are diet and sex. The latter lies beyond the scope of this paper, but we should take a proactive approach to the issue of nutrition in our patients. Pointing out that our best knowledge supports simple principles of nutrition for liver disease provides relief and satisfaction to most patients.

Herbalism: the predominant practice

Herbalism is the most widely used type of CAM. This is not surprising given the extensive historical basis for the extraction of medicinal principals from botanicals. One need only consider foxglove, chincona bark, the poppy, and Fleming's bacterial culture gone moldy with Penicillium to

Table 2. Various Herbal and Alternative Remedies Recommended for Liver Diseases

Black cohosh	Licorice
Boneset	Milt thistle
Coltsfoot	Maitake
Comfrey*	Olive leaf extract
Dandelion	Schizandra
Fennel	Turmeric
Ginseng	

Data from Weil [11•], Youngkin and Israel [14•], and Castleman [15].
*Reported hepatotoxin (see Table 3).

appreciate this truism **In many** instances **the therapeutic efficacy of** herbal or botanical remedies has been dramatic: other remedies have been accepted into the mainstream eventually by withstanding the stringency of scientific testing and by demonstrating efficacy in well-designed. peer-reviewed clinical trials.

The herbs and botanical preparations in use through CAM number in excess of 1400 species [14], and most have not yet shown any true *efficacy* by trusted standards. Herbal treatments have enjoyed a protected status since 1362, when manufacturers were able to bypass US Food and Drug Administrations regulation by selling herbs as "food' products off the shelves of health food stores [14]. The confusion between opinion and fact in the field of herbalistic practice is apparent both from the breadth *of* claimed hepatic remedies and from the inconsistencies and disagreements among the manufacturers' and herbal practitioners' views of what constitutes a liver remedy (see Table 2). There is certainly no lack of debate among medical specialists regarding even some state-of-the-art conventional therapies, but it is odd to find a book on the shelves of a major drugstore chain that claims to be 'the ultimate guide to the curative power of natures medicines" listing a variety of herbal remedies posited to aid and heal the liver, with no mention, even in the index, of milk thistle

Milk Thistle

Milk thistle (*Silybum marianum*) is by far the most widely used herbal remedy among patients with liver disease. It enjoys a considerable and ancient reputation, based on a combination of historical legacy and interesting. often positive, but essentially flawed data. For a detailed and excellent review of this interesting herbal remedy. the reader is referred to the recent paper by Flora et *al.* [16••]. Milk thistle derives its name from its spiked leaves and white veins, the latter. according to legend, believed to carry the milk of the Virgin Mary. The plant has bright purple flowers and stout spines (Fig. 1). It is native to Europe but is grown commercially throughout the United States. The use of milk thistle as an herbal remedy dates back 2000 years, and Pliny the Elder is credited with observing that its seeds were "excellent for carrying off bile" [16••]. After holding a consistent place in the herbal armamentarium over the

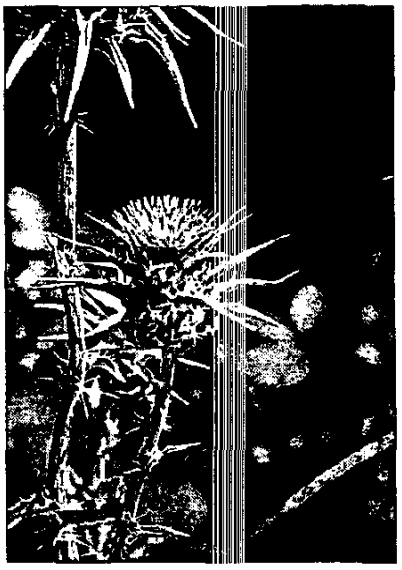

Figure 1. Milk thistle in bloom. Photographed by Brother Alfred Brousseau, June 11, 1974 in Napa County, California. Reproduced with permission.

centuries, the active principal, silymarin (a mixture of flavonoids of which silibin appears to be the most active) was extracted in 1968. This marked the beginning of the marketing of this agent as a liver *protectant* under the trade name of Legalon in Germany and continental Europe. Milk thistle is currently marketed in the United States under various labels of differing purity and silymarin content. Popular brands include Thisilyn (Nature's Way, Hamilton, OH) and Milk Thistle Plus, Liv-a-gen (BenSalem Naturals, Bensalem, PA). Most formulations are sold as capsules, and some are sold as liquid preparations. Prices range from $26 to 532 per 100 capsules.

