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

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Preface

The Agency for Healthcare Research and Quality (AHRQ), formerly the Agency for Healthcare 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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Contents

Summary........................................................................................................................................1

EVIDENCE REPORT

Chapter 1. Introduction ..................................................................................................................9
  Scope and Objectives .........................................................................................................................9
  Effects of Milk Thistle on Hepatic Disease .................................................................................9
  Clinical Adverse Effects of Milk Thistle ...................................................................................9
  Background ................................................................................................................................9
    The Plant ....................................................................................................................................11
    Historical Uses of Milk Thistle..........................................................................................11
    The Milk Thistle Industry ..................................................................................................12
  Chemistry and Pharmacokinetics of Milk Thistle ..............................................................13
  Mechanisms of Milk Thistle ....................................................................................................14
    Antioxidant Activity ..........................................................................................................14
    Toxin Blockade ..................................................................................................................15
    Enhanced Protein Synthesis ...............................................................................................15
    Antifibrotic Activity ...........................................................................................................15
    Other Postulated Mechanisms ............................................................................................16
  Current Preparations of Milk Thistle .......................................................................................16
  Challenges in Interpreting the Evidence ..................................................................................16

Chapter 2. Methodology ...............................................................................................................17
  Expert Input ...............................................................................................................................17
  Questions Addressed in Evidence Report ................................................................................17
  Literature Search and Selection Methods ................................................................................19
    Sources and Search Methods .............................................................................................19
    Selection Processes ............................................................................................................19
  Data Abstraction Process .........................................................................................................22
    Unpublished Data ...............................................................................................................22
  Data Analysis Process ...........................................................................................................22
    Exploratory Meta-Analysis ................................................................................................23

Chapter 3. Results .........................................................................................................................25
  Overview of the Evidence ..........................................................................................................25
  Milk Thistle Preparations and Doses .......................................................................................25
  Milk Thistle and Liver Disease ................................................................................................27
    Milk Thistle and Alcohol-Related Liver Disease ..............................................................27
    Milk Thistle and Chronic Liver Disease of Mixed Etiology .............................................27
    Milk Thistle and Viral Liver Disease ...............................................................................28
    Milk Thistle and Cirrhosis ...................................................................................................28
    Milk Thistle and Toxin-Induced Liver Disease ...................................................................29
    Milk Thistle and Cholestasis ............................................................................................30
    Milk Thistle and Primary Hepatic Malignancy ...............................................................30
  Effectiveness of Different Preparations of Milk Thistle ......................................................30
  Exploratory Meta-Analyses Results .......................................................................................31
Appendix C. Contributors

We owe a major debt of gratitude to the following groups of multidisciplinary experts from around the world who assisted in preparing this report: 10 national advisory panel members, 3 technical experts who helped define the scope and shape the content, 14 peer reviewers representing a variety of backgrounds and viewpoints, and 5 scientific authors who provided additional data from their studies.

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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).

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.

Methodology

Search Strategy

Eleven electronic databases, including AMED, CISCOM, 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.

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.

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.

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.

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.

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.

**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.

**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.
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.
Chapter 1. Introduction

Scope and Objectives

This evidence report about milk thistle was requested by the National Center for Complementary and Alternative Medicine, a component of the National Institutes of Health, and was contracted by the Agency for Healthcare Research and Quality. This chapter highlights the history of milk thistle, its chemistry, recent research, the variety in available commercial preparations, and challenges in conducting research and interpreting the evidence in humans. The evidence report is a systematic review that summarizes studies in humans that address the effects of milk thistle in treating liver disease of alcohol, viral, toxin, cholestatic, and primary malignancy etiologies. Figure 1 shows the evidence model, which was formulated by the national advisory and technical expert panels that guided the review.

Effects of Milk Thistle on Hepatic Disease

Results of trials comparing milk thistle preparations with placebo or other agents are presented. A formal summary of the evidence uses only available placebo controlled trials. Effects on the following outcomes are addressed: laboratory tests, histologic findings, morbidity, and mortality.

Clinical Adverse Effects of Milk Thistle

Various reported adverse effects, including dermatologic, gastrointestinal, and anaphylactoid reactions, are summarized.

Background

Milk thistle has been used since the time of ancient physicians and herbalists to treat a range of liver and gallbladder disorders, including hepatitis, cirrhosis, and jaundice, and to protect the liver against poisoning from chemical and environmental toxins, including snake bites, insect stings, mushroom poisoning, and alcohol.

