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REVIEW

Silymarin treatment of viral hepatitis: a systematic review

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SUMMARY. Silymarin from the milk thistle herb (*Silybum marianum*) is used by many patients with chronic viral hepatitis, but its efficacy remains unknown. We performed a systematic review of silymarin for the treatment of chronic viral hepatitis B and C. An exhaustive search strategy identified 148 papers that studied silymarin compounds in liver disease. Of these, four trials included patients with hepatitis C, one included hepatitis B patients, and two, unspecified chronic viral hepatitis. However, only one trial exclusively studied patients with hepatitis C, and none involved patients with only hepatitis B. Silymarin treatment resulted in a decrease in serum transaminases compared with baseline in four studies, and compared with placebo in only one study. There is no evidence that silymarin affects viral load or improves liver histology in hepatitis B or C. No studies were found that investigated the use of silymarin concomitantly with interferon, nucleoside analogues, or other conventional treatments for hepatitis B or C. In conclusion, silymarin compounds likely decrease serum transaminases in patients with chronic viral hepatitis, but do not appear to affect viral load or liver histology. Nevertheless it may be worthwhile to determine its effects in conjunction with standard antiviral treatment.

Keywords: chronic hepatitis B, chronic hepatitis C, chronic viral hepatitis, milk thistle, *Silybum marianum*.

INTRODUCTION

Current standard therapies for chronic viral hepatitis remain unsatisfactory in many patients, especially those with chronic hepatitis B. Rates of hepatitis B viral seroconversion to a nonreplicative state in patients with chronic hepatitis B with nucleoside analogues or interferon range from 18 to 30% [1,2]. Sustained virological response rates with pegylated interferon-alpha and ribavirin in patients with hepatitis C are approximately 54–63% [3–5].

The side effects and high failure rates associated with standard therapy sometimes lead patients to explore alternative treatments, such as milk thistle or silymarin. Milk thistle (*Silybum marianum*) has been used since ancient times as a liver tonic. Pliny the Elder (AD 23–79) wrote that the juice of the milk thistle plant was excellent for 'carrying off bile'. The English herbalist and physician Nicolas Culpepper (1616–1654) noted that milk thistle can be used 'to open the obstructions of the liver and spleen, and thereby is good against the jaundice', and its use in liver disease was also documented by the Swiss physician Albrecht von Haller (1708–1777) [6].

This review examines the pharmacology, mode of action, efficacy and safety of silymarin compounds in chronic liver diseases with a particular emphasis on a systematic review of its effects in patients with chronic viral hepatitis B and C.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotrasferase; AST, aspartate aminotransferase; CAM, Complementary and Alternative Medicine; GGT, γ-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; MDA, malonaldehyde.

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SEARCH METHODS OF REVIEW

The literature search engines Pubmed, Medline, EMBASE, EBM Reviews – Cochrane Controlled Trials Register, AMED (Allied and Complementary Medicine), EBM Reviews – ACP Journal Club, and MD Consult were searched using the terms: milk thistle, carduus marianus, silybum marianum, silybum, silymarin, silibinin, silybin, silicristin, silidianin, Legalon, silipide, IdB1016, carsil, and spelling variants; hepatitis C, hepatitis B, viral hepatitis, chronic hepatitis, and chronic liver disease.

The date range for the search was from 1966 to June 2004, but the studies actually used range from 1977 to 2000; trials published before the discovery of hepatitis C in 1989 were of limited usefulness. No limitation was made regarding the publication type because of the lack of information on silymarin in viral hepatitis in general. Search results were not restricted by language, and abstracts and review articles were used to aid in gleaning information from papers not published in English, Hungarian, or Spanish. The bibliographies of references used were perused for additional

papers. Efforts were made to trace the information to primary sources. Thus, the search yielded 365 results, and 148 articles were reviewed, of which four studies included patients with serologically proven hepatitis C, one with chronic hepatitis B, and two with unspecified chronic viral hepatitis.

PREVIOUS REVIEWS OF SILYMARIN IN LIVER DISEASE

A number of reviews of silymarin and other complementary and alternative medicine (CAM) in liver disease have been published. A systematic review of herbs used in hepatitis C virus (HCV) has been published by the Cochrane Library [7], but it includes only one small study involving silymarin [8]. A protocol has also been prepared on silymarin in chronic liver disease [9]. An exhaustive 149-page review [10] of milk thistle compounds in various diseases examined 16 trials, three of which involved patients with acute or chronic viral hepatitis [8,11,12]. However, because of its sheer volume it is not easily accessible. These same three trials were also included in the systematic review by Jacobs *et al.* [13]. Although the review by Saller [14] includes more trials [8,11,12,15,16], it provides only a very brief synopsis of each. A more recent systematic review of CAM in hepatitis C did not cover silymarin in its scope [17].

This systematic review focuses on the evidence surrounding silymarin use in viral hepatitis, which is discussed in detail, while placing it in the broader context of silymarin therapy for liver disease of other aetiologies. Alas, completing a formal meta-analysis was not possible because of the small number of trials, the lack of adequately rigorous methodology in those trials, and heterogeneous patient groups and interventions.

