Review of Clinical Trials Evaluating Safety and Efficacy of Milk Thistle (Silybum marianum [L.] Gaertn.)

Carmen Tamayo, MD, and Suzanne Diamond, MSc

Milk thistle extracts have been used as traditional herbal remedies for almost 2000 years. The extracts are still widely used to protect the liver against toxins and to control chronic liver diseases. Recent experimental and clinical studies suggest that milk thistle extracts also have anticancer, antidiabetic, and cardioprotective effects. This article reviews clinical trials of milk thistle conducted in the past 5 years including pharmacokinetic and toxicity studies, herb-drug interactions, and other safety issues. Several trials have studied the effects of milk thistle for patients with liver diseases, cancer, hepatitis C, HIV, diabetes, and hypercholesterolemia. Promising results have been reported in the protective effect of milk thistle in certain types of cancer, and ongoing trials will provide more evidence about this effect. In addition, new established doses and improvement on the quality and standardization of this herb will provide the much-awaited evidence about the efficacy of milk thistle in the treatment of liver diseases. Milk thistle extracts are known to be safe and well tolerated, and toxic or adverse effects observed in the reviewed clinical trials seem to be minimal. The future of milk thistle research is promising, and high-quality randomized clinical trials on milk thistle versus placebo may be needed to further demonstrate the safety and efficacy of this herb.

Keywords: milk thistle; silymarin; clinical trials; randomized controlled trials; drug interactions; pharmacokinetics; cancer; liver disease

A number of clinical trials of milk thistle (Silybum marianum [L.] Gaertn. [Asteraceae]) and some of its components (flavonolignans) have been published in the past 15 years. The available evidence suggests that milk thistle (MT) extracts have an important hepatoprotective as well as anticancer, antidiabetic, and cardioprotective effect. However, high-quality clinical studies are limited, and very few have rigorously evaluated the purported anticancer and other pharmacological activities of this interesting herb. The number is even smaller for pediatric trials and trials evaluating the safety of MT.

The most recent meta-analysis published by the Cochrane Collaboration concludes that MT does not seem to significantly influence the course of the disease in patients with alcoholic or hepatitis B or C liver diseases. However, all-cause mortality was reduced by 50% in patients with alcoholic liver disease without hepatitis C virus (HCV) antibodies who took MT extracts compared to placebo (P < .05). The quality of these trials was low, and it is difficult to say if the lack of information about MT efficacy reflects poor scientific quality of study methods, poor reporting quality, or both.

Despite negative reports, MT seems to have some effect in chronic liver diseases, particularly alcohol-related liver disease, toxin-induced liver disease, and viral liver disease. The beneficial effect of MT in drug interactions is also noteworthy. The whole herb and its constituents may prevent nephrotoxicity associated with the use of acetaminophen, cisplatin, vincristine, and cyclosporine, as well as radiotherapy. Nevertheless, researchers suggest that careful administration of silybin with drugs primarily cleared by CYP450 3A4 or 2C9 would be advisable.

Recent clinical studies have addressed the effect of MT in the pharmacokinetics of other drugs such as digoxin, indinavir, rifampin, and erythromycin, suggesting in general a lack of associated toxicity or interference in the metabolism of these commonly used conventional drugs. Several trials have reported the antioxidant effect of MT in preventing liver damage due to exogenous exposure to alcohol, drugs, occupational toxins, and toxic mushrooms.

A randomized double-blind study on medical treatments for cirrhosis of the liver found a significantly higher survival rate among those suffering from alcoholic cirrhosis in the group treated with MT silymarin...
The authors attributed the results to the protective influence of this herb against toxic alcohol injuries.

One prospective clinical study on the protective effect of Legalon MT extract (Madaus, Cologne, Germany) in workers exposed to organic solvents documented a significant improvement in liver function test for those taking Legalon compared with those receiving no treatment.\(^{21}\)

Administration of silybin within approximately 48 hours after poisoning produced by the mushroom *Amanita phalloides* (death cap) seems to be an effective measure to prevent severe liver damage.\(^{22}\) Combination of standard therapy along with silybin produced a rapid resolution of clinical symptoms.\(^{23}\) A retrospective analysis of 205 cases of clinical poisoning during 1971 to 1989 found positive results for MT's silybin extract in increasing survival rates for adults and children exposed to this potentially lethal mushroom.\(^{27}\) In January 2007, 6 family members in California suffering from amatoxin poisoning, caused by *Amanita phalloides* mushrooms were treated with intravenous MT. The drug Legalon SI® was provided by Madaus Pharma (Brussels, Belgium; division of Madaus AG, Cologne, Germany). The FDA granted permission to use MT after considering that all patients were going to die of liver failure. Only 1 of the 6 patients died, and all of the rest have had a full recovery after treatment (http://www.herbalgram.org/80/default.asp?i=8284ThistleMushroom).