Milk thistle’s history begins with its name. The scientific name for milk thistle is *Silybum marianum*: “Silybum” is the name Dioscorides gave to edible thistles,1 and “marianum” comes from the legend that the white veins running through the plant’s leaves were caused by a drop of the Virgin Mary’s milk. 1-4 While looking for a place to nurse the infant Jesus when leaving Egypt, Mary could only find shelter in a bower formed by the thorny leaves of the milk thistle.5 From this story was born the folk belief that the plant was good for nursing mothers.6 Other names that have been attributed to milk thistle include Marian thistle, Mary thistle, St. Mary’s thistle, Lady’s thistle, Holy thistle, sow thistle, thistle of the blessed virgin, Christ’s crown, Venus thistle, heal thistle, variegated thistle, and wild artichoke.

Milk thistle is a member of the aster or daisy family (*Asteracae*), which includes, in addition to asters and daisies, a host of other thistles and the artichoke.7 Milk thistle is one of the most important medical members of this genus.8
Figure 1. Evidence model: Milk thistle and liver disease
The Plant

Milk thistle is a tall plant that can grow up to 10 feet with thorny stems, dark glossy green leaves, and milky-white veins running throughout. Its most distinguishing feature is the large, bright purple flower sprouting at the top.\(^3,7,8\)

Historical Uses of Milk Thistle

For centuries, nearly every part of the plant—from root to hull—has been used in some way.\(^4,6\) In her famous book, Maud Grieve explained several ways the milk thistle can be eaten, including the heads like an artichoke, raw stalks (which are considered palatable and nutritious), and the leaves as a salad.\(^8\) She also quoted Bryant, who wrote in his *Flora Dietetica*, “The young shoots in the Spring, cut close to the root with part of the stalk on, is one of the best boiling salads that is eaten, and surpasses the finest cabbage. They were sometimes baked in pies. The roots may be eaten like those of Salsify.”\(^8\)

Milk thistle has also historically been used for animal feed. Grieve wrote that in parts of England, the leaves are called “pig leaves” because pigs liked them; also, the seeds are a favorite food of goldfinches.\(^8\) In Scotland, the leaves were used extensively as food for cattle and horses (the leaves were beaten and crushed to rid them of prickles) before the introduction of special green crops.\(^8\) The milk thistle prickles have also been used historically as a substitute for barbed wire.\(^8\) Despite this wide spectrum of perceived value, farmers considered it and other thistles a sign of untidiness and neglect.\(^8\)

Most sources on milk thistle, which is native to southern Europe (specifically Mediterranean areas) and Asia,\(^5\) put its beginning at 2,000 years ago.\(^1,2,6,9\) One of the earliest mentions of thistles in general is in the Bible (Genesis 3:18). In this verse, God told Adam and Eve when they were banished from the Garden of Eden that “thorns also and thistles shall it bring forth to thee.”

Some of the earliest people to use and write about milk thistle were ancient Greek and Roman physicians and herbalists, each of whom seemed to have their own name for the herb. Dioscorides called it “sillybon,” Pliny the Elder called it “sillybum,” and Theophrastus called it “pternix.”\(^5\) Dioscorides’ use of milk thistle is one of the oldest known references to the medicinal use of this plant. He suggested preparing it in a tea “for those that be bitten of serpents.”\(^10\) Another famous ancient herbalist, Pliny the Elder, wrote that mixing the juice of the plant with honey was good for “carrying off bile.”\(^1,9\)

Milk thistle is mentioned in several works from the Middle Ages, one of the first being in a record of old Saxon remedies, which claimed that “this wort if hung upon a man’s neck it setteth snakes to flight.”\(^8\) One of the best known herbalists from this time, John Gerard (1545-1612), recommended milk thistle for expelling melancholy and its related diseases (melancholy diseases were described in medicine in the Middle Ages as related to the liver and also called “black bile”).\(^8,10\) Another well known English herbalist, Nicholas Culpeper (1616-54), recommended milk thistle for several maladies: breaking and expelling stones, removing obstructions of the liver and spleen, treating jaundice and infections of the plague, and cleansing the blood.\(^8,9\)

Maud Grieve, who compiled her book of herbal information in 1931, quoted several early English herbalists on their love for and use of milk thistle. She reports that in 1694 Westmacott wrote of milk thistle, “It is a friend to the liver and blood: the prickles cut off, they were formerly used to be boiled in the spring and eaten with other herbs; but as the World decays, so
does the use of good old things and other more delicate and less virtuous brought in.” She also reports that John Evelyn wrote, “Disarmed of its prickles and boiled it is worthy of esteem, and thought to be a great breeder of milk and proper diet for women who are nursing.”

Although milk thistle’s use during the 17th century is most often associated with English herbalists, many monasteries cultivated and used the plant for medicinal purposes as well. St. Hildegard von Bingen (1098-1179) recommended the roots, herbs, and leaves for swelling and erysipelas.