PREVALENCE OF USE

Complementary and alternative medicine may be appealing to patients due to their seemingly low side-effect profile and optimistic anecdotal evidence, especially when more conventional treatments have high failure rates or numerous side effects. The prevalence of herbal medication use in the United States has increased from 2.5% in 1990 to 12.1% in 1997 [18]. A study by Verhoef *et al.* [19] in Calgary found that 9% of patients attending a university-based gastroenterology clinic also sought alternative medical care for the problem for which they were seeing a gastroenterologist. CAM use appears even more prevalent among patients with chronic liver disease. According to a survey by Flora *et al.* [20] alternative remedies, such as milk thistle, were used by 31% of patients attending a hepatology clinic in Oregon. Another survey in California estimated the prevalence of CAM use in patients with chronic liver disease to be 80% [21]. Among 92 patients with chronic hepatitis C attending a viral hepatitis clinic in Calgary, 56 (61%) had a record of using CAM, which included vitamins (42%), minerals (17%), herbals (41%), and others (18%). Milk thistle use was reported in 16 (17%) (K.E. Mayer, unpublished results).

PHARMACOLOGY

Silymarin comprises at least 70% of standardized milk thistle [22]. Silymarin is composed of the flavonolignans silybin, silydianin and silycristin, as well as isosilybin (a diastereomer of silybin) [23]. Most of its hepatoprotective properties are attributed to silybin (also called silibinin), the main constituent (60–70%) [24,25]. Silymarin is not regulated in North America, and the silymarin content of milk thistle extracts can vary from 40 to 80% [26]. The geographical source and cultivating conditions of the herbs also affect composition [7,27,28]. The pharmacokinetics of various silymarin preparations have been studied. Milk thistle teas contain only about 10% of silymarin because of poor water solubility [22]. Silymarin is poorly absorbed in the intestine (20–50%) [22], and undergoes primarily biliary excretion [29]. Peak plasma concentrations for Legalon® (manufactured by Madaus, and the brand of silymarin used in a number of German and Hungarian studies) occur in 1–2 h, and the half-life is 6 h [20,29]. In an assay of three batches of Legalon®, each capsule was found to have 52 mg silybin, 22 mg isosilybin, 23 mg silycristin and 28 mg silydianin [23]. Another formulation, silipide, has a phosphatidylcholine unit attached to it, which enhances its bioavailability [30,31]. It is not known how variations in plasma concentrations of silymarin impact its effectiveness. The German Commission E monographs (compiled by a expert committee which evaluates the safety and efficacy of herbal remedies sold in Germany) recommend 100–200 mg of silymarin two or three times per day for the treatment of liver diseases [22].

MECHANISM OF ACTION

The mechanisms of action of silymarin are not completely understood, but a variety of mechanisms have been proposed. Silymarin is reported to have antioxidant properties, by increasing superoxide dismutase activity in erythrocytes and lymphocytes [32,33]. It is also reported to stabilize hepatocyte membrane structure, thereby preventing toxins from entering the cell through enterohepatic recirculation, and to promote liver regeneration by stimulating nucleolar polymerase A and increasing ribosomal protein synthesis [22,26]. Silybin selectively inhibits leukotriene formation by Kupffer cells [34]. Silymarin is a mild chelator of iron [35]. It also prevents gluthatione depletion in human hepatocyte cultures, protecting cells from methotrexate and ethanol induced damage *in vitro* [36]. Counteraction of the CYP2E1 stimulation by chronic alcohol consumption could partly explain the beneficial effects of silymarin seen in alcoholic

liver disease, but there is no evidence of P450 2E1 involvement by silymarin [37,38]. Silymarin has immunostimulatory effects, and augments secretion of IFN-γ, IL-4, and IL-10 in mixed lymphocyte culture [39]. It also inhibits nitric oxide production in macrophages [40]. Silymarin may have antineoplastic effects, and has been found to inhibit the secretion of proangiogenic factors from tumour cells, inhibit growth and promote apoptosis of endothelial cells in mice with xenografts of human prostate cancer [41], as well as inhibiting endogenous tumour promoter tumour necrosis factor alpha in mouse models of skin cancer [42].

The mechanisms of injury in hepatitis C include oxidative stress as a result of the altered mitochondrial function suspected to be a direct effect of the HCV core protein [43], and is present in noncirrhotic patients as well as those with cirrhosis [44]. Thus, it could be anticipated that antioxidant therapy may have beneficial effects in hepatitis C patients. A randomized controlled trial of vitamin E in 26 patients with chronic hepatitis C showed a decrease in aminotrasferase levels (but not normalization) after 4 weeks of treatment that was not sustained after cessation of therapy [45]. Antioxidants, such as vitamin E, have also been shown to inhibit the activation of hepatic stellate cells, which are involved in fibrogenesis [46,47]. It is possible that silymarin may work through a similar mechanism.

The putative hepatocyte membrane-stabilizing, regeneration-promoting [22] and iron-binding [35] properties of silymarin may be of benefit in hepatitis C or B. Silymarin has not been reported to have any effect on viral load in hepatitis [24]. In an *in vitro* system, silymarin was not found to have any anti-HBs like activity [48]. In rat models, silymarin had direct antifibrotic activity [26,49], and also slowed fibrosis progression secondary to alcohol in baboons [50].

SAFETY AND SIDE EFFECTS

Silymarin is generally regarded to be safe, although allergic reactions, including anaphylaxis, have been reported in three cases [51,52]. The most common side effect of silymarin is a mild laxative effect. Other reported adverse events include nausea, epigastric discomfort, arthralgia, pruritus, headache and urticaria [25]. In one study of patients with alcoholic liver disease, side effects were reported in seven of 46 (15%) receiving silymarin compared with four of 29 (14%) receiving placebo over 2 years of use [53]. Concern has been raised regarding alterations of drug metabolism by silymarin. For example, as a result of cytochrome P450 enzyme inhibition and decreased bilirubin conjugation, silymarin may lead to reduced clearance and possible toxicity in patients treated with drugs conjugated by UGT1A6/9 [54]. While silymarin appears to have few negative effects, it is not known whether it has any interactions with interferon, ribavirin, lamivudine, or other conventional treatments for hepatitis B or C.