A recent case report mentions that MT may offer protection from liver toxicity caused by the pharmaceutical drug phenytoin.\(^{28}\) Clinical trials of the use of MT in diabetic patients, patients undergoing peritoneal dialysis, and patients with hypercholesterolemia are becoming more common.\(^{30}\) Promising results also have been reported in the preventive effect of MT in cancer of the skin,\(^{31}\) colorectal cancer,\(^{32}\) and other cancers.\(^{33}\) Preclinical data suggest that the antioxidant and antidiabetic effect is quite strong, but at this time, no definitive results confirm these effects, and more research has been recommended.\(^{34-36}\)

Several MT clinical trials are ongoing at this time. A large collaborative study is currently under way for treatment of hepatitis C. This study is funded by the National Center for Complementary and Alternative Medicine, the National Institute of Allergy and Infectious Diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases.\(^{37}\) Research updates are available online at www.nci.c.gov.

One study was recently completed, and another study is planned to evaluate the effects of MT to normalize and preserve liver function in pediatric patients with acute lymphocytic leukemia (Elena Ladas, personal communication, November, 2006).\(^{38}\) The anticancer preventive and therapeutic efficacy of silibinin is also being evaluated in a phase I clinical trial in prostate cancer patients.\(^{39}\)

In addition, manufacturing companies of MT extracts are also conducting clinical trials with their own products that will elucidate effects of specific preparations. These studies will increase both the quality and amount of efficacy and safety data about this herb.

Clinical studies of MT extracts generally have suffered from the same shortcomings found in many other trials of herbal medicines such as small sample size, lack of appropriate randomization, allocation concealment or blinding, very different periods of treatment, lack of information about type and dose of extract used as well as product characterization, ill-defined patient population, and a lack of etiology, severity of disease, and discussion of potential confounders. Both methodological quality and reporting of MT are improving and will continue to improve if researchers in academia and industry follow available guidelines and regulatory requirements for properly conducting and reporting clinical trials. Recently an academic group led by researchers at the University of Toronto published guidelines to report results of randomized control trials (RCTs) of herbal medicines, adding to the already accepted Consolidated Standards of Reporting Trials (CONSORT) statement.\(^{40-41}\) There are also a number of regulatory guidelines available from different countries that will aid in the development of high-quality clinical trials using both a well-characterized, well-defined product and good clinical practices (see regulatory guidance references in appendix).

**Major Findings From Current Clinical Trials**

It is beyond the scope of this article to address MT efficacy in detail, particularly due to the variability of extracts and compounds tested in clinical trials as well as the availability of several reviews and meta-analyses of trials published in the past few years. This section addresses mainly clinical trials conducted in the past 5 years.

Detailed trial information and general conclusions are available in evidence-based reports, monographs, and several meta-analyses that have been published and are available from the Internet (Cochrane Collaboration, Natural Standard Database, American Herbal Pharmacopoeia, American Botanical Council, and others). A comprehensive list of clinical trials available up to 2003 is available in the HerbMed database (www.herbmed.org). Studies addressing the anticancer activity of MT, including cytotoxic and preventive effects, control of side effects of conventional...
treatments, and enhancing the efficacy of chemotherapeutic agents, have been reviewed elsewhere.\textsuperscript{62}

It is important to emphasize that RCTs are still the gold standard to evaluate both efficacy and safety of medical interventions. However, in general, RCTs are not designed or powered to pick up adverse events, nor are they long enough to detect long-term adverse effects. This is particularly true when adverse events are rare or uncommon. Therefore, information about the safety of MT reported here is limited to the authors' observations in available clinical trials.

