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21. Milk Thistle: Effects on Liver Disease and Cirrhosis and Clinical Adverse Effects

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Evidence Report/Technology Assessment

Number 21

Prepared for:
Agency for Healthcare Research and Quality

U.S. Department of Health and Human Services
2101 East Jefferson Street
Rockville, MD 20852

Contract No. 290-97-0012

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AHRQ Publication No. 01-E025

October 2000 [↑ TOP](#)

Preface

The Agency for Healthcare Research and Quality (AHRQ), formerly the Agency for Health Care Policy and Research, through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives. This evidence report summarizes studies of efficacy and adverse effects of milk thistle in humans with alcohol, viral, or toxin-related liver disease.

Search Strategy. English and non-English citations were identified through December 1999 from 11 electronic databases, references of pertinent articles and reviews, manufacturers, and technical experts.

Selection Criteria. Selection criteria regarding efficacy were placebo-controlled trials of milk thistle. For adverse effects, all studies in humans were used.

Data Collection and Analysis. Abstractors independently abstracted data from published reports. Relationships between clinical outcomes and methodologic characteristics were examined in evidence tables and graphic summaries. Exploratory meta-analyses were used to examine possible patterns of effects.

Main Results.

- Sixteen prospective placebo-controlled trials were identified.
- Interpreting the evidence was difficult because of inadequate reporting and study design regarding severity of liver disease, subject characteristics, and potential confounders. Outcome measures, dose, duration, and followup widely varied among studies.
- Four of six studies of chronic alcoholic liver disease reported significant improvement in at least one parameter of liver function or histology with milk thistle.
- In three of six studies that reported multiple outcome measures, at least one outcome measure improved significantly with milk thistle compared with placebo, but there were no differences between milk thistle and placebo for

one or more of the other outcome measures in each study.

- Three studies evaluated the effects of milk thistle on viral hepatitis. The acute hepatitis study showed no improvement in liver function. Improvement in aspartate aminotransferase and bilirubin was significant in the study of acute hepatitis. Two studies of chronic viral hepatitis showed improvement in aminotransferases with milk thistle in one and a trend toward histologic improvement in the other.
- There were two studies of patients with alcoholic or nonalcoholic cirrhosis. In one study, milk thistle showed a positive effect, but no data were given. In the other, milk thistle showed a trend toward improved survival and significantly improved survival for subgroups with alcoholic cirrhosis or Child's Group A severity.
- Two trials specifically studied alcoholic cirrhosis. One showed no improvement in liver function, hepatomegaly, jaundice, ascites, or survival but did show nonsignificant trends favoring milk thistle in the incidence of encephalopathy, gastrointestinal bleeding, and death in subjects with hepatitis C. The other reported significant improvements in aminotransferases with milk thistle.
- Three trials evaluated thistle as therapy or prophylaxis in the setting of hepatotoxic drugs; results were mixed.
- Meta-analyses generally showed small effect sizes, some statistically significant and some not, favoring milk thistle.
- Available evidence does not define milk thistle's effectiveness across preparations or doses.
- Little evidence is available regarding causality, but evidence suggests milk thistle is associated with few, generally minor, adverse effects.

Conclusions. Milk thistle's efficacy is not established. Published evidence is clouded by poor design and reporting. Possible benefit has been shown most frequently, but inconsistently, for aminotransferases, but laboratory tests are the most common outcome measure studied. Survival and other clinical outcomes have been studied less, with mixed results. Future research should include definition of multifactorial mechanisms of action, well-designed clinical trials, and clarification of adverse effects.

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Suggested Citation:

Lawrence V, Jacobs B, Dennehy C, et al. Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects. Evidence Report/Technology Assessment No. 21 (Contract 290-97-0012 to the San Antonio Evidence-based Practice Center, based at the University of Texas Health Science Center at San Antonio, and The Veterans Evidence-based Research, Dissemination, and Implementation Center, a Veterans Affairs Services Research and Development Center of Excellence). AHRQ Publication No. 01-E025. Rockville, MD: Agency for

Healthcare Research and Quality. October 2000. [↑ TOP](#)

Summary

Overview

This evidence report details a systematic review summarizing clinical studies of milk thistle in humans. The scientific name for milk thistle is *Silybum marianum*. It is a member of the aster or daisy family and has been used by ancient physicians and herbalists to treat a range of liver and gallbladder diseases and to protect the liver against a variety of poisons. Two areas are addressed in the report: (1) effects of milk thistle on liver disease of alcohol, viral, toxin, cholestatic, and primary malignancy etiologies; and (2) clinical adverse effects associated with milk thistle ingestion or contact. The report was requested by the National Center for Complementary and Alternative Medicine, a component of the National Institutes of Health, and sponsored by the Agency for Healthcare Research and Quality (AHRQ). [↑ TOP](#)