SILYMARIN IN NONVIRAL LIVER DISEASES

Silymarin has been shown to reduce CCl_4-induced liver damage in rats [55]. In Eastern Europe, intravenous silibinin is used in cases of *Amanita* mushroom poisoning [22]. The proposed mechanism for hepatoprotection in this setting is through inhibition of phalloidin and amanitin-transporters, and possibly by decreasing the enterohepatic circulation of the toxins. It has also been used to treat workers exposed to organic solvents like xylene [56]. Early randomized controlled trials of the effects of silymarin in alcoholic liver disease yielded promising results [20,57,58]. However, a more recent large randomized controlled trial indicated that there was no difference in survival over 2.5 years in 200 patients with alcoholic cirrhosis treated with silymarin compared with placebo [53]. In a randomized-controlled trial (RCT) involving 60 patients with alcoholic liver disease in whom other causes of liver disease including hepatitis C were excluded, no significant change was found in aspartate (AST) and alanine (ALT) aminotransferases, alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), albumin, prothrombin time (PT), platelets, or Child-Pugh score, after 6 months of treatment with either silymarin MZ-80 450 mg daily or placebo, even though the 49 patients who completed the trial abstained from alcohol [59]. According to the German Commission E, silymarin may be efficacious in cases of hepatitis A, alcoholic cirrhosis, and exposure to hazardous chemicals [22].

In a RCT by Ferenci *et al.*, 92 alcoholic and 78 nonalcoholic patients with otherwise undifferentiated chronic hepatitis and cirrhosis were randomized to receive 140 mg silymarin three times daily ($n = 87$) *vs* placebo ($n = 83$). The silymarin group included 47 patients with alcoholic liver disease and nine who were hepatitis B surface antigen (HBsAg)-positive, compared with 45 and 12 in the placebo group, respectively. The placebo group had a greater number of Child class C patients, and the average bilirubin level was higher, although the difference was not statistically significant ($P > 0.3$). All patients were requested to abstain from alcohol. Treatment lasted 2–6 years, with an average of 41 months follow-up, but only 105 of the original 170 patients completed at least 2 years in the study. There were 10 withdrawals from the silymarin group and 14 from the placebo group, two in each category because of side effects of nausea and epigastric discomfort. There were also 28 deaths in the silymarin group and 39 in the placebo arm. Patients were also withdrawn for noncompliance. Biochemical parameters did not change significantly, but there was a significantly improved survival in the treated group (77% *vs* 67% overall). The authors state that the fate of all 170 patients was considered in the survival analysis. Four-year survival was 58% in the silymarin group compared with 39% in controls ($P = 0.036$). Improvement was greatest in alcoholics. Among nonalcoholics, only Child class A patients had improved survival [57,60]. A statistically significant

difference in mortality was present even 6 years after the end of treatment [61].

SILYMARIN IN ACUTE VIRAL HEPATITIS

An RCT of 57 patients with acute hepatitis A or B given 420 mg daily of silymarin or placebo found that significantly more patients achieved normalization of AST and bilirubin with silymarin after 21 days of treatment. However, bilirubin was only determined in 20 of the original 29 patients receiving silymarin at day 21. Differences in normalization of ALT and ALP between the two groups were not significant [11]. An unblinded study of 151 patients with acute viral hepatitis did not find any difference between those receiving silymarin 420 mg daily and those with no treatment in terms of ALT, AST, ALP, total bilirubin, or PT 5 weeks after the onset of jaundice [15]. A three-armed study by Flisiak *et al.*, examined 52 patients with acute hepatitis B (alcoholism and hepatitis C and D excluded) treated with misoprostol, silymarin 210 mg daily, or receiving no treatment. A significant difference was noted between the silymarin and control group in ALP levels at 5 weeks of illness, but otherwise differences in hepatomegaly, bilirubin, ALT, AST and GGT were nonsignificant. HBsAg was cleared after 6 months in 85% of those treated with silymarin and 83% of controls [62]. However this means that 15% of those treated with silymarin and 17% of controls became chronic carriers, which is much higher than the expected rate of chronicity (1–5%) after acute hepatitis B virus in otherwise healthy adults. Thus some of the apparent 'acute' cases may actually have been acute flares in patients with chronic HBsAg carriage. Outcomes such as differences in rates of liver failure or liver transplantation were not reported.

SILYMARIN IN CHRONIC VIRAL HEPATITIS

Only one trial was found investigating silymarin in which the entire study population had hepatitis C and in whom other causes of chronic liver disease had been excluded [63]. Four other studies included patients with serologically proven hepatitis C, one with hepatitis B, and two with unspecified chronic viral hepatitis (Table 1).

Biochemistry

The impact of treatment with silymarin on patients with viral hepatitis in different studies is difficult to compare because of the disparity in treatment populations and treatment regimens. However, as a general trend there is improvement in the transaminases with treatment compared with baseline, but only equivocal effects on other liver enzymes (Table 2).