A summary of general findings is provided below, and detailed trial information is available in Tables 1 to 3. For the clinical trials evaluated in this review, an attempt was made to determine compliance with the CONSORT statement as well as an evaluation of the quality of the trials using the Jadad Scale.\textsuperscript{63} However, this was not possible because not all new trials are phase III (RCT) trials.

**Phase III: Dose Finding, Pharmacodynamic, and Pharmacokinetic Studies**

Several doses of MT (silymarin) have been tested both alone and in conjunction with other drugs in several populations. Up to 13 g, divided in 3 daily doses of silybin phytosome (Siliphos\textsuperscript{8}), was evaluated in prostate cancer patients and was determined as the recommended dose to further evaluate anticancer effects of silybin.\textsuperscript{64} Dosages of 360, 720, or 1440 mg of silybin daily for 7 days achieved high silybin levels in the colorectal mucosa of 24 colorectal cancer patients after consumption of phosphatidylcholine (Silipide\textsuperscript{8}). This finding may support further exploration of silybin as a potential preventive agent for colorectal cancer.\textsuperscript{52}

Flavonoids from MT (i.e., silybinin, Legalon) seem to normalize immunoregulatory defects via restoration of the cellular thiol status. T-cell activation (CD69), along with a significant decrease in TNFα release ($P < .05$), was observed in 30 patients with end-stage diabetic nephropathy.\textsuperscript{65}

A bioavailability study of 3 silybin-containing products (Liverman capsule, Legalon capsule, and silymarin tablet) suggested that Liverman capsules are better absorbed and have a greater bioavailability.\textsuperscript{46}

**Phase III: Herb-Drug Interaction Studies**

Milk thistle does not seem to alter the disposition of anticancer drugs metabolized by the CYP3A4 and UGT1A1 enzymes,\textsuperscript{67} and it does not affect indinavir levels in healthy individuals\textsuperscript{12,13} or in patients with HIV.\textsuperscript{16} Milk thistle does not have clinically relevant effects on CYP3A activity\textsuperscript{19} or CYP1A2, CYP2D6, and CYP2E1 activity\textsuperscript{8} and does not interfere with P-glycoprotein (P-gp) modulation.\textsuperscript{15}

In testing the effect of silybinon on chemotherapy agents in vitro, silybinin at low doses (10 μM) caused no negative interactions with vincristine or Lasparaginase on a T cell acute lymphoblastic leukemia cell line. At higher concentrations (30 μM), silybinin was synergistic with vincristine and not with Lasparaginase.\textsuperscript{40}

**Phase III (Randomized Double-Blind Clinical Trials)**

In a phase III RCT in cancer, a dietary supplement, containing silymarin, soy, lycopene, and antioxidants as the main ingredients, was shown to delay prostate-specific antigen progression significantly ($P < .05$) after prostatectomy and radiotherapy in prostate cancer patients.\textsuperscript{59}

In chronic hepatitis C virus (HCV) (Table 3), 375.5 mg of MT was safe and well tolerated for up to 1 year.\textsuperscript{51} In a follow-up study, 420 mg daily did not prevent complications of HCV but improved general health and symptoms for up to 2 years.\textsuperscript{85} Higher doses of 600 and 1200 mg/d were tolerated but had no significant effect on serum HCV ribonucleic acid titer ($P = .52$) and serum alanine aminotransferase (ALT) and other liver chemistries ($P = .28$) and did not improve quality of life or psychological well-being.\textsuperscript{59} A small beneficial, but not significant, effect of MT was observed in patients with chronic hepatitis C on sustained biochemical response and virologic response. However, the clinical effect of interferon therapy was 10-fold greater than MT.\textsuperscript{54} In another study, MT had an effect on liver chemistries but no apparent effect on viral load, suggesting that S. marisannus may have a protective effect in the inflammatory response to HCV but no role as an antiviral agent.\textsuperscript{66} An open-label study of 50 patients testing MT and other antioxidants suggested that the combination may have a beneficial effect on necroinflammatory variables.\textsuperscript{52}