Reporting the Evidence

Specifically, the report addresses 10 questions regarding whether milk thistle supplements—compared with no supplement, placebo, other oral supplements, or drugs—alter the physiological markers of liver function, reduce mortality or morbidity, or improve the quality of life in adults with alcohol-related, toxin-induced, or drug-induced liver disease, viral hepatitis, cholestasis, or primary hepatic malignancy. One question addresses the constituents of commonly available milk thistle preparations, and three questions address the common and uncommon symptomatic adverse effects of milk thistle. [↑ TOP](#)

Methodology

Search Strategy

Eleven electronic databases, including AMED, CISCOP, and the Cochrane Library (including DARE and the Cochrane Controlled Trials Registry), EMBASE, MEDLINE, and NAPRALERT, were searched through July 1999 using the following terms: *carduus marianus*, *legalon*, *mariendistel*, *milk thistle*, *silybin*, *silybum marianum*, *silybum*, *silychristin*, *silydianin*, and *silymarin*. An update search limited to PubMed was conducted in December 1999. English and non-English citations were identified from these electronic databases, references in pertinent articles and reviews, drug manufacturers, and technical experts. [↑ TOP](#)

Selection Criteria

Preliminary selection criteria regarding efficacy were reports on liver disease and clinical and physiologic outcomes from randomized controlled trials (RCTs) in humans comparing milk thistle with placebo, no milk thistle, or another active agent. Several of these randomized trials had dissimilar numbers of subjects in

study arms, raising the question that these were not actually RCTs but cohort studies. In addition, among studies using nonplacebo controls, the type of control varied widely. Therefore, qualitative and quantitative syntheses of data on effectiveness were limited to placebo-controlled studies. For adverse effects, all types of studies in humans were used to assess adverse clinical effects. [↑ TOP](#)

Data Collection and Analysis

Abstractors (physicians, methodologists, pharmacists, and a nurse) independently abstracted data from trials; a nurse and physician abstracted data about adverse effects. Data were synthesized descriptively, emphasizing methodologic characteristics of the studies, such as populations enrolled, definitions of selection and outcome criteria, sample sizes, adequacy of randomization process, interventions and comparisons, cointerventions, biases in outcome assessment, and study designs. Evidence tables and graphic summaries, such as funnel plots, Galbraith plots, and forest plots, were used to examine relationships between clinical outcomes, participant characteristics, and methodologic characteristics. Trial outcomes were examined quantitatively in exploratory meta-analyses that used standardized mean differences between mean change scores as the effect size measure. [↑ TOP](#)

Findings

Mechanisms of Action

Evidence exists that milk thistle may be hepatoprotective through a number of mechanisms: antioxidant activity, toxin blockade at the membrane level, enhanced protein synthesis, antifibrotic activity, and possible anti-inflammatory or immunomodulating effects. [↑ TOP](#)

Preparations of Milk Thistle

The largest producer of milk thistle is Madaus (Germany), which makes an extract of concentrated silymarin. However, numerous other extracts exist, and more information is needed on comparability of formulations, standardization, and bioavailability for studies of mechanisms of action and clinical trials. [↑ TOP](#)

Benefit of Milk Thistle for Liver Disease

- Sixteen prospective trials were identified. Fourteen were randomized, blinded, placebo-controlled studies of milk thistle's effectiveness in a variety of liver diseases. In one additional placebo-controlled trial, blinding or randomization was not clear, and one placebo-controlled study was a cohort study with a placebo comparison group.
- Seventeen additional trials used nonplacebo controls; two other trials studied milk thistle as prophylaxis in patients with no known liver disease who were starting potentially hepatotoxic drugs. The identified studies addressed alcohol-related liver disease, toxin-induced liver disease, and viral liver disease. No studies were found that evaluated milk thistle for cholestatic

liver disease or primary hepatic malignancy (hepatocellular carcinoma, cholangiocarcinoma).