A double-blind, randomized, crossover study involving 10 patients with hepatitis C not responsive to interferon α2b found a significant decrease in transaminases in those treated with silybin compared with placebo. The participants failed to respond to a 6-month course of interferon α2b 3 million units three times per week 6–12 months before entering the study. There was no mention of exclusion criteria or alcohol use in the participants. Half of the group was given silipide 260 mg daily for 2 months, followed by a period of washout lasting 1 month, and finally placebo for 2 months. The second group was given placebo for 2 months, with washout for 1 month and silipide 260 mg daily for 2 months. Significant decreases in AST were found compared with baseline in the silybin group [63]. However, baseline ALT and AST levels in patients given silymarin were higher than for those receiving placebo.

In another study, 20 patients with chronic hepatitis B, C, or both were randomized to receive a silybin complex (IdB1016) or placebo. Patients with an ethanol intake >30 g daily or with other liver diseases were excluded. Compared with baseline and the group receiving placebo, the silymarin group had statistically significant decreases in transaminases and GGT. A decrease in bilirubin compared with baseline was also seen, but no significant change in ALP was observed. The exclusion criteria included clinical signs of cholestasis or having ALP or total bilirubin values at more than twice the upper limit of normal, and the authors speculated that this may have been a reason why there was no significant decrease in ALP levels with treatment. The histological stage of the patients before or after treatment was not reported, although it was stated that liver biopsy was part of the diagnostic criteria for at least some of the patients. The malonaldehyde (MDA) was recorded as a marker of lipid peroxidation. The baseline MDA values were twice the normal level, indicating that lipid peroxidation may occur in some patients with viral hepatitis infection, however no significant decrease was noted over the 7-day treatment period. The authors mention that this could be due to the short duration of therapy. The plasma silybin concentrations measured in eight patients on the seventh day of treatment varied quite markedly, from 78 to 1665 ng/mL (927 ± 191 ng/mL) [8].

In a randomized crossover study in which 21 patients with chronic liver disease and compensated cirrhosis who were HBsAg-positive and hepatitis B e antigen (HBeAg)-negative were treated with either 420 mg silymarin daily or 600 mg ursodeoxycholic acid for 6 months, silymarin was found to decrease ALT and AST, but had no effect on other liver enzyme levels [16]. Interestingly, a recent Cochrane Review has shown that treatment of patients with hepatitis B or C with ursodeoxycholic acid results in significant decrease in the transaminases, although there was not enough evidence regarding antiviral activity or the possible impact on histology or mortality [64].

In a phase II randomized open-label trial involving 60 patients with chronic hepatitis of either alcoholic ($n = 35$) or viral ($n = 25$) origin, a statistically significant dose–response to silymarin was present for AST (but not ALT)

Table 1 Studies investigating silymarin in patients with chronic liver disease, including hepatitis C

Study	Formulation used*	Study population	Study design	Efficacy
Buzzelli [63]	Silipide 360 mg daily ×2 months	10 nonresponder HCV patients	Crossover, double-blind, randomized trial	Significant decrease in AST compared to baseline with silymarin but not with placebo. No significant change in ALT, ALP, GGT, or bilirubin.
Buzzelli [8]	Silipide 480 mg daily ×1 week	20 chronic viral hepatitis: 8 HCV, 5 HBV, 7 HCV + HBV	Randomized-controlled trial	Significant decrease in AST, ALT, and GGT compared to placebo, and significant decrease in AST, ALT, GGT, and total bilirubin compared to baseline in silymarin group but not in placebo group.
Par [66]	Hegrimarin® 300 mg daily ×1 week, then 200 mg daily ×1 month	16 patients: 6 HCV + alcoholic liver disease, 4 alcoholic hepatitis, 6 alcoholic cirrhosis.	Uncontrolled trial	Significant decrease in AST, ALT, LDH, and bilirubin compared to baseline after treatment with silymarin. Significant increase in serum carotinoids and glutathione, and decrease in malonaldehyde.
Pares [53]	Legalon® 450 mg daily × ≥ 2 years	200 chronic, alcoholic cirrhosis	Randomized-controlled trial	Trend towards significance ($P = 0.059$) for survival in HCV patients taking silymarin compared with placebo. Also a trend towards lower prevalence of encephalopathy and upper gastrointestinal bleeding in patients receiving silymarin
Vailati [65]	Silipide 160, 240, or 360 mg daily × 2 weeks	25 viral hepatitis, 35 alcoholic hepatitis	Phase II randomized open-label trial	Significant decrease in ALT and AST compared with baseline in patients treated with silymarin at 240 and 360 mg daily doses. A statistically significant dose–response was present for AST but not ALT.
Kiesewetter 1977 [12]	Silymarin® 420 mg daily × 3 to 12 months	36 chronic, presumably viral hepatitis	Combined analysis of two double-blind studies	No difference was found in liver enzyme levels between the silymarin and control groups. Some histological improvement in terms of mesenchymal intralobular reaction was noted in the silymarin group compared to placebo ($P < 0.05$)

ALT, alanine aminotrasferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; LDH, lactate dehydrogenase.
*Silipide is silymarin with a phosphatidylcholine attached. Hegramarin® and Legalon® are silymarin compounds.

over 2 weeks of treatment, and there were significant decreases in the transaminases compared with baseline. However the results were not categorized by liver disease aetiology. The 240 mg daily silymarin group also had a greater proportion of female patients [65].

In a survey by Flora *et al.*, more than 50% of patients taking silymarin reported subjective improvement of symptoms, but the data was insufficient to determine whether or not this correlated with improved liver biochemistry [20]. No other studies were found which examined the effect of silymarin on quality of life.