In hepatic cirrhosis, silymarin MZ-80 (S) did not produce any changes in routine liver test results, but it had an antiperioxidative effect in peripheral blood cells.\textsuperscript{67} In patients with alcoholic liver disease and concomitant noninsulin-dependent diabetes mellitus, silybinβ-cyclodextrin 135 mg daily did not change liver function test results or insulin secretion but significantly reduced fasting glucose ($P < .03$) and serum triglyceride levels ($P < .01$) compared to placebo. The effects seem to be through reduced glycosylated hemoglobin (HbA1c) levels and insulin sensitivity.\textsuperscript{58} In an RCT of 51 type II diabetic patients, 600 mg daily MT over 4 months improved the glycemic profile compared to placebo, confirming reductions in HbA1c, fasting glucose, and cholesterol and triglyceride levels.\textsuperscript{59}
Table 1. Pharmacokinetic Trials of Milk Thistle (MT) in Healthy Participants (past 5 years)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Objective/Design</th>
<th>MT Extract</th>
<th>Reference Group</th>
<th>Outcomes Parameters</th>
<th>Adverse Events</th>
<th>Results/Conclusions</th>
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<tr>
<td><strong>Pharmacokinetics of indinavir</strong></td>
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<tr>
<td>D'Onze et al (2003)</td>
<td>Sequential crossover trial to determine if silymarin alters PK of indinavir</td>
<td>MT seed extract</td>
<td>Same group: crossover; 4 days washout period</td>
<td>Indinavir 900 mg every 8 h</td>
<td>None reported</td>
<td>No effect on indinavir plasma concentrations. The geometric mean (95% confidence interval [CI]) steady-state indinavir area under the plasma concentration-time curve was 20.7 h·mg·L⁻¹ (15.9-26.2 h·mg·L⁻¹) when given without MT and 19.4 h·mg·L⁻¹ (15.8-29.6 h·mg·L⁻¹) with MT. The trough plasma concentration was 0.840 mg·L⁻¹ (0.292-0.437 mg·L⁻¹) alone and 0.232 mg·L⁻¹ (0.129-0.418 mg·L⁻¹) with MT.</td>
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<td>Healthy individuals (N = 10)</td>
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<td>Mills et al (2003)</td>
<td>Three-period, open-label, RCT to determine if MT affects PK of indinavir</td>
<td>MT silymarin extract (Kare and Hope Inc, Toronto, Canada)</td>
<td>Control - no extract</td>
<td>Indinavir 900 mg TID</td>
<td>None reported</td>
<td>No significant differences. Indinavir levels were not reduced with MT, and no inhibitory effect on CYP3A4 was observed. In MT group, mean AUC (0-3) of indinavir decreased 4.4% (90% CI, -27.5% to 28%, P = .75) from phase I to phase II and by 17.5% (90% CI, -37.6% to 3% ; P = .29) in phase III. Control group mean AUC (0-3) decreased by 21.5% (90% CI, -43% to -1%, P = .2) from phase I to phase II and by 39.5% (90% CI, -55.3% to -15%, P = .01) of baseline at phase III. MT did not alter significantly the overall exposure of indinavir (9% reduction in the indinavir AUCs after 3 weeks of MT). The least squares mean trough level (CE), however, was significantly decreased by 26%.</td>
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<td>Healthy HIV-negative males aged 18-35 years (N = 16)</td>
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<td>Rischel et al (2002)</td>
<td>Prospective open-label interaction study to characterize PK and determine effect of MT on indinavir</td>
<td>MT seed extract (confirmed to contain 153 mg silymarin) TID for 3 weeks</td>
<td>Multivitamin in &quot;placebo&quot; pill</td>
<td>Indinavir PK</td>
<td>None reported</td>
