

Milk Thistle

FRANCINE RAINONE, D.O., PH.D., M.S.

Albert Einstein College of Medicine of Yeshiva University, Bronx, New York

Milk thistle has been used as a cytoprotectant for the treatment of liver disease, for the treatment and prevention of cancer, and as a supportive treatment of *Amanita phalloides* poisoning. Clinical studies are largely heterogeneous and contradictory. Aside from mild gastrointestinal distress and allergic reactions, side effects are rare, and serious toxicity rarely has been reported. In an oral form standardized to contain 70 to 80 percent silymarin, milk thistle appears to be safe for up to 41 months of use. Significant drug reactions have not been reported. Clinical studies in oncology and infectious disease that are under way will help determine the efficacy and effectiveness of milk thistle. (*Am Fam Physician* 2005;72:1285-8. Copyright © 2005 American Academy of Family Physicians.)

Milk thistle (*Silybum marianum*) was used in classical Greece to treat liver and gallbladder diseases and to protect the liver against toxins. It recently has been investigated for use as a cytoprotectant, an anticarcinogen, and a supportive treatment for liver damage from *Amanita phalloides* poisoning. Its active ingredient is silymarin, found primarily in the seeds. Silymarin undergoes enterohepatic recirculation, which results in higher concentrations in liver cells than in serum.¹ It is made up of components called flavonolignans, the most common being silybin.²

Pharmacology

A number of studies have suggested that silymarin is an anti-inflammatory. It regulates inflammatory mediators such as tumor necrosis factor (TNF),³ TNF- α ,⁴ nitrous oxide, interleukin-6, and interleukin-1 receptor antagonist.⁵ Silymarin also increases lymphocyte proliferation, interferon gamma, interleukin-4, and interleukin-10 cytokines, in a dose-dependent manner.^{6,7} Taken together, these effects suggest a possible role in preventing or treating infectious disease.

Several mechanisms of cytoprotection have been identified. In some studies,⁸ milk thistle promoted neuronal differentiation and survival. In others, silymarin inhibited leukotriene formation by Kupffer cells⁹ and

increased expression of growth factor beta-1 and c-myc.¹⁰ In animal studies, it has shown protective effects against damage to the pancreas from cyclosporine (Sandimmune)¹¹; damage to the kidney from acetaminophen, cisplatin (Platinol), and vincristine (Oncovin)¹²; and damage to the liver from carbon tetrachloride,^{13,14} partly by reducing lipid peroxidation. In another study,¹⁵ silymarin slowed the progression of alcohol-induced liver fibrosis in baboons. In vitro and animal studies support the possibility that milk thistle has anticarcinogenic effects for cancers of the prostate, breast, skin, colon, tongue, and bladder.¹⁶⁻²⁴

Uses and Effectiveness

LIVER DISEASE

In the United States, milk thistle is most commonly used to treat viral infections and cirrhosis of the liver. Clinical trials have produced conflicting results. In a study²⁵ of patients with cirrhosis, 170 patients (46 with alcoholism) were randomized to Legalon, a proprietary product standardized to contain 70 to 80 percent silymarin, or placebo. In the 146 patients who completed 24 to 41 months of therapy, there was a lower mortality rate among the patients treated with Legalon. The greatest benefit occurred in those whose cirrhosis was caused by alcoholism and in those who had less severe cirrhosis on entry.²⁵

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Patients should be informed that there is insufficient evidence to recommend milk thistle for viral hepatitis and alcoholic liver disease, but that it appears to be safe.	B	25-33
Patients who ask about milk thistle for hepatic cytoprotection from a variety of toxins should be informed that there is weak evidence for its effectiveness.	C	26
Milk thistle shows promise as supportive therapy for <i>Amanita phalloides</i> poisoning.	C	37

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1154 or <http://www.aafp.org/afpsort.xml>.

In a six-month double-blind study²⁶ of 36 patients with chronic alcoholic liver disease, the group given Legalon showed normalization of their bilirubin, aspartate transaminase and alanine transaminase serum levels, and also showed improvement in histology. These effects did not occur in the placebo group. In another study,²⁷ 106 patients with mild acute and subacute liver disease characterized by elevated serum transaminase levels were randomized to receive silymarin or placebo. Of the 97 patients who completed the four-week study, there was a statistically significant greater decrease in transaminase levels in the silymarin group. In addition, results of a smaller study²⁸ of 20 patients with chronic active hepatitis randomized to placebo or silybin showed that the milk thistle group had significantly lower transaminase, bilirubin, and gamma-glutamyltranspeptidase levels than the placebo group. This study used a complex of silybin with phosphatidylcholine, which appears to increase bioavailability.

Other studies have not duplicated these positive effects. In a study²⁹ of 200 patients with alcoholic cirrhosis, there were no differences in time to death or progression to liver failure in the 125 patients who completed 24 months of therapy. Similarly, in a study³⁰ of 72 patients with alcoholic liver disease, there were no differences in mortality or laboratory values between the placebo and silymarin groups. Finally, a three-month study³¹ of 116 patients with histologically proven alcoholic hepatitis randomized to placebo or silymarin showed no

significant differences in serum transaminase activity or histologic fibrosis scores.