In an uncontrolled study of six patients with chronic hepatitis C and 10 with alcoholic liver disease treated with silymarin 300 mg daily for 1 week, followed by 200 mg daily for 1 month, significant decreases in AST, ALT, lactate dehydrogenase (LDH) and bilirubin were found compared with baseline. AST normalized in 45%, ALT in 29%, LDH in 29% and bilirubin in 55% of patients. There were also significant increases in serum carotinoids and glutathione, and a decrease in MDA. Unfortunately, the absence of an untreated control group and information regarding alcohol use during the study limits any meaningful interpretation of these apparent biochemical improvements [66].

Viral load

Silymarin has not been reported to have any effect on viral load in hepatitis [24,67].

Table 2 Liver enzymes in patients with chronic liver disease including hepatitis C before and after treatment with silymarin or placebo

Study	ALT (U/L)	AST (U/L)	GGT (U/L)	Bilirubin (μmol/L)
Buzzelli [63]				
Silymarin baseline	145 ± 22	107 ± 21	64 ± 12	17.1 ± 3.4
After silymarin	120 ± 20	88 ± 18*	71 ± 13	15.4 ± 3.4
Placebo baseline	108 ± 13	79 ± 8	58 ± 13	17.1 ± 3.4
After placebo	122 ± 20	80 ± 14	57 ± 12	13.7 ± 1.7
Buzzelli [8]				
Silymarin baseline	115.9 ± 12.9	88 ± 13.3	51.4 ± 9.3	13.0 ± 1.4
After silymarin	82.5 ± 10.6*,†	69.5 ± 7.5*,†	41.3 ± 4.2*,†	9.1 ± 0.7*
Placebo baseline	97.9 ± 12.8	93.3 ± 13.5	64.9 ± 8.6	15.4 ± 1.9
After placebo	90.5 ± 11.1	90.5 ± 13.7	59.7 ± 7.6*	12.8 ± 2.2
Par [66]				
Silymarin baseline	96.7 ± 23.3	128.5 ± 28		38.3 ± 11.5
After silymarin	49.8 ± 11*	66.1 ± 12.4*		23.8 ± 6.2*
Pares [53]				
Silymarin baseline	50 ± 41	68 ± 47	168 ± 153	39.3 ± 34.2
After silymarin	50 ± 37	58 ± 37	137 ± 150	34.2 ± 44.5
Placebo baseline	52 ± 45	71 ± 53	183 ± 203	44.5 ± 39.3
After placebo	41 ± 34	50 ± 34	99 ± 106	44.5 ± 95.8
Vailati [65]				
Silymarin 360 mg daily baseline	101.8 ± 4.6	98.1 ± 6.3	138.4 ± 18.7	23.6 ± 1.5
After silymarin 360 mg daily	53.3 ± 6.1*	39.3 ± 5.0*	88.1 ± 7.6*	20.2 ± 1.4*

*Statistically significant difference compared with baseline.
†Statistically significant difference compared with placebo.

A case series of three patients with chronic hepatitis C and cirrhosis given a variety of supplements (including silymarin) and put on a diet and exercise programme, did find improvement in liver enzyme levels and viral loads. However, in the absence of a control group, no conclusion can be drawn regarding the efficacy of silymarin in reducing HCV viral load [68]. Surprisingly, this case series is often cited in the lay literature as proof of its efficacy.

Histology

In two double-blind studies of patients with chronic, presumably viral, hepatitis with or without cirrhosis which excluded those who consumed >80 g/day alcohol, no difference was found in liver enzyme levels between the silymarin and control groups. However, some histological improvement was noted in the silymarin group compared with placebo [12,20]. It should be noted that treatment lasted 3–12 months, and 24 of the 60 patients enrolled were lost to follow-up, and the final histological analysis only involved 19 patients from the silymarin group and 17 from the placebo group [12,20]. In the second study, three of six patients randomized to silymarin, *vs* none of the placebo controls, were HBsAg-positive. No study involving patients with serologically proven hepatitis C examined histological outcomes.

Mortality

In an RCT of 200 patients with histologically-proven, alcoholic cirrhosis, 103 patients were given silymarin 450 mg daily and 97 patients were randomized to placebo for a 2-year period. Abstinence from alcohol during the trial was achieved by 54 patients in the silymarin group and 59 controls. A concern is the large number of withdrawals from the study – only 125 of 200 patients completed the trial, 57 in the silymarin group and 68 controls. Analysis of survival data was reported on an intention to treat basis. Sera were stored for 75 of these patients, and analysis after trial completion revealed antibodies to HCV in 29 (13 in the silymarin group and 16 controls). None of the 13 anti-HCV positive patients receiving silymarin died during the trial, compared with four of 16 in the placebo group ($P = 0.059$). Of the 29 deaths during the trial, 22 were attributed to end-stage liver disease, nine of whom were receiving silymarin and 13 on placebo. There was also a trend towards a lower prevalence of encephalopathy and upper gastrointestinal bleeding in patients receiving

silymarin. The biochemical markers studied were not reported according to HCV status [53].

DISCUSSION

Studies of the effects of silymarin in patients with hepatitis B or C are limited by the small number of participants, the lack of double-blinding or placebo controls, the grouping of hepatitis of various aetiologies under one category (e.g. as chronic, nonalcoholic hepatitis), the confounding effect of alcohol, and the use of multiple interventions carried out at once, with no possibility of distinguishing their respective effects. The biochemical markers and other outcomes studied were often not reported according to HCV status. The different dosage regimens, treatment durations, and endpoints used also make drawing meaningful comparisons between studies difficult. Furthermore, it is not known how surrogate outcomes, such as biochemical response, can be translated into patient-relevant outcomes including progression to end-stage liver disease and mortality [7]. This warrants further investigation.