<td>MT in commonly administered dosages should not interfere with indinavir therapy in patients infected with HIV.</td>
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<td>Healthy volunteers (N = 10)</td>
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<td>Sample</td>
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| Gurley et al (2006)* | Randomized phase I trial to assess effects of MT and black cohosh on CYP3A activity, compared to rifampin (inducer) and clarithromycin (inhibitor) | MT seed extract [Enzymatic Therapy Inc, Green Bay, Wi] | Positive controls: black cohosh 80 mg, rifampin 600 mg, clarithromycin 1000 mg x 7 days | CYP3A activity, midazolam (MDZ) PK | No serious events MT: headache (n = 3) | No significant changes in the disposition of MDZ, a clinically recognized CYP3A substrate. MDZ PK was unaffected by MT or black cohosh, which pose no clinically significant risk for CYP3A-mediated drug-herb interactions. 
CYP3 activity was affected by rifampin and clarithromycin. |
| Healthy volunteers [N = 19], 9 women, 10 men | | 900 mg x 14 days | 30 days washout period | Midazolam before and after each period | | |
| Gurley et al (2004)* | Randomized phase I study to determine effect of long-term MT, *Citrus aurantium*, *Echinacea*, or saw palmetto on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity | MT extract (standard flavonolignans) | Probe drug cocktails of midazolam and caffeine, followed 24 h later by chloroquine and chlordecone before and after supplementation | CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity MDZ and caffeine PK | None observed | Pre-post supplementation phenotypic ratios suggest no effect of these supplements on CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity. MT poses a minimal risk for CYP-mediated herb-drug interactions in humans. 
Quantities of flavonolignans were consistent with label claims of MT. |
| Healthy volunteers [N = 12] | | 500 mg x 26 days | | | | |
| Gurley et al (2006)* | Randomized crossover design to assess drug interactions through P-glycoprotein | MT seed extract [Enzymatic Therapy Inc, Green Bay, Wi] Lot # 41678 | Black cohosh 40 mg x 14 days, rifampin 800 mg x 7 days, clarithromycin 1000 mg x 7 days | Serial serum concentration-time profiles of P-gp substrate, digoxin, and digoxin PK | None observed in MT group | No significant effects on digoxin PK following supplementation with either MT or black cohosh, although digoxin AUC (1-3) and AUC (0-24) approached significance (P = .08) following MT. 
Compared with rifampin and clarithromycin, these formulations of MT or black cohosh did not affect digoxin PK, suggesting these supplements are not potent modulators of P-gp in vivo and do not pose a significant interaction risk with digoxin. |
<p>| Healthy volunteers [N = 16], 8 females, mean age of 26 years | | 900 mg/d for 14 days, 30-day washout | | | | |</p>
<table>
<thead>
<tr>
<th>Bioavailability</th>
<th>Kim et al. (2003)</th>
<th>Phase 1 3 × 3 crossover design to compare bioavailability of silibinin from 3 products</th>
<th>MT extract standardized to silibinin content: Liverman (capsule), Legalon (capsule) and silymarin (tablet)</th>
<th>None (same group)</th>
<th>Plasma concentration of silibinin: AUC (0-12h), Cmax, Tmax</th>
<th>None reported</th>
<th>Oral bioavailability of silibinin after Liverman capsule was faster and greater than Legalon and silymarin: AUC (0-12h), Cmax, Tmax. Liverman: 15.1; Legalon: 6.00; silymarin: 4.63. T0.5: Liverman: 0.875; Legalon: 1.03; silymarin: 1.13.</th>
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## Table 2. Clinical Trials of Milk Thistle in Cancer (past 5 years)

