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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.[1-9] 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[3] concludes that MT does not seem to significantly influence the course of the disease in patients with alcoholic and/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 ($P < .05$).[2,3] The quality of these trials was low,[8] 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.[2,3,8]

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.[10-14] Nevertheless, researchers suggest that careful administration of silybin with drugs primarily cleared by CYP450s 3A4 or 2C9 would be advisable.[12]

Recent clinical studies have addressed the effect of MT in the pharmacokinetics of other drugs such as digoxin,[15] indinavir,[16-18] rifampin, and erythromycin,[19] suggesting in general a lack of associated toxicity or interference in the metabolism of these commonly used conventional drugs. Several trials have reported the antitoxic effect of MT in preventing liver damage due to exogenous exposure to alcohol, drugs, occupational toxins, and toxic mushrooms.[20-23]

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

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extract.[24] 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.[22]

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.[25] Combination of standard therapy along with silibinin produced a rapid resolution of clinical symptoms.[26] A retrospective analysis of 205 cases of clinical poisoning during 1971 to 1980 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 Sil® 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? c= 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.[29] Promising results also have been reported in the preventive effect of MT in cancer of the skin,[30,31] colorectal cancer,[32] and other cancers.[33] Preclinical data suggest that the anticancer 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.nccam.nih.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.[42]

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.[43] However, this was not possible because not all new trials are phase III (RCT) trials.

Phase I/II: Dose Finding, Pharmacodynamic, and Pharmcokinetic 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 silibinin phytosome (Siliphos®), was evaluated in prostate cancer patients and was determined as the recommended dose to further evaluate anticancer effects of silibin.[44] Dosages of 360, 720, or 1440 mg of silibinin daily for 7 days achieved high silibinin levels in the colorectal mucosa of 24 colorectal cancer patients after consumption of phosphatidylcholine (Silipide®). This finding may support further exploration of silibinin as a potential preventive agent for colorectal cancer.[32]

Flavonoids from MT (ie, silibinin, Legalon) seem to normalize immunoregulatory defects via restoration of the cellular thiol status. T-cell activation (CD69), along with a significant decrease in TNF-α release ($P <$ .05), was observed in 30 patients with end-stage diabetic nephropathy.[45]

A bioavailability study of 3 silibinin-containing products (Liverman capsule, Legalon capsule, and silymarin tablet) suggested that Liverman capsules are better absorbed and have a greater bioavailability.[46]

Phase I/II: Herb-Drug Interaction Studies

Milk thistle does not seem to alter the disposition of anticancer drugs metabolized by the CYP3A4 and UGT1A1 enzymes,[47] and it does not affect indinavir levels in healthy individuals[17,18] or in patients with HIV.[16] Milk thistle does not have clinically relevant effects on CYP3A activity[19] or CYP1A2, CYP2D6, and CYP2E1 activity[48] and does not interfere with P-glycoprotein (P-gp) modulation.[15]

In testing the effect of silibinin on chemotherapy agents in vitro, silibinin at low doses (10 µM) caused no negative interactions with vincristine or L-asparaginase on a T cell acute lymphoblastic leukemia cell line. At higher concentrations (30 µM), silibinin was synergistic with vincristine and not with L-asparaginase.[49]

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 ($P <$ .030) after prostatectomy and radiotherapy in prostate cancer patients.[50]

In chronic hepatitis C virus (HCV) (Table 3), 373.5 mg of MT was safe and well tolerated for up to 1 year.[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.[52] Higher doses of 600 and 1200 mg/d were tolerated but had no significant effect on serum HCV ribonucleic acid titers ($P =$ .52) and serum alanine aminotransferase (ALT) and other liver chemistries ($P =$ .28) and did not improve quality of life or psychological well-being.[53] 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.[54] In another study, MT had an effect on liver chemistries but no apparent effect on viral load, suggesting that *S marianum* may have a protective effect in the inflammatory response to HCV but no role as an antiviral agent.[55] An open-label study of 50 patients testing MT and other antioxidants suggested that the combination may have a beneficial effect on necroinflammatory variables.[56]