Silymarin treatment resulted in a statistically significant decrease in transaminases in four studies compared with baseline and in one compared with placebo in patients with chronic viral hepatitis. It is not clear whether a reduction in transaminase levels (with or without normalization) has any clinical significance. However, in some long-term, uncontrolled follow-up studies it has been found that HCV patients with sustained biochemical but not virological response to interferon therapy had a significantly reduced incidence of cirrhosis and hepatocellular carcinoma compared with biochemical nonresponders [69,70], suggesting that patients may benefit from therapies that do not eliminate the virus. Thus a purely biochemical response may be beneficial.

It is worth bearing in mind that ribavirin, when used alone in patients with hepatitis C, has no effect on viraemia, while it does decrease ALT. However, when ribavirin is used in combination with interferon, the sustained virological response rate is increased over that achieved with interferon alone [71]. By analogy, if silymarin does indeed lower ALT levels and help achieve a biochemical response, it may also act synergistically with interferon to increase the rates of sustained virological response, but this hypothesis has yet to be clinically investigated.

A multi-centre study is underway in Germany, in which 840 mg/day silymarin is given to patients with chronic hepatitis C resistant to interferon and ribavirin combination therapy. The study is scheduled to last 2 years, and has fibrosis progression as the primary endpoint. The authors did not state if the study is randomized or placebo-controlled [72]. The National Centre for Complementary and Alternative Medicine (NCCAM) also lists two phase II trials that are currently investigating silymarin treatment in hepatitis C [73,74].

To date, no studies have examined the effect of combining silymarin with interferon or ribavirin therapy in patients with hepatitis C, and only a few studies have been conducted on the effects of silymarin alone in hepatitis B or C. Until RCTs of adequate size and duration are performed with a patient population with serologically proven hepatitis B or C, excluding other causes of liver disease such as alcohol, no definitive conclusion can be drawn. Future studies should also have clearly defined primary endpoints, utilize intention-to-treat analysis, and report reasons for withdrawal. Given the prevalence of patients who take milk thistle as complementary or alternative therapy, it would be important to determine if there are any interactions or possible synergistic effects with the standard treatment so both physicians and patients can make more evidence-based treatment decisions.

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Note added in proof: Since this paper was submitted, a large prospective Egyptian study has reported that silymarin for 12 months does not affect HCV viremia, ALT levels or serum and ultrasound indices of hepatic fibrosis (Tanamly *et al.,* Dig Liver Dis 2004; 36 (11): 752–759).

REFERENCES

1 Conjeevaram HS, Lok AS. Management of chronic hepatitis B. *J Hepatol* 2003; 38(Suppl. 1): S90–103.
2 Karayiannis P. Hepatitis B virus: old, new and future approaches to antiviral treatment. *J Antimicrob Chemother* 2003; 51(4): 761–785.
3 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358(9286): 958–965.
4 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347(13): 975–982.
5 Hadziyannis SJ Jr, Sette H, Morgan TR *et al.* PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140(5): 346–355.
6 DerMarderosian A. (ed.) Milk Thistle. Review of Natural Products. Fact and Comparisons. St Louis, MO: Facts and Comparisons Publishers, 2003.
7 Liu JP, Manheimer E, Tsutani K, Gluud C. Medicinal herbs for hepatitis C virus infection (Cochrane Review). *Am J Gastroenterol* 2003; 98(3): 538–544.
8 Buzzelli G, Moscarella S, Giusti A, Duchini A, Marena C, Lampertico M. A pilot study on the liver protective effect of silybin-phosphatidylcholine complex (IdB1016) in chronic active hepatitis. *Int J Clin Pharmacol Ther Toxicol* 1993; 31(9): 456–460.

9 Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases. Cochrane Hepato-Biliary Group. *Cochrane Database of Systematic Reviews* 2005; (2): CD003620.

10 Mulrow C, Lawrence VA, Jacobs BP *et al.* Milk Thistle: zEffects on Liver Disease and Cirrhosis and Clinical Adverse Effects. Evidence Report/Technology Assessment No. 21. AHRQ Publication No. 01-E025. Rockville, MD: Agency for Healthcare Research and Quality, 2000.

11 Magliulo E, Gagliardi B, Fiori GP. Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centres. *Med Klin* 1978; 73(28–29): 1060–1065.

12 Kiesewetter E, Leodolter I, Thaler H. Results of two double-blind studies on the effect of silymarine in chronic hepatitis. *Leber Magen Darm* 1977; 7(5): 318–323.

13 Jacobs BP, Dennehy C, Ramirez G, Sapp J, Lawrence VA. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med* 2002; 113(6): 506–515.

14 Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs* 2001; 61(14): 2035–2063.

15 Bode JC, Schmidt U, Durr HK. Silymarin for the treatment of acute viral hepatitis? Report of a controlled trial. *Med Klin* 1977; 72(12): 513–518.

16 Lirussi F, Okolicsanyi L. Cytoprotection in the nineties: experience with ursodeoxycholic acid and silymarin in chronic liver disease. *Acta Physiol Hung* 1992; 80(1–4): 363–367.

17 Thompson Coon J, Ernst E. Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review. *J Hepatol* 2003; 40(2004): 491–500.

18 Eisenberg DM, Davis RB, Ettner SL *et al.* Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998; 280(18): 1569–1575.

19 Verhoef MJ, Sutherland LR, Brkich L. Use of alternative medicine by patients attending a gastroenterology clinic. *CMAJ* 1990; 142(2): 121–125.