An abundance of experimental *in vitro* and animal data supports a hepatoprotective effect of silymarin, with acute toxicology studies suggesting a similar protective effect to *N*-acetylcysteine and a variety of other compounds that have "made the grade' in this type of study [17–20]. Available evidence from seemingly reliable experimental studies suggests a broader spectrum of biologic actions including functioning as an antioxidant. affecting cellular membrane permeability; providing stability against xenobiotic injury: increasing the synthesis of ribosomal RNA by stimulating DNA polymerase I; exerting a steroidlike regulatory action on DNA transcription [20]; and exerting antifibrotic [21,22] and anti-inflammatory effects through inhibition of Kupffer cell production of cytokines [23]. Much of the early research into the hepatoprotective properties of silymarin, including animal studies and small, uncontrolled patient studies, was completed in the late 1970s, and most was sponsored by the manufacturer [24]. There have been several subsequent clinical trials of the efficacy of this agent in a variety of settings including acute viral hepatitis.

toxic hepatitis, alcoholic liver disease. and cirrhosis [16••] The results for the most part have been published in the more obscure literature. and although they are interesting from the point of view of the potential for a true hepatoprotective effect from silymarin in some situations, these studies are difficult to interpret because of small numbers: poor study design; heterogeneity of etiologies, dosing. and control groups. and poorly defined endpoints.

In Europe, many physicians accept silymarin as part of standard therapy for *Amanita phalloides* mushroom poisoning. This practice is based on one controlled animal study in which silymarin administered to beagles poisoned with powdered *Amanita* reduced biochemical evidence of liver damage as well as mortality [25]. A subsequent uncontrolled study in humans suggested a relationship between the brevity of the interval from presentation to silymarin administration and the favorability of outcome [26]. A retrospective study of 250 patients suggested that the combination of penicillin with silybin was associated with increased survival [27]. Several human studies. mostly uncontrolled or poorly designed controlled studies, have reported a protective or ameliorative effect of silymarin in acute or chronic viral hepatitis or toxin-, alcohol-, or drug-induced liver damage [16••,28–30]. When statistically significant improvements have been reported. they have usually been in biochemical parameters and occasionally histology. It is abundantly clear from all studies to date that the preparations used have been safe and without side effects. The overall positive body of largely uncontrolled or poorly controlled data encourages the further exploration of silymarin as a therapy for liver disease. At the very least, silymarin may assume a place similar to that of ursodeoxycholic acid as a harmless treatment that has some true. albeit modest, benefit in cholestatic as well as other liver diseases.

In the few available studies of treatment of patients with established cirrhosis, in which endpoints have been more stringent and more realistic with respect to survival. outcomes with silymarin have been less clearly positive. Ferenci *et* al. [31] recently published a double-blind. prospective, randomized study enrolling 170 patients with cirrhosis. Eighty-seven patients received 140 mg of silymarin three times daily, and 83 patients received a placebo. The mean observation period was 41 months. The 4-year survival rate was 58% ± 9% in the silymarin-treated patients and 37% ± 8% in the placebo group ($P = 0.036$). Subgroup analysis indicated that treatment was effective in patients with alcoholic cirrhosis ($P = 0.01$) and in patients initially rated "Child A" ($P = 0.03$). Thus, select subgroups appeared to benefit in this study, but in the end the numbers were small, and the reasons for this selective benefit are unclear. Countering this report are findings from a well-designed randomized, double-blind, multicenter trial from Spain [32•] in which the effect of silymarin was studied in alcoholics with cirrhosis with respect to survival and clinical and laboratory changes Two hundred alcoholics with proven cirrhosis were randomly assigned to receive either 450 mg of silymarin per day or placebo. The primary outcome was time to death, and the secondary outcome was the progression of liver disease. One hundred and three patients were assigned to receive silymarin and 97 to receive placebo. A 2-year study period was completed in 125 patients (57 receiving silymarin and 68 receiving placebo). Survival was similar in patients receiving silymarin and those receiving placebo The effect of silymarin on survival was not influenced by sex. persistent alcohol abuse, histologic alcoholic hepatitis, or seventy of liver dysfunction. Silymarin clearly did not have any signiticanr effect on the course of the disea e in these patients.