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.[57] In patients with alcoholic liver disease and concomitant noninsulin-dependent diabetes mellitus, silybin-β-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.[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 HbA(1)c, fasting glucose, and cholesterol and triglyceride levels.[59]

Table 1. Pharmacokinetic Trials of Milk Thistle (MT) in Healthy Participants (past 5 years)

Sample	Objective/Design	MT Extract	Reference Group	Outcomes Parameters	Adverse Events	Results/Conclusions
Pharmacokinetics of indinavir						
DiCenzo et al (2003)[17] Healthy individuals (N = 10)	Sequential crossover trial to determine if silymarin alters PK of indinavir	MT seed extract 480 mg/d (160 mg TID) on days 3-15	Same group: crossover; 4 days washout period Indinavir 800 mg every 8 h: 4 doses on days 1, 2 and days 16, 17	Indinavir pharmacoki-netics	None reported	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 (15.3-28.2 h mg/L) when given without MT and 19.4 h × mg/L (15.8-23.6 h × mg/L) with MT. The trough plasma concentration was 0.340 mg/L (0.232-0.497 mg/L) alone and 0.232 mg/L (0.129-0.419 mg/L) with MT.
Mills et al (2005)[18] Healthy, HIV-negative males aged 18-35 years (N = 16)	Three-period open-label RCT to determine if MT affects PK of indinavir	MT silymarin extract (Kare and Hope Inc, Toronto, Canada) 1368 mg/d (456 mg TID) from day 2 to 30	Control - no extract Indinavir 800 mg TID Washout period of 7 days	Indinavir levels AUC (phase I)	None reported	No significant between-group differences. Indinavir levels were not reduced with MT, and no inhibitory effect on CYP3A4 was observed. In MT group, mean AUC (0-8) of indinavir decreased 4.4% (90% CI, −27.5% to −26%, *P* = .78) from phase I to phase II and by 17.3% (90% CI, −37.3% to +9%, *P* = .25) in phase III. Control group mean AUC (0-8) decreased by 21.5% (90% CI, −43% to +8%, *P* = .2) from phase I to phase II and by 38.5% (90% CI, −55.3% to −15.3%, *P* = .01) of baseline at phase III.
Piscitelli et al (2002)[16] Healthy volunteers (N = 10)	Prospective open-label interaction study to characterize PK and determine effect of MT on indinavir	MT seed extract: 175 mg (confirmed to contain 153 mg silymarin) TID for 3 weeks Indinavir 800 mg TID	Multivitamin in "placebo" pill	Indinavir PK	None reported	MT did not alter significantly the overall exposure of indinavir (9% reduction in the indinavir AUC8 after 3 weeks of MT). The least squares mean trough level (C8), however, was significantly decreased by 25%. MT in commonly administered dosages should not interfere with indinavir therapy in patients infected with HIV.

(*continued*)

Table 1. (continued)