20 Flora K, Hahn M, Rosen H, Benner K. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol* 1998; 93(2): 139–143.

21 Bass NM. Is there any use for nontraditional or alternative therapies in patients with chronic liver disease? *Current Gastroenterology Reports* 1999; 1(1): 50–56.

22 Blumenthal M. (Sr. Ed.) Herbal Medicine: Expanded Commission E monographs, 1st edn. Newton, MA: Integrative Medicine Communications, 2000: 257–263.

23 Ding T, Tian S, Zhang Z *et al.* Determination of active component in silymarin by RP-LC and LC/MS. *J Pharm Biomed Anal* 2001; 26(1): 155–161.

24 Chavez ML. Treatment of hepatitis C with milk thistle? *J Herb Pharmacother* 2001; 1(3): 79–90.

25 Wellington K, Jarvis B. Silymarin: a review of its clinical properties in the management of hepatic disorders. *Biodrugs* 2001; 15(7): 465–489.

26 Leng-Peschlow E. Properties and medical use of flavonolignans (Silymarin) from *Silybum marianum*. *Phytother Res* 1996; 10(Suppl. 1): S25–S26.

27 Chiavari G, Galletti GC, Marotti M, Piccaglia R. Silymarin content of different *Silybum marianum* L. Gaertn. cultivars. *Herba Hungarica* 1991; 30(1–2): 23–34.

28 Hammouda FM, Ismail SI, Hassan NM, Zaki AK, Kamel A, Rimpler H. Evaluation of the silymarin content in *Silybum marianum* (L.) Gaertn. cultivated under different agricultural conditions. *Phytother Res* 1993; 7(1): 90–91.

29 Lorenz D, Lucker PW, Mennicke WH, Wetzelsberger N. Pharmacokinetic studies with silymarin in human serum and bile. *Methods Find Exp Clin Pharmacol* 1984; 6(10): 655–661.

30 Barzaghi N, Crema F, Gatti G, Pifferi G, Perucca E. Pharmacokinetic studies on IdB 1016, a silybin- phosphatidylcholine complex, in healthy human subjects. *Eur J Drug Metab Pharmacokinet* 1990; 15(4): 333–338.

31 Morazzoni P, Montalbetti A, Malandrino S, Pifferi G. Comparative pharmacokinetics of silipide and silymarin in rats. *Eur J Drug Metab Pharmacokinet* 1993; 18(3): 289–297.

32 Feher J, Lang I, Nekam K, Muzes G, Deak G. Effect of free radical scavengers on superoxide dismutase (SOD) enzyme in patients with alcoholic cirrhosis. *Acta Medica Hungarica* 1988; 45(3–4): 265–276.

33 Varga Z, Czompa A, Kakuk G, Antus S. Inhibition of the superoxide anion release and hydrogen peroxide formation in PMNLs by flavonolignans. *Phytother Res* 2001; 15(7): 608–612.

34 Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. *Hepatology* 1996; 23(4): 749–754.

35 Masini A, Ceccarelli D, Giovannini F, Montosi G, Garuti C, Pietrangelo A. Iron-induced oxidant stress leads to irreversible mitochondrial dysfunctions and fibrosis in the liver of chronic iron-dosed gerbils. The effect of silybin. *J Bioenerg Biomembr* 2000; 32(2): 175–182.

36 Neuman MG, Cameron RG, Haber JA, Katz GG, Malkiewicz IM, Shear NH. Inducers of cytochrome P450 2E1 enhance methotrexate-induced hepatocytoxicity. *Clin Biochem* 1999; 32(7): 519–536.

37 Miguez MP, Anundi I, Sainz-Pardo LA, Lindros KO. Hepatoprotective mechanism of silymarin: no evidence for involvement of cytochrome P450 2E1. *Chem Biol Interact* 1994; 91(1): 51–63.

38 Beckmann-Knopp S, Rietbrock S, Weyhenmeyer R *et al.* Inhibitory effects of silibinin on cytochrome P-450 enzymes in human liver microsomes. *Pharmacol Toxicol* 2000; 86(6): 250–256.

39 Wilasrusmee C, Kittur S, Shah G *et al.* Immunostimulatory effect of *Silybum marianum* (milk thistle) extract. *Med Sci Monit* 2002; 8(11): BR439–43.

40 Kang JS, Jeon YJ, Kim HM, Han SH, Yang KH. Inhibition of inducible nitric-oxide synthase expression by silymarin in lipopolysaccharide-stimulated macrophages. *J Pharmacol Exp Ther* 2002; 302(1): 138–144.

41 Singh RP, Sharma G, Dhanalakshmi S, Agarwal C, Agarwal R. Suppression of advanced human prostate tumor growth in athymic mice by silibinin feeding is associated with reduced cell proliferation, increased apoptosis, and inhibition of angiogenesis. *Cancer Epidemiol Biomarkers Prev* 2003; 12(9): 933–939.