<table>
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<tr>
<th>Phase</th>
<th>Sample</th>
<th>Objective/Design</th>
<th>MT Extract</th>
<th>Reference Group</th>
<th>Outcomes</th>
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<th>Results</th>
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<tr>
<td>Phase I</td>
<td>Flee et al (2007)</td>
<td>Prostate cancer</td>
<td>Dosage: 2.5-20 g daily x 4 weeks (3 divided doses)</td>
<td>Silybrox (Indena Corp, Seattle, Wash)</td>
<td>Before treatment</td>
<td>PSA, ALT, bilirubin levels, fever, neutropenia, thrombocytopenia</td>
<td>8 of 13 patients had grade 1-2 hyperbilirubinemia; 1 patient had grade 3 toxicity (ALT elevation)</td>
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<td></td>
<td>Ho et al (2000) &amp; 2002</td>
<td>Colorectal cancer</td>
<td>Dosage: 360, 720, and 1440 mg daily x 7 days</td>
<td>Silybrox (Indena Corp)</td>
<td>Following treatment group</td>
<td>Silybin levels: Plasma 4.0% silybin (60 mg) with 60% soy phosphatidylcholine</td>
<td>None</td>
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<tr>
<td>Phase II</td>
<td>van Erp et al (2005)</td>
<td>Cancer: colorectal, genitourinary</td>
<td>Effect on PK of irinotecan, a substrate for CYP3A4 and UGT1A1 proteins</td>
<td>Silybin MT seed extract (80% silymarin)</td>
<td>None</td>
<td>Irinotecan clearance</td>
<td>None</td>
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<tr>
<td>Phase III</td>
<td>Schroeder et al (2005)</td>
<td>Prostate cancer, raising PSA</td>
<td>Dosage: 160 mg x 10 weeks (plus other ingredients)</td>
<td>Silimar (160 mg) plus</td>
<td>Placebo</td>
<td>PSA slope and doubling time</td>
<td>None</td>
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<td>Sample</td>
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<tr>
<td><strong>Chronic hepatitis C</strong></td>
<td>RCT trial to prevent complications of HCV (12-month follow-up)</td>
<td>Legalan 1400(^{a}) silymarin capsules (Madaus, Cologne, Germany)</td>
<td>Low-dose (low antioxidant) multivitamin</td>
<td>Clinical outcomes: symptoms, well-being, QoL. Liver ultrasound. Serum HCV RNA. HCV Ab. HCV viremia. ALT, fibrosis markers.</td>
<td>Fatigue: 4.4 per person weeks in placebo vs 3.5 in silymarin group. DNVR rate in both groups. No one discontinued because of side effects.</td>
<td>All patients improved over time: no differences in symptoms or QoL between groups. No detectable HCV Ab in 1 patient in each group. Undetectable HCV RNA: 2 in silymarin and 3 in multivitamin group. No effect of silymarin on serum markers.</td>
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<td>Tanamty et al. (2004)(^{a})</td>
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<td>Verbal dose of silymarin: 375.3 mg (\times) 12 months (124.5 mg TID)</td>
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<td><strong>Egyptian patients with chronic HCV N = 177</strong></td>
<td>Safety and efficacy</td>
<td>Legalan 1400(^{a}) silymarin (Madaus)</td>
<td>Low-dose (low antioxidant) multivitamin</td>
<td>Clinical outcomes: symptoms, well-being, QoL. Liver ultrasound. Serum HCV RNA. HCV Ab. HCV viremia. ALT, fibrosis markers. QoL (SF-36) and psychological assessments.</td>
<td>Similar between groups and 2 different doses</td>
<td>At 24 months of therapy, 66/68 in silymarin group and 72/73 in vitamin group still had anti-HCV Ab. HCV RNA persisted in 64/68 in silymarin and 71/73 in vitamin group. Recommended dose is safe up to 2 years but no effect on outcomes.</td>
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<td>Strickland et al. (2005)(^{a})</td>
<td>RCT trial to prevent complications of HCV (24-month follow-up)</td>
<td>420 mg/d, 140 mg TID</td>
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<td><strong>Patients with chronic HCV in Australia N = 17</strong></td>
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<td>Gordon et al. (2006)(^{a})</td>
<td>Safety and efficacy</td>
<td>MT extract in tablet: 60% silymarin (MediHerb, Australia)</td>
<td>Placebo: identical matching tablet (MediHerb)</td>
<td>Biochemical, virological, and HCV RNA titer</td>
<td>Similar between groups and 2 different doses</td>
<td>No differences in SF-36 or RNA titers or ALT levels between groups. Well tolerated but no effect on outcomes in this sample.</td>
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<td>600 or 1200 mg/d (\times) 12 weeks</td>
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<td>El-Zayady et al. (2006)(^{a})</td>
<td>RCT: effect on necro-inflammatory response</td>
<td>MT: silymarin extract</td>
<td>Noninterferon-based therapy (NIF-NBT) with ribavirin (600-800 mg) plus amantadine (200 mg) and ursooxygenol acid (500 mg)</td>
<td>ALT levels. Virologic response (ETVR) Sustained biochemical response (SPR). Sustained virologic response (SVR).</td>
<td>None observed</td>
<td>NIF-NBT more effective than silymarin: 4-fold higher ETVR, 10-fold higher SER than silymarin. Greater normalization of ALT (58.5% vs 15.3%). Viral response 24% vs 0%. SBR 28% vs 2.8%. SVR 2.4% vs 0%.</td>
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<td>Patients in Egypt with detectable HCV-RNA and elevated ALT N = 170</td>
<td>Compare silymarin (n = 83) to standard therapy (n = 87)</td>
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<td>Follow-up at 48 weeks</td>
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<tbody>
<tr>
<td>Torres et al (2004)</td>
<td>Safety and efficacy</td>
<td>MT seed extract</td>
<td>No treatment control</td>
<td>Serum: viral load, liver enzymes (ALT/AST)</td>
<td>None in abstract</td>
<td>Silybum well tolerated. No effect on viral load. Decreased ALT and AST compared to control.</td>
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<td>Chronic HCV with no antiviral therapy, Puerto Rico N = 84</td>
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<td>160 mg, 3 times per week × 4 weeks</td>
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<td>No antiviral effects. Possible protective effect on inflammation.</td>
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<tr>
<td>Mehlum et al (2005)</td>
<td>Safety, effect, and tolerability of intravenous and oral antioxidants and vitamins</td>
<td>Silymarin capsules plus other antioxidants and vitamins</td>
<td>No control</td>
<td>Liver enzymes (ALT) HCV RNA levels Liver biopsy Histology SF-36 QoL</td>
<td>No major adverse reactions; well tolerated</td>
<td>Well tolerated. Favorable response in 46% of patients (n = 24). ALT normalized from pretreatment high in 44%, remained normal in 72.7%. Decreased viral load in 25%. Histologic improvement in 38.1%, SF-36 increased in 58%.</td>
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**Chronic alcoholic liver disease**