In this setting of scientific curiosity but ongoing uncertainty regarding any real benefit from silymarin in patients with liver disease. especially chronic liver disease, the next wave of alternative treatments is already on the horizon. As has often been the case with silymarin, data supporting its use come from the uncritical interpretation of the experimental literature and the assumption that if it is good for one ailment it must be good for others. Some examples illustrate how the boundaries between conventional and alternative therapies m ay become blurred and include rigorously studied agents such as *S*-adenosyl methionine [33] and *N*-acetylcysteine [34]. For the purpose of preventing necrosis and liver failure from acetaminophen, the latter is hardly regarded by hepatologists as an alternative therapy, but the broader purposes for which it may come to be used by patients could soon wit it in that light.

Chinese *herbal* medicine

Chinese herbal medicines are probably next in popularity among patients with liver disease. Claims for their efficacy, mainly in chronic viral hepatitis, range from the purely anecdotal [35] to rare controlled studies that suggest that certain Chinese herbal medicines may have a role in the management of chronic liver diseases. Batey et *al.* [36] recently reported a placebo-controlled study in which a Chinese herbal preparation, CH-100, was associated with a significant reduction in alanine aminotransferase levels over the 6-month study period in patients with chronic hepatitis C infection. Experimental studies of the preparation sho saiko-to. popular in Japan for treatment of liver disease, have provided evidence for an antifibrotic effect in the liver (Bissell, personal communication]. Paradoxically, the same preparation has been associated with liver damage in humans (see the section on "The Dark Side: Hazards of Alternative Therapies"). The major difference between Chinese herbal medicines and single herbal therapies such as milk thistle lies in the often complex and unknown contents of the Chinese herbal preparations, which may vary from batch to batch and can contain adulterants of considerable potential harm to the patient. This is also discussed in "The Dark Side: Hazards of Alternative Therapies."

Table 3. Nutritional, Folk. and Herbal Therapies Reported to Cause Liver Disease

Asafetida	Abnormal liver test results
Chaparral leaf	Zonal necrosis
Chinese herbs	
Jin Bu Huan Anodyne tablets	Hepatitis, fibrosis, steatosis
Xiao-chai-hu-tang (*sho-saiko-to*)	Zonal, bridging necrosis, fibrosis, microvesicular fat
Comfrey	Veno-occlusive disease
Gentian	Abnormal liver test results
Germander	Zonal necrosis, fibrosis
Kombucha mushroom	Hepatitis
Lady's mantle	Abnormal liver test results
Life root (*Senecio aureus*)	Veno-occlusive disease
Megavitamin A therapy	Hepatic fibrosis
Mistletoe	Abnormal liver test results
Senna fruit extracts	Abnormal liver test results
Shark cartilage	Hepatitis
Skullcap	Abnormal liver test results

Data from Youngkin and Israel [14], Farrell [48••], Picciotto *et al.* [49], Ashar and Vargo [50], Perharic *et al.* [51], and Perron *et al.* [52].

Antioxidants and vitamins

Oxidative stress has emerged as a key pathophysiologic mechanism in liver disease [37,38]. Not surprisingly, antioxidants are becoming increasingly attractive and popular as alternative therapies for a variety of liver diseases, with vitamins A, C, and E as well as selenium receiving most attention [11]. **Most are generally safe with the exception of** megadose vitamin **A** therapy, the potential hepatotoxicity of which is generally known, even among practitioners of alternative therapy. There may be other, less established long-term adverse impacts from the indiscriminant use of popular mixed antioxidant formulations. Thus, there is a reasonable practice among **some hepatologists to** counsel patients wirh potential or proven **hepatic** iron overload (including hereditary hemochromatosis, hepatitis C infection, and alcoholic liver disease) to avoid dietary vitamin C supplementation given the **proabsorptive** effect of vitamin Con nonheme iron [39] and also the evidence for **a prooxidant** effect of **ascorbate** in the liver in the presence of iron overload [40].