Milk thistle was popular with German herbalists and scientists, also. Otto Brunfels (1488-1534), Hieronymus Bock (1498-1554), Jacob Theodorus (1520-90), Adam Lonicerus (1528-86), and Pietro Andrea Mattioli (1501-77) all recommended milk thistle for treating liver diseases. Another German physician from the 19th century, Johannes Gottfried Rademacher, developed a tincture made from milk thistle seeds for his liver patients. Rademacher’s Tincture is an ethanol extract from the seeds used for hepatosplenic disorders.

In the United States, milk thistle enjoyed popularity in the 19th century with the Eclectics movement, an officially recognized branch of North American medicine that predominantly used Native American herbs. The Eclectics used milk thistle for varicose veins, menstrual difficulty, and congestion of the liver, spleen, and kidneys. Milk thistle was also used as part of the naturopathic medical tradition and Native American medical practices. So popular was milk thistle that a tincture of the whole plant was listed in the first United States Homeopathic Pharmacopoeia.

Available history does not seem to tell us how (i.e., by what anecdotal or empirical evidence) milk thistle came to be advised for liver and gallbladder problems. Although milk thistle is most often associated with treating liver disorders, physicians have tried to apply its curative properties to other ailments, including stimulating breast-milk production and bile secretion, treating depression, and protecting against the poisonous mushroom Amanita phalliodes and other environmental toxins.

The Milk Thistle Industry

Milk thistle enjoys significant popularity in the current herbal industry. The World Health Organization estimates that 4 billion people (nearly two-thirds of persons in developing countries) use herbal medicine for some aspect of health care. Herbal medicine is a major component in all indigenous peoples’ traditional medicine and a common element in Ayurvedic, homeopathic, naturopathic, traditional oriental, Chinese, and Native American Indian medicine.

Milk thistle has been available in Europe since 1969, and more than $180 million worth of products were sold in one recent year. In Germany alone, milk thistle was the 11th most frequently prescribed monopreparation herbal, with $16 million (U.S. dollars) in sales in 1996. In the United States, the herbal market was estimated at about $1.6 billion in 1994 with some projections reaching about $3.5 billion in 1997. Of the 14 top-selling herbal supplements in the United States in 1997 in food, drug, and mass-market retail outlets, milk thistle ranked 13th (more than $3 million). However, it is difficult to determine the actual size of the herbal market because herbal products were formerly sold mostly through channels of distribution normally not subject to econometric tracking services (e.g., health food stores, mail order, multilevel marketing organizations).

Attesting to milk thistle’s popularity in this country, a recent poll of patients attending a hepatology clinic at Oregon Health Sciences University found that 31 percent of patients were
using over-the-counter “alternative agents” for the therapy of their liver disease. The most commonly used nontraditional therapy was milk thistle, and over 50 percent of those patients felt they had experienced subjective improvement in their symptoms. In the United States, milk thistle is now being tested for safety by the U.S. National Toxicology Program, along with aloe vera, ginseng, and kava.

**Chemistry and Pharmacokinetics of Milk Thistle**

Flavonoids, of bioflavonoids, are a ubiquitous group of polyphenolic substances that are present in most plants and concentrated in seeds, fruit skin or peel, bark, and flowers. A great number of plant medicines contain flavonoids, which have been reported as having antibacterial, anti-inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, antithrombotic, and vasodilatory actions. The structural components common to these molecules include two benzene rings on either side of a three-carbon ring. Multiple combinations of hydroxyl groups, sugars, oxygens, and methyl groups attached to these structures create the various classes of flavonoids: flavanols, flavanones, flavones, flavan-3-ols (catechins), anthocyanins, and isoflavones. Flavonoids have been shown in a number of studies to be potent antioxidants, capable of scavenging hydroxyl radicals, superoxide anions, and lipid oxygen radicals due to lipid peroxidation.

As reviewed by Bindole, et al., in 1968 Wagner isolated and called the flavonoid complex in milk thistle “silymarin.” Silymarin, the active component of milk thistle responsible for its putative hepatoprotective actions, is a mixture of silybin (also known as silybinin or silibinin), silychristin (or silicristin), and silydianin (also silidianin). Silybin is the most prevalent of the three (about 50 percent of silymarin) and the most biologically active. Silydianin is very heavily metabolized, whereas silychristin is only absorbed to a very slight extent in the gastrointestinal tract. Silymarin is found throughout the entire plant, but concentrations of silymarin are highest in the seeds and leaves. It is typically extracted with 95 percent ethyl alcohol, yielding a bright yellow fluid (“flavonoids” is derived from “flavus,” meaning yellow) or acetone. However, the leading manufacturer of milk thistle, (Madaus, a German company) prepares its product Legalon® with ethylacetate as the primary solvent. Subsequent research in Germany has revealed other constituents in milk thistle, including dehydrosilybin, desoxysilydianin (silymonin), silandrin, and silybinomer.