Two meta-analyses of milk thistle for liver disease^{32,33} detail the major limitations of prior studies and conclude that data are insufficient to support its use at this time. The two main limitations are the heterogeneity of the study populations, caused by lack of precise inclusion and exclusion criteria and the noncomparability of doses received. Most studies did not report or use objective criteria to determine the severity and etiology of cirrhosis and did not control for confounding factors such as infection with hepatitis B or C and ongoing alcohol intake. In addition, the trials vary considerably in duration, ranging from one week to 41 months, without agreement on the minimum duration needed to see effect. The effect of silymarin is thought to be dose-dependent, and it is not known whether the bioavailability of different formulations is equivalent.^{6,7} Because the studies used different products, it is not known whether participants in the different studies received equivalent doses. These limitations make comparisons of studies difficult to interpret. Efforts are under way to isolate, semisynthesize, and extensively characterize the biologic activities of the flavonolignans that constitute silymarin.³⁴ Developing products that contain standardized percentages of precise ratios of the components of silymarin will improve the ability to test its effectiveness.

CYTOPROTECTANT

Studies of the use of milk thistle as a cytoprotectant in humans have been limited. In one study,³⁵ 49 of 200 workers exposed to toluene or xylene for five to 20 years developed persistent elevations in transaminase levels; 30 of these heterogeneous patients were treated with Legalon, whereas the others were not treated. In the Legalon group, transaminase activity decreased and platelet count increased when compared with the untreated group. Patients two to 21 years of age with acute lymphoblastic leukemia who are receiving hepatotoxic chemotherapy are being recruited for a second phase randomized pilot trial of silymarin.

The Author

FRANCINE RAINONE, D.O., PH.D., M.S., is assistant professor of family medicine at Albert Einstein College of Medicine of Yeshiva University, Bronx, N.Y., where she teaches in the Montefiore Medical Center Residency Program in social medicine. Dr. Rainone also is the program director of the Palliative Care Suite at Montefiore and the program director of the Fellowship in Palliative Care.

Address correspondence to Francine Rainone, D.O., PH.D., M.S., Montefiore Medical Center, Department of Family Medicine, 3544 Jerome Ave., Bronx, NY 10467 (e-mail: frainone@montefiore.org). Reprints are not available from the author.

TABLE 1
Key Points About Milk Thistle

Efficacy	Acute and chronic viral hepatitis, alcoholic liver disease: conflicting evidence Cytoprotection: rigorous randomized controlled trials ongoing; limited evidence suggests benefit. Anticarcinogen: clinical trials ongoing Amanita phalloides poisoning: insufficient data
Adverse effects	Generally well tolerated; infrequent reports of gastrointestinal disturbances; rare reports of pruritus, eczema, rash, and anaphylaxis* CAUTION: do not use in patients with allergies to members of the aster family.
Interactions	No significant drug interactions
Dosage	Milk thistle seed extract, 150- to 175-mg capsule, standardized to 80 percent silymarin, three times daily Ultrathistle (seed extract bound to phosphatidylcholine), 360-mg capsule, three times daily
Cost	\$15 to \$30 per month at 150 to 175 mg three times daily \$42 per month at 360 mg three times daily
Bottom line	Safe, no known drug interactions; insufficient data to recommend for treatment of liver disease; under investigation for anticarcinogenic and chemoprotective effects

*—Three nonfatal case reports, only one of which is sufficiently attributed to the herb.

ANTICARCINOGEN

Researchers are investigating the use of milk thistle's active ingredients for the prevention and treatment of cancer. Two additional animal studies on prostate cancer chemoprevention and treatment are ongoing, and a third phase trial in human prostate cancer patients with rising prostate-specific antigen also is under way.

AMANITA PHALLOIDES POISONING

The *A. phalloides* mushroom, called the "death cap," produces severe nausea, vomiting, and watery diarrhea within five to 12 hours of ingestion. This often causes hypovolemia and hypoglycemia. Silymarin inhibits the binding of the toxins in the mushroom to hepatocytes and interrupts the enterohepatic circulation of the toxins.³⁶ Several journals have published case reports of silymarin treatment (intravenously and orally) for *A. phalloides* poisoning in humans, but the largest series³⁷ followed only 18 patients. In every case, silymarin was used in combination with other agents, usually being added when standard treatment appeared to fail. The relative contribution of silymarin to these treatment regimens is unknown. The intravenous form of silymarin was used in these studies, but it is not available in the United States.

ADVERSE EFFECTS AND INTERACTIONS

The Agency for Healthcare Research and Quality reviewed the effects of milk thistle on liver disease and cirrhosis,³² noting that serious adverse reactions are virtually unheard of. The most common reported complaints were gastrointestinal disturbances, but the overall incidence was no different from placebo. Allergic reactions, ranging from pruritus and rash to eczema and anaphylaxis, are rare.

Drug interactions do not appear to be problematic.

Silybin inhibits the activities of CYP2D6, CYP2E1, and CYP3A4, but at physiologic concentrations far higher than those given clinically.³⁸ In a study³⁹ of 10 healthy volunteers, administration of 175 mg of milk thistle three times daily for three weeks had no significant effect on concomitantly administered indinavir (Crixivan).

DOSAGE

Most clinical trials have used daily dosages of 420 to 480 mg silymarin, divided into two or three doses daily. Until the specific effects of each of the flavonolignans is known and products are available that contain standardized ratios of these components, the optimal dosage will remain unknown. *Table 1* outlines the efficacy, safety, tolerability, dosage, and cost of milk thistle.

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