Sample	Objective/Design	MT Extract	Reference Group	Outcomes Parameters	Adverse Events	Results/Conclusions
Drug/MT interaction						
Gurley et al (2006)[19] Healthy volunteers (N = 19), 9 women, 10 men	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, Wis) 900 mg × 14 days	Positive controls: black cohosh 80 mg, bifampin 600 mg, clarithromycin 1000 mg × 7 days; 30 days washout period; Midazolam before and after each period	CYP3A activity, midazolam (MDZ) PK	No serious events MT: headache (n = 3) Clarithromycin: nausea, indigestion, "metallic taste" Rifampin: mild indigestion, urine reddish discolor Black cohosh: "vivid dreams" (n = 1)	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 CYP3-mediated drug-herb interactions. CYP3 activity was affected by rifampin and clarithromycin.
Gurley et al (2004)[48] Healthy volunteers (N = 12)	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 flavolignans) 900 mg × 28 days	Probe drug cocktails of midazolam and caffeine, followed 24 h later by chlorzoxazone and debrisoquin (INN, debrisoquine) 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.
Gurley et al (2006)[15] Healthy volunteers (N = 16), 8 females, mean age of 26 years	Randomized crossover design to assess drug interactions through P-glycoprotein	MT seeds extract (Enzymatic Therapy Inc, Green Bay, Wis) Lot # 41678; 900 mg/d for 14 days, 30-day washout	Black cohosh 40 mg × 14 days Rifampin 600 mg × 7 days Clarithromycin 1000 mg × 7 days Digoxin Lanoxicaps®, (0.4 mg) before- and after- each period	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 (0-3) and AUC (0-24) approached significance ($P = .06$) following MT. Compared with rifampin and clarithromycin, these formulations of MT or black cohosh did not affect digoxin PK, suggesting that these supplements are not potent modulators of P-gp in vivo and do not pose a significant interaction risk with digoxin.

Bioavailability

Kim et al (2003)[46] Healthy male volunteers (Korea) (N = 24)	Phase I 3 × 3 crossover design to compare bioavailability of silibinin from 3 products	MT extract standardized to silibinin content: Liverman (capsule), Legalon (capsule), and silymarin (tablet) 120 mg silibinin for 12 h	None (same group)	Plasma concentration of silibinin: AUC inf: area under the plasma concentration-time curve from time 0 to infinity; Cmax: maximum plasma drug concentration; and Tmax: time to reach Cmax	None reported	Oral bioavailability of silibinin after Liverman capsule was faster and greater than Legalon and silymarin: AUC (0-12h): [mu]g/mL × h Liverman PK: 13.9; Legalon PK: 25.59; silymarin tablet PK: 4.24 AUC inf: [mu]g/mL × h Liverman: 15.1; Legalon: 6.00; silymarin: 4.63 Cmax: [mu]g/mL Liverman: 6.04; Legalon: 1.33; silymarin: 1.13 Tmax: Liverman: 0.875; Legalon: 1.83;

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Table 2. Clinical Trials of Milk Thistle in Cancer (past 5 years)

Sample	Objective/ Design	MT Extract	Reference Group	Outcomes	Adverse Events	Results
Phase I						
Flaig et al (2007)[44] Prostate cancer N = 13	Toxicity/dose escalation Dose: 2.5-20 g daily × 4 weeks (3 divided doses)	Siliphos® (Indena Corp, Seattle, Wash) Silybin/ phosphatidyl- choline 30% silibinin by weight	Before treatment	PSA, ALT, bilirubin levels, fever, neutropenia, thrombocytopenia	9 of 13 patients had grade 1-2 hyper- bilirubinemia 1 patient had grade 3 toxicity (ALT elevation) No grade 4 toxicity	15-20 g daily caused asymptomatic liver toxicity 13 g divided in 3 doses is well tolerated
Hoh et al (2006)[32] Colorectal cancer N = 24 12 adenoCA, 12 hepatic metastases	Test if serum and tissue levels (colon/liver) are consistent with pharmacologic activity Dose: 360, 720, and 1440 mg daily × 7 days	Silipide (Indena Corp) 40% silibinin (120 mg) with 60% soy phosphatidyl- choline	Same as treatment group	Silibinin levels Plasma metabolites Serum IGFBP-3, IGF-1 Oxidative DNA damage M2dG pyrimidopuri- none adduct of deoxyguanosine Tissue resection	None	Achieved silibinin levels of 0.3 to 4 mm/L in plasma, 0.3 to 2.5 nmol/g in liver, 20-141 nmol/g in colorectal tissue; potential chemoprotective role in colorectal cancer
Phase II						
van Erp et al (2005)[47] Cancer: colorectal, genitourinary N = 6	Effect on PK of irinotecan, a substrate for CYP3A4 and UGT1A1 proteins	Silybin MT seed extract (80% silymarin) Dose: 600 mg divided in 3 daily doses × 14 days	None	Irinotecan clearance Silybin plasma concentration	None	Silybin concentrations were too low to affect CYP3A4 or UGT1A1 in vivo. No differences in 4-day vs 12-day intake Little risk of interaction with these pathways
Phase III						
Schroder et al (2005)[50] Prostate cancer, rising PSA N = 49 Surgery: n = 34 Radiation therapy: n = 15	Evaluate effect rate of increase of PSA (efficacy) Dose: 160 mg/d × 10 weeks (plus other ingredients)	Silymarin (160 mg) plus others: Soy isoflavones (62.5 mg) Selenium (128 mcg) Lycopene (15 mg) Zinc (18 mg) Ascorbic acid (225 mg) N-acetyl- L-cysteine (500 mg) Folic acid (400 mcg)	Placebo	PSA slope and doubling time	None	Significant decrease in PSA slope; placebo had 2.6-fold increase in PSA doubling time from 445 to 1150 days Delays PSA progression after potentially curative treatment