- There were problems in assessing the evidence because of incomplete information about multiple methodologic issues, including etiology and severity of liver disease, study design, subject characteristics, and potential confounders. It is difficult to say if the lack of information reflects poor scientific quality of study methods or poor reporting quality or both.
- Detailed data evaluation and syntheses were limited to the 16 placebo-controlled studies. Distribution of durations of therapy across trials was wide (7 days to 2 years), inconsistent, and sometimes not given. Eleven studies used Legalon[®], and eight of those used the same dose. Outcome measures varied among studies, as did duration of therapy and the followup for which outcome measures were reported.
- Among six studies of milk thistle and chronic alcoholic liver disease, four reported significant improvement in at least one measurement of liver function (i.e., aminotransferases, albumin, and/or malondialdehyde) or histologic findings with milk thistle compared with placebo, but also reported no difference between groups for other outcome measures.
- Available data were insufficient to sort six studies into specific etiologic categories; these were grouped as chronic liver disease of mixed etiologies. In three of the six studies that reported multiple outcome measures, at least one outcome measure improved significantly with milk thistle compared with placebo, but there were no differences between milk thistle and placebo for one or more of the other outcome measures in each study. Two studies indicated a possible survival benefit.
- Three placebo-controlled studies evaluated milk thistle for viral hepatitis. The one acute viral hepatitis study reported latest outcome measures at 28 days and showed significant improvement in aspartate aminotransferase and bilirubin. The two studies of chronic viral hepatitis differed markedly in duration of therapy (7 days and 1 year). The shorter study showed improvement in aminotransferases for milk thistle compared with placebo but not other laboratory measures. In the longer study, milk thistle was associated with a nonsignificant trend toward histologic improvement, the only outcome measure reported.
- Two trials included patients with alcoholic or nonalcoholic cirrhosis. The milk thistle arms showed a trend toward improved survival in one trial and significantly improved survival for subgroups with alcoholic cirrhosis or Child's Group A severity. The second study reported no significant improvement in laboratory measures and survival for other clinical subgroups, but no data were given.
- Two trials specifically studied patients with alcoholic cirrhosis. Duration of therapy was unclear in the first, which reported no improvement in laboratory measures of liver function, hepatomegaly, jaundice, ascites, or survival. However, there were nonsignificant trends favoring milk thistle in incidence of encephalopathy and gastrointestinal bleeding and in survival for subjects with concomitant hepatitis C. The second study, after treatment for 30 days, reported significant improvements in aminotransferases but not

bilirubin for milk thistle compared with placebo.

- Three trials evaluated milk thistle in the setting of hepatotoxic drugs: one for therapeutic use and two for prophylaxis with milk thistle. Results were mixed among the three trials.
- Exploratory meta-analyses generally showed positive but small and nonsignificant effect sizes and a sprinkling of significant positive effects.
- No studies were identified regarding milk thistle and cholestatic liver disease or primary hepatic malignancy.
- Available evidence does not establish whether effectiveness of milk thistle varies across preparations. One Phase II trial suggested that effectiveness may vary with dose of milk thistle.

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Adverse Effects

Adverse effects associated with oral ingestion of milk thistle include gastrointestinal problems (e.g., nausea, diarrhea, dyspepsia, flatulence, abdominal bloating, abdominal fullness or pain, anorexia, and changes in bowel habits), headache, skin reactions (pruritus, rash, urticaria, and eczema), neuropsychological events (e.g., asthenia, malaise, and insomnia), arthralgia, rhinoconjunctivitis, impotence, and anaphylaxis. However, causality is rarely addressed in available reports. For randomized trials reporting adverse effects, incidence was approximately equal in milk thistle and control groups. [↑ TOP](#)

Conclusions

Clinical efficacy of milk thistle is not clearly established. Interpretation of the evidence is hampered by poor study methods and/or poor quality of reporting in publications. Problems in study design include heterogeneity in etiology and extent of liver disease, small sample sizes, and variation in formulation, dosing, and duration of milk thistle therapy. Possible benefit has been shown most frequently, but not consistently, for improvement in aminotransferases and liver function tests are overwhelmingly the most common outcome measure studied. Survival and other clinical outcome measures have been studied least often, with both positive and negative findings. Available evidence is not sufficient to suggest whether milk thistle may be more effective for some liver diseases than others or if effectiveness might be related to duration of therapy or chronicity and severity of liver disease. Regarding adverse effects, little evidence is available regarding causality, but available evidence does suggest that milk thistle is associated with few, and generally minor, adverse effects.

Despite substantial *in vitro* and animal research, the mechanism of action of milk thistle is not fully defined and may be multifactorial. A systematic review of this evidence to clarify what is known and identify gaps in knowledge would be important to guide design of future studies of the mechanisms of milk thistle and clinical trials. [↑ TOP](#)

Future Research

The type, frequency, and severity of adverse effects related to milk thistle preparations should be quantified. Whether adverse effects are specific to dose, particular preparations, or additional herbal ingredients needs elucidation, especially in light of equivalent frequencies of adverse effects in available randomized trials. When adverse effects are reported, concomitant use of other medications and product content analysis should also be reported so that other drugs, excipients, or contaminants may be scrutinized as potential causal factors.

Characteristics of future studies in humans should include longer and larger randomized trials; clinical as well as physiologic outcome measures; histologic outcomes; adequate blinding; detailed data about compliance and dropouts; systematic standardized surveillance for adverse effects; and attention to specific study populations (e.g., patients with hepatitis B virus [HBV], or hepatitis C virus [HCV], or mixed infection or coinfection with human immunodeficiency virus [HIV]), comorbidities, alcohol consumption, and potential confounders. There also should be detailed attention to preparation, standardization, and bioavailability of different formulations of milk thistle (e.g., standardized silymarin extract and silybin-phosphatidylcholine complex).

Precise mechanisms of action specific to different etiologies and stages of liver disease need explication. Further mechanistic investigations are needed and should be considered before, or in concert with, studies of clinical effectiveness. More information is needed about effectiveness of milk thistle for severe acute ingestion of hepatotoxins, such as occupational exposures, acetaminophen overdose, and amanita poisoning. [↑ TOP](#)

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