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FILE: ▪Milk Thistle (*Silybum marianum*)

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RE: Efficacy and Safety of Milk Thistle

Tamayo C, Diamond S. Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum* [L.] Gaertn.). *Integr Cancer Ther.* 2007;6(2):146-157.

Milk thistle (*Silybum marianum*) is one of the most effective herbs known for treating liver disorders (e.g., viral hepatitis). Studies have shown the herb to provide relief of symptoms associated with hepatitis, cirrhosis, and inflammation of the liver. These effects of milk thistle are commonly attributed to silymarin, the active constituent.

The available scientific evidence suggests that milk thistle extracts have an important hepatoprotective as well as anticancer, antidiabetic, and cardioprotective effect. 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. However, high-quality clinical studies are limited, and very few have evaluated the purported anticancer and other pharmacological activities. To complicate matters, there is a wide variability of extracts and compounds tested in clinical trials. Likewise, data on safety is limited as most clinical trials are not powered to detect adverse effects. Lastly, in pediatric and elderly populations, there is a paucity of published trials. The object of this review was to mainly address clinical trials conducted in the past five years.

The most recent meta-analysis concluded that milk thistle does not significantly influence the course of the disease in subjects with alcoholic and/or hepatitis C virus (HCV) or liver diseases; even though, all-cause mortality was reduced by 50% in subjects with alcoholic liver disease without HCV antibodies who took the extracts compared with placebo ($P<0.05$). However, this lack of definitive efficacy may be due to poor scientific quality of study methods, poor reporting quality, or both.

In Phase I/II, dose-finding, pharmacodynamic, and pharmacokinetic trials, silibinin (a flavonoid from milk thistle) at doses of 360, 720, or 1440 mg daily for 7 days produced high silibinin levels in the colorectal mucosa of colorectal cancer subjects after consumption of

phosphatidylcholine. This finding may support silibinin as a potential preventive agent for colorectal cancer.

Flavonoids from milk thistle seem to normalize immunoregulatory defects by restoration of the cellular thiol status. Furthermore, T-cell activation, along with a significant decrease in TNF-α release ($P<0.05$), was observed in subjects with end-stage diabetic nephropathy.

Phase I/II, herb-drug interaction studies demonstrate that milk thistle does *not* have clinically relevant effects on CYP3A, CYP1A2, CYP2D6, or CYP2E1 activity, and does not interfere with P-glycoprotein modulation. 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.

In a Phase III randomized clinical trial (RCT) of cancer, a dietary supplement, containing silymarin (among other ingredients) was shown to delay prostate-specific antigen progression significantly ($P<0.03$) after prostatectomy and radiotherapy in prostate cancer subjects. 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. Higher doses (600 and 1200 mg/day) were tolerated but had no significant effect on HCV-RNA titers and other liver chemistries. A small beneficial, but not significant, effect of milk thistle was observed in subjects with chronic HCV; albeit, the response was ten-fold less than that following interferon treatment. Other studies suggest that milk thistle may have a protective effect in the inflammatory response to HCV, but no role as an antiviral agent.

In subjects with alcoholic liver disease and concomitant noninsulin-dependent diabetes, 135 mg of silybin-β-cyclodextrin daily did not change liver function test or insulin secretion, but significantly reduced fasting glucose ($P<0.03$) and serum triglyceride levels ($P<0.01$) compared with placebo. The effects appear to be via reduced glycosylated hemoglobin levels and insulin sensitivity. In an RCT of type II diabetic subjects, 600 mg daily of milk thistle over 4 months improved the glycemic profile compared with placebo.

In general, milk thistle has been recognized as a safe and well-tolerated herb with a limited adverse event profile similar to placebo. Although no short-term trials of high silymarin intake have been done in healthy populations, it seems clear that under the restricted conditions of available trials, milk thistle appears to be quite safe. In a long-term trial of subjects with chronic HCV, 373.5 mg of milk thistle was safe and well tolerated for up to 1 year. In another trial, an oral form standardized to contain 70% to 80% silymarin given at a dosage of 420 mg daily, was safe for up to 41 months of use, and significant drug reactions were not reported.

The majority of reported adverse events are unrelated to the product, or difficult to separate from the concomitant disease. Adverse effects associated with oral ingestion of milk thistle are rare and include gastrointestinal problems. Headache/dizziness and pruritus were reported in one trial. Asymptomatic liver toxicity has been observed in recent clinical trials done in cancer subjects administered very high dosages of silybin-phytosome (between

10 and 20 g daily). At doses greater than 1.5 g per day, a laxative effect is possible due to increased bile secretion and flow. Mild non-serious allergic reactions have also been noted.

Milk thistle may be a good preventive and therapeutic intervention for HCV and other liver diseases. High-quality clinical trials are needed to evaluate the hepatoprotective effect of milk thistle in the course of liver diseases and in the hepatotoxicity produced by certain medications. In addition, future clinical studies in HCV should focus on the role of milk thistle in combination with other herbal therapies, as well as other hepatoprotective agents; should evaluate milk thistle for cholestatic liver disease or primary hepatic malignancy; and should investigate the potential for anticancer and antidiabetic effects.

—Jennifer Minigh, PhD

The American Botanical Council has chosen not to include the original article.