MT = milk thistle; PSA = prostate-specific antigen; ALT = alanine aminotransferase; PK = pharmacokinetics.

In testing the efficacy of MT for functional dyspepsia, STW-5 (Iberogast), a combination of MT fruits and other 8 herbs, improved dyspeptic symptoms earlier than the herbs alone (without MT). The MT seed extract used in this combination is referred to by its German name as *Cardui mariae fructus.*[60]

Safety Results in Control Trials

Milk thistle has been recognized as a "safe and well tolerated herb" with a limited adverse event profile usually reported to be similar to placebo.[2,8,61] Similar to other plant products commonly used as foods and herbs, MT extracts do not seem to lead to toxic

Table 3. Clinical Trials of Milk Thistle in Liver Diseases (past 5 years)

Sample	Objective/Design	MT Extract	Reference Group	Outcomes Parameters	Adverse Events	Results
Chronic hepatitis C						
Tanamly et al (2004)[51] Egyptian patients with chronic HCV N = 177	RCT trial to prevent complications of HCV (12-month follow-up)	Legalon 140® silymarin capsules (Madaus, Cologne, Germany) Verified dose of silymarin: 373.5 mg × 12 months (124.5 mg TID)	Low-dose (low antioxidant) multivitamin	Clinical outcomes: symptoms, well-being, QoL Liver ultrasound Serum HCV RNA HCV Ab HCV viremia ALT, fibrosis markers	Fatigue: 4.4 per person weeks in placebo vs 3.5 in silymarin group D/N/V rare in both groups No one discontinued because of side effects	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.
Strickland et al (2005)[52] Egyptian patients with chronic HCV N = 141 (Follow-up study to Tanamly)	RCT trial to prevent complications of HCV (24-month follow-up)	Legalon 140® silymarin (Madaus) 420 mg/d, 140 mg TID	Low-dose (low antioxidant) multivitamin	Clinical outcomes: symptoms, well-being, QoL Liver ultrasound Serum HCV RNA HCV Ab HCV viremia ALT, fibrosis markers	None noted	At 24 months of therapy, 65/68 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.
Gordon et al (2006)[53] Patients with chronic HCV in Australia N = 17	Safety and efficacy	MT extract in tablet 80% silymarin (MediHerb, Australia) 600 or 1200 mg/d × 12 weeks	Placebo: identical matching tablet (MediHerb)	QoL (SF-36) and psychological assessments Biochemical, virological, and HCV RNA titer	Similar between groups and 2 different doses	No differences in SF-36 or RNA titers or ALT levels between groups. Well tolerated but no effect on outcomes in this sample.
El-Zayadi et al (2005)[54] Patients in Egypt with detectable HCV-RNA and elevated ALT N = 170	RCT: effect on necro-inflammatory response Compare silymarin (n = 83) to standard therapy (n = 87)	MT: silymarin extract 450 mg/d × 24 weeks Follow-up at 48 weeks	Noninterferon-based therapy (NIFN-BT) with ribavirin (600-800 mg) plus amantadine (200 mg) and ursodeoxycholic acid (500 mg)	ALT levels Virologic response (ETVR) Sustained biochemical response (SBR) Sustained virologic response (SVR)	None observed	NIFN-BT more effective than silymarin: 4-fold higher ETVR 10-fold higher SBR than silymarin Greater normalization of ALT (58.5% vs 15.3%) Viral response 2.4% vs 0% SBR 28% vs 2.8% SVR 2.4% vs 0%