Lucena et al (2002) | Double-blind RCT to investigate antiperoxidative effects of silymarin MZ-80 | Silymarin MZ-80 (S) | Placebo | Erythrocyte total glutathione (GSH) Platelet malondialdehyde (MDA) Serum amino-terminal propeptide of procollagen type III (PiNP) | No clinically relevant side effects observed in either group | Well tolerated. Silymarin increased GSH and decreased lipid peroxidation. No changes in liver enzymes. Silymarin: GSH increased at 6 months (4.5 × 3.4 to 5.8 × 4.0 mmol/L) Hb vs placebo (4.1 × 3.9 to 4.4 × 4.1 mmol/L) Silymarin: PiNP decreased (1.82 × 1.03 to 1.36 × 0.5 U/mL) vs placebo (1.31 × 0.4 to 1.27 × 0.6 U/mL). Placebo: platelet-derived nondonor MDA decreased by 30%. | | |

| Patients with alcoholic liver cirrhosis (Spain) N = 60 | | 150 mg TID × 6 months | | | | | |

49 completed; silymarin = 24, placebo = 25 | | | | | | | |

Lirussi et al (2002) | Double-blind RCT to assess effects of silybin on rebalancing of cell redox levels, liver function, glucose, and lipid metabolism | Silybin-beta cyclodextrin (IBS) | Placebo (n = 21) | Fasting plasma glucose Glycosylated hemoglobin (HbA1c) Basal, stimulated C-peptide and insulin levels Total, HLD cholesterol Triglycerides, LFTs, insulin sensitivity (HOMA-IR) MDA | No clinically relevant side effects observed | Fasting glucose decreased 14.7% from baseline in silymarin group (148.4 mg/dL). Placebo unchanged. Triglycerides decreased 165 mg/dL to 111 mg/dL in silymarin group. MDA decreased in silymarin group. No change in insulin levels, total and HDL cholesterol, and LFTs in either group. Consistent with reduced lipid peroxidation and improved insulin activity. | | |

| Chronic alcoholic liver disease and type 2 diabetes mellitus (Italy) N = 60, 42 completed | | 135 mg silybin for 6 months | | | | | |

MT = milk thistle; RCT = randomized control trial; PK = pharmacokinetics; AUC = area under the curve.
effects. However, a strict dose-dependency curve has not yet been reported, and short-term trials of high silymarin intake have not been done in healthy populations.

The model commonly reflected in the safety data of clinical trials is the direct toxicity model, as opposed to a model of the potentiation of the toxicity of other drugs. It is not clear from the reviewed literature if this latter model has been evaluated in MT trials. Nevertheless, it seems clear that under the restricted conditions of available trials, MT appears to be quite safe.

The limitations of available clinical trials with regard to establishing safety are the same as they are with regard to establishing efficacy. Clinical trials testing safety very poorly predict the fate of extracts in real-world settings, where patients ingest multiple drugs and herbs, take different formulations of the same product, and add alcohol and other compounds, often for extremely extended periods.