The experimental literature is replete with evidence for a **hepatoprotective** role for vitamin **E in toxin-induced liver damage and** in preventing hepatic oxidant **stress** [37]. The argument supporting supplementation **with** vitamin E has perhaps been **best substantiated** in patients with **cholestatic** liver disease. who **may absorb** it poorly [41,42]. **However,** evidence for vitamin E deficiency as a much broader phenomenon in patients with liver diseases has been presented [43]. A small experimental study in human subjects showed that vitamin **E** administration altered parameters **of oxidative stress** and **fibrogenesis** determined in liver biopsies [44]. A prospective, randomized, double-blind crossover study of vitamin E **treatment** in 23 patients with hepatitis C infection showed a significant improvement in aminotransferase levels [45•]. A small nonplacebo controlled study of vitamin E treatment in patients with hepatitis B infection has reported a greater frequency of alanine aminotransferase normalization and loss of detectable hepatitis B DNA in treated patients [46]. The authors of this study have suggested that these results point to an effect of vitamin E on the immune system beyond its effects as an antioxidant. As promising as these results may seem, not all therapeutic studies have been equally positive. A long-term double-blind trial of vitamin E supplementation in patients with alcoholic cirrhosis found no influence on hepatic laboratory parameters, mortality. or hospitalization rates for decompensated patients with alcoholic cirrhosis, although serum levels of the vitamin increased significantly [47]. Vitamin E. taken even in large doses. appears to be innocuous and is therefore in the same class of safety as milk thistle as an alternative therapy. The experimental literature and small body ofclinical studies to date are encouraging. however, and show that larger, well-designed studies with this agent are now indicated.

The Dark Side: Hazards of Alternative Therapies

Certain alternative therapies, even some purported to be of particular value in treating liver disease, may be potentially harmful and produce liver disease [14,48••,49,52]. This may result from excessive use of plant products or extracts thereof with relatively mild hepatotoxic potential, from adulterants or contaminants present in complex formulations, or even from potent hepatotoxicity of preparations taken for other purposes (Table 3). Among those most commonly implicated have been Chinese herbal or traditional medicines. which commonly comprise multiple products, some of which have caused serious illness [53]. Paradoxically, an herbal remedy or traditional medicine such as ***xiao-chai-hu-tang (sho-saiko-to)*** that has been used in the treatment of liver disease has been implicated in causing liver injury [48••]. Finally, the potential for acupuncture to transmit hepatitis C and B infection is well recognized [54], but other more obscure therapies such as autohemotherapy may do so as well [55].

Conclusions

There appears to be a growing and understandable **backlash of irritation among some physicians with the growth and uncritical use of CAM. The recent editorial by Angell** and **Kassirer** [9••] draws **a line in the sand by stating that there can be only one type of medicine, that which has been adequately tested and which works by current scientific standards. Although few physicians would** disagree with this **point** of view, it is likely that patients with liver **disease will continue to avail themselves of the broad base of information and treatments offered by both their conventional physicians** and the **practitioners of CAM** therapies. I **believe it is important that we as physicians keep the lines of communi-**

cation open. In this manner we can counsel our patients most appropriately. Renner, of the National Council Against Health Fraud (personal communication quoted by Carroll [1]), has proposed a useful five-point classification scheme within which to frame discussions of any therapeutic modality with patients. The five categories include quackery folklore. unproven or untested treatments. investigational or research treatments, and proven remedies. This classification defines the spectrum of treatments ranging from those we would regard as completely dishonest and exploitative to those we would accept as effective and valuable therapy. proven by scientific evidence. If a treatment is harmless and may or may not be of benefit. we can afford to be more tolerant of what may be little more than a placebo, especially when we have little to offer that is more effective. The only harm that may come in such circumstances is to a patient's bank balance. If a treatment may produce illness, interfere with the efficacy of conventional treatment. or lead patients to reject more effective conventional therapies, we must inform our patients unequivocally *of these facts. It* has been my experience that most are willing to follow **advice and guidance, as long as it is** given with an attitude of concern and respect, both for the patient's freedom to choose and for the potential, although unproven, benefit of some unconventional therapies. In answer to the question of whether there is any use for nontraditional or alternative therapies in patients with chronic liver disease. the best answer at this time is 'it depends.. We should not succumb, in the words of Angell and Kassirer [9••], to "giving alternative medicine a free ride." Selected alternative therapies for which the available critical literature suggests *some* promise should be subjected to rigorous scientific testing in well-designed experimental studies and clinical trials before we accept or reject them. An alternative therapy that passes this scrutiny will soon cease to be regarded as alternative. Ursodeoxycholic acid, a constituent of bear bile, **prized for centuries in China as a remedy for liver ailments and now an accepted and extensively prescribed therapy in hepatology, can be cited as one such case.**

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