(continued)

Table 3. (continued)

Sample	Objective/Design	MT Extract	Reference Group	Outcomes Parameters	Adverse Events	Results
Torres et al (2004) (abstract only)[55] Chronic HCV with no antiviral therapy Puerto Rico N = 34	Safety and efficacy	MT seed extract 160 mg, 3 times per week × 4 weeks	No treatment control	Serum: viral load, liver enzymes (ALT/AST)	None in abstract	Silybum well tolerated. No effect on viral load. Decreased ALT and AST compared to control. No antiviral effects. Possible protective effect on inflammation.
Melhem et al (2005)[56] Chronic HCV in Israel N = 50	Safety, effect, and tolerability of intravenous and oral antioxidants and vitamins	Silymarin capsules plus other antioxidants and vitamins/herbals 250 mg TID × 20 weeks (intravenous 2 times per week)	No control Vitamins: Glycyrrhiza, Schizandra, ascorbate, L-glutathione, lipoic acid, d-alpha-tocopherol, B complex	Liver enzymes (ALT) HCV RNA levels Liver biopsy Histology SF-36 QoL	No major adverse reactions; well tolerated	Well tolerated. Favorable response in 48% of patients (n = 24). ALT normalized from pretreatment high in 44%. Remained normal in 72.7%. Decreased viral load in 25%. Histologic improvement in 36.1%. SF-36 increased in 58%.
Chronic alcoholic liver disease						
Lucena et al (2002)[57] Patients with alcoholic liver cirrhosis (Spain) N = 60 49 completed: silymarin = 24, placebo = 25	Double-blind RCT to investigate antiperoxidative effects of silymarin MZ-80	Silymarin MZ-80 (S) 150 mg TID × 6 months	Placebo	Erythrocyte total glutathione (GSH) Platelet malondialdehyde (MDA) Serum amino terminal propeptide of procollagen type III (PIIINP)	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/g Hb) vs placebo (4.1 × 3.9 to 4.4 × 4.1 mmol/g Hb)*** Silymarin: PIIINP 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 noninduced MDA decreased by 33%.
Lirussi et al (2002)[58] Chronic alcoholic liver disease and type 2 diabetes mellitus (Italy) N = 60, 42 completed	Double-blind RCT to assess effects of silybin on rebalancing of cell redox levels, liver function, glucose, and lipid metabolism	Silybin-beta cyclodestrin (IBI/S) 135 mg silybin for 6 months	Placebo (n = 21)	Fasting plasma glucose Glycosylated hemoglobin (HbA1c) Basal, stimulated C-peptide and insulin levels Total, HDL 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 186 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.

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.[53] 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 studied that included patients older than 65 years.

Adverse effects associated with oral ingestion of MT include mainly gastrointestinal problems, but these are rare.[9] Headache/dizziness and pruritus were reported in 1 trial.[53] 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-phytosome between 10 and 20 g daily.[44] 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.[62] 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.[61]

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."[63] 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 RCTs 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.[7] 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.[53]

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.[36] There are limited clinical trials evaluating choledolithiasis 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 monohydroxylated bile salts.[1]

Anticancer, antidiabetic activity, and the effects of MT phytoestrogens (flavonolignans) on estrogen metabolism, particularly on the occurrence of catechol-estrogen-quinones known to cause carcinogenic depurinating DNA adducts within cells,[64] also deserve further investigation.

Appendix

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