For randomized trials reporting adverse effects, incidence was approximately equal in the MT and control groups. The majority of adverse events observed were unrelated to the product or difficult to separate from the concomitant disease, and causality is rarely addressed in available reports. There is no safety data in children or older adults, as there were no reported studies in children and very few studies that included patients older than 65 years.

Adverse effects associated with oral ingestion of MT include mainly gastrointestinal problems, but these are rare. Headache/dizziness and pruritus were reported in 1 trial. Asymptomatic liver toxicity has been observed in recent clinical trials done in cancer patients, where hyperbilirubinemia and increases in ALT have been observed, but only with very high dosages of silybin-phytoasome between 10 and 20 g daily. At high doses (>1.5 g/d), a laxative effect is possible due to increased bile secretion and flow. Mild allergic reactions have also been noted but were not serious. In an oral form standardized to contain 70% to 80% silymarin given at a dosage of 420 mg daily, MT appears to be safe for up to 41 months of use, and significant drug reactions have not been reported.

The Future of Milk Thistle Clinical Trials

The majority of researchers agree that more high-quality clinical trials are needed to evaluate the hepatoprotective effect of MT in the course of liver diseases and in the hepatotoxicity produced by certain medications. A National Institutes of Health consensus conference on the management of hepatitis C held in 2002 concluded, "There is a need to assess the effectiveness of supportive therapy to ameliorate the side effects of antiviral therapy." In addition, "Trials are needed in combination therapy non-responders and those who cannot tolerate conventional therapies, comparing combinations of antifibrotic and anti-inflammatory agents, as well as immunomodulatory drugs and drugs that are directed specifically at HCV replication. Studies are also needed to assess the efficacy of alternative and nontraditional medicines." Although not mentioned specifically, MT may be a good preventive and therapeutic intervention for hepatitis C and other liver diseases, including hepatobiliary obstruction and cholelithiasis, and should be further evaluated.

In addition, older trials reporting positive effects of MT in preventing liver damage due to exogenous exposures to alcohol, drugs, occupational toxins, and toxic mushrooms described above should be replicated with more appropriate designs.

Another evidence-based report prepared by the Agency for Healthcare Research and Quality evaluated the effects of MT on liver disease of alcohol, viral, toxin, cholestatic, and primary malignancy etiologies as well as clinical adverse effects associated with MT ingestion or contact. This report concludes that MT's efficacy is not well established. Survival and other clinical outcomes in RC13 have been inadequately evaluated or reported with mixed results. Future research should include definition of multifactorial mechanisms of action, well-designed clinical trials, and clarification of adverse effects. According to other authors, future clinical studies in chronic hepatitis C should focus on the role of S marianum in combination with other herbal therapies in improving appropriate and reliable clinical and laboratory parameters in this condition.

No studies have evaluated MT for cholestatic liver disease or primary hepatic malignancy (hepatocellular carcinoma, cholangiocarcinoma) or for combined use of MT with other hepatoprotective agents, although experimental studies on hepatocarcinoma cells (HCC) show promise in this area. There are limited clinical trials evaluating cholelithiasis or cholangitis. Further clinical research in this area is warranted based on recent findings showing that silymarin modulates bile flow and bile salt secretion, exerts beneficial changes in overall bile salt metabolism, and has novel anticholestatic properties in experimental models of hepatocellular cholestasis, including those induced by estrogens and monohydroxylation bile salts. Anticancer, antidiabetic activity, and the effects of MT phytoestrogens (flavonolignans) on estrogen metabolism, particularly on the occurrence of catechol-estradiol-thiones known to cause carcinogenic depurinating DNA adducts within cells, also deserve further investigation.
Appendix

Regulatory References
Australia, New Zealand Therapeutic Product Authority. Regulation of Herbal Substances: http://www.anztpa.org/anztpa/herbal.htm

Internet Databases
American Botanical Council: http://www.herbalgram.org
American Herbal Pharmacopoeia: http://www.herbal-sup.org
Cochrane Library: http://www.cochrane.org/reviews/clinintro.htm
Natural Standards Database: http://www.naturalstandards.com
Herb Med: http://www.herbmed.org/herbs/herb120.htm

References
Milk Thistle Clinical Trials