42 Singh RP, Agarwal R. Flavonoid antioxidant silymarin and skin cancer. *Antioxid Redox Signal* 2002; 4(4): 655–663.
43 Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM *et al.* Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002; 122: 366–375.
44 Jain SK, Pemberton PW, Smith A *et al.* Oxidative stress in chronic hepatitis C: not just a feature of late stage disease. *J Hepatol* 2002; 36(6): 805–811.
45 von Herbay A, Stahl W, Niederau C, Sies H. Vitamin E improves the aminotransferase status of patients suffering from viral hepatitis C: a randomized, double-blind, placebo-controlled study. *Free Radic Res* 1997; 27(6): 599–605.
46 Li D, Friedman SL. Liver fibrogenesis and the role of hepatic stellate cells: new insights and prospects for therapy. *J Gastroenterol Hepatol* 1999; 14(7): 618–633.
47 Wu J, Zern MA. Hepatic stellate cells: a target for the treatment of liver fibrosis. *J Gastroenterol* 2000; 35(9): 665–672.
48 Mehrotra R, Rawat S, Kulshreshtha DK, Patnaik GK, Dhawan BN. In vitro studies on the effect of certain natural products against hepatitis B virus. *Indian J Med Res* 1990; 92: 133–138.
49 Jia JD, Bauer M, Cho JJ *et al.* Antifibrotic effect of silymarin in rat secondary biliary fibrosis is mediated by downregulation of procollagen alpha1(I) and TIMP-1. *J Hepatol* 2001; 35(3): 392–398.
50 Lieber CS, Leo MA, Cao Q, Ren C, DeCarli LM. Silymarin retards the progression of alcohol-induced hepatic fibrosis in baboons. *J Clin Gastroenterol* 2003; 37(4): 336–339.
51 Adverse Drug Reactions Advisory Committee. An adverse reaction to the herbal medication milk thistle (*Silybum marianum*). *Med J Aust* 1999; 170(5): 218–219.
52 Geier J, Fuchs Th, Wahl R. Anaphylactic shock due to an extract of *Silybum marianum* in a patient with immediate-type allergy to Kiwi fruit. *Allergologie* 1990; 13(10): 387–388.
53 Pares A, Planas R, Torres M *et al.* Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol* 1998; 28(4): 615–621.
54 Venkataramanan R, Ramachandran V, Komoroski BJ, Zhang S, Schiff PL, Strom SC. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. *Drug Metab Dispos* 2000; 28(11): 1270–1273.
55 Mourelle M, Muriel P, Favari L, Franco T. Prevention of CCL4-induced liver cirrhosis by silymarin. *Fundam Clin Pharmacol* 1989; 3(3): 183–191.
56 Szilard S, Szentgyorgyi D, Demeter I. Protective effect of Legalon in workers exposed to organic solvents. *Acta Medica Hungarica* 1988; 45(2): 249–256.
57 Ferenci P, Dragosics B, Dittrich H *et al.* Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 1989; 9(1): 105–113.
58 Feher J, Deak G, Muzes G *et al.* Liver-protective action of silymarin therapy in chronic alcoholic liver diseases. *Orv Hetil* 1989; 130(51): 2723–2727.
59 Lucena MI, Andrade RJ, de la Cruz JP, Rodriguez-Mendizabal M, Blanco E, Sanchez de la Cuesta F. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. *Int J Clin Pharmacol Therapeut* 2002; 40(1): 2–8.
60 Ferenci P, Dragosics B, Frank H, Benda L, Dittrich H, Meryn S. Controlled prospective study on the effects of silymarin-treatment on patients with cirrhosis of the liver. *J Hepatol* 1985; 1(Suppl. 2): X229.
61 Ferenci P, Dragosics B, Csomos G, Schneider B. Treatment with silymarin in patients with cirrhosis of the liver – results of a controlled prospective study and of the post study surveillance. *Hepatology* 1986; 6(4): 790.
62 Flisiak R, Prokopowicz D. Effect of misoprostol on the course of viral hepatitis B. *Hepatogastroenterology* 1997; 44(17): 1419–1425.
63 Buzzelli G, Moscarella S, Barbagli S, Marena C, Gentilini P. Therapeutic effect of silipide in patients with chronic hepatitis C non-responders (NTs) to interferon (IFN) treatment. *J Hepatol* 1994; 21(Suppl. 1): S100.
64 Chen W, Liu J, Gluud C. Bile acids for viral hepatitis. Cochrane Hepato-Biliary Group. *Cochrane Database Systemat Rev* 2003; (2): CD003181.
65 Vailati A, Aristia L, Sozze E *et al.* Randomized open study of the dose–effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. *Fitoterapia* 1993; 64(3): 219–228.
66 Par A, Roth E, Rumi G Jr, Kovacs Z, Nemes J, Mozsik G. Oxidative stress and antioxidant defense in alcoholic liver disease and chronic hepatitis C. *Orv Hetil* 2000; 141(30): 1655–1659.
67 Seeff LB, Lindsay KL, Bacon BR, Kresina TF, Hoofnagle JH. Complementary and alternative medicine in chronic liver disease. *Hepatology* 2001; 34(3): 595–603.
68 Berkson BM. A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories. *Med Klin* 1999; 94(Suppl. 3): 84–89.
69 Shindo M, Hamada K, Oda Y, Okuno T. Long-term follow-up study of sustained biochemical responders with interferon therapy. *Hepatology* 2001; 33(5): 1299–1302.
70 Blendis L, Oren R, Halpern Z. Interferon treatment of HCV: do we need a virological response? *Gastroenterology* 2002; 122: 237–238.
71 Poynard T, Marcellin P, Lee SS *et al.* Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998; 352(9138): 1426–1432.
72 Schuppan D, Hahn EG. Clinical studies with silymarin: fibrosis progression is the end point. *Hepatology* 2001; 33(2): 483–484.
73 NCCAM. Evaluating Silymarin for Chronic Hepatitis C. http://www.clinicaltrials.gov/show/NCT00030030. Site last accessed 22-04-2005
74 NCCAM. IdB 1016 Treatment for Hepatitis C Disease. http://www.clinicaltrials.gov/show/NCT00055445. Site last accessed 22-04-2005