German research initially led to a standardized milk thistle extract of 70 percent silymarin. Standardized silymarin extract now contains 70 to 80 percent silymarin. Madaus’ Legalon® is sold in tablets containing 70 or 140 milligrams (mg) silymarin and is given in a dose of one to two tablets up to three times daily, with a maximum dosage of 420 mg. Madaus now outsources production of crude silymarin to the Italian firm Indena in Milan. This crude extract is made exclusively for Madaus according to their standards, cannot be sold to other companies, and is further processed back in Madaus’ facilities to produce the extract sold as Legalon®. Silymarin preparations, although standardized on silymarin content, differ regarding the in vitro release of silymarin or silybin; as a result, the availability of silybin for absorption differs also. In two studies of nine and six silymarin preparations, respectively, release of silybin from Legalon® was more rapid and higher compared with other preparations.

From standardized silymarin, silybin can be isolated and complexed with phosphatidylcholine. This formulation, called IdB 1016, is now sold as Silipide® (Inverni, Italy) and is expressed as silybin equivalents. Silipide® has been shown to be more bioavailable
than standardized silymarin after oral ingestion in normal volunteers, cirrhotics, and patients after cholecystectomy.\textsuperscript{9,25-28} The bioavailability of silybin in Silipide® is approximately tenfold greater than the silybin content of standard milk thistle preparations.\textsuperscript{5}

Various methods have been developed to identify the constituents of silymarin, including thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), colorimetry, and electrophoresis.\textsuperscript{18,29-34} There are two species of the silymarin plant: \textit{S. marianum} (L.) Gaertn. and \textit{S. eburneum} Coss. Dur. Of the \textit{S. marianum} species, there are two varieties: the common purple flower and the much less common white flower. HPLC can distinguish between the two species.\textsuperscript{28} There are also two chemotypes for the purple variety, which can be distinguished by TLC and HPLC. One has a relatively high silybin content and a high silybin:silydianin ratio. The other has a relatively high silydianin content and low silybin:silydianin ratio. They appear to be stable chemotypes with characteristic silybin and silydianin contents and proportions for several generations under the same field conditions.\textsuperscript{28} In summary, chromatography can thus far distinguish four biochemical profiles: three for \textit{S. marianum} and one for \textit{S. eburneum}. Differences are smaller between \textit{S. marianum} and \textit{S. eburneum} than between the white and purple varieties of \textit{S. marianum}.

**Mechanisms of Milk Thistle**

Currently, milk thistle (silymarin, silybin, and Silipide®) is primarily advocated as a therapeutic and hepatoprotective agent, especially in the settings of cirrhosis, chronic hepatitis, alcohol consumption, and environmental toxin exposure. Silymarin, silybin, and Silipide® have multiple mechanisms of action that may be hepatoprotective, including antioxidant activity, toxin blockade, enhanced protein synthesis, and antifibrotic activity.

**Antioxidant Activity**

Silymarin is thought to have antioxidant activity in the liver, as well as the small intestine and stomach. As an antioxidant, this compound may reduce free radical production and lipid peroxidation in the setting of hepatotoxicity. Lipid peroxidation is the end result of unstable free radicals’ damage to membrane lipids. These membranes contain fatty acids that are transformed to lipoperoxidases, peroxides, and lipidic hydroperoxides. Malondialdehyde is a biproduct of phospholipid turnover and linoleic acid and is frequently used in clinical and in vitro studies as a surrogate marker for oxidation activity. Multiple in vitro studies have demonstrated lipid peroxidation inhibition using malondialdehyde as a marker in rat hepatic microsomes and mitochondria.\textsuperscript{35-38} Furthermore, the phenolic conformation of silymarin is thought to permit the formation of stable compounds from hydroxyl and oxygen radicals.\textsuperscript{39,40} Primary defenses against oxidation or free radical production include glutathione, catalase, and superoxide dismutase. In the setting of an acute toxic event, if stores of these compounds are depleted in intracellular or extracellular (sinusoidal) compartments, oxidative injury is unimpeded.\textsuperscript{41-43}

The phenol structure of silymarin led investigators to postulate that silymarin might have potential activity as an antioxidant. In vivo studies in rats indicate that silymarin can reduce the free radical load. One study exposed rats to acetaminophen at toxic doses, and then measured levels of reduced glutathione and superoxide dismutase in experimental and control rats. In another study, mice exposed to acetaminophen at toxic doses had increased levels of reduced glutathione and superoxide dismutase when treated with silymarin compared with the levels in
controls. Another study demonstrated preserved hepatic glutathione stores and improved reduced:oxidized glutathione ratios in rats exposed to acetaminophen and ethyl alcohol at high doses when compared with those in controls. Similarly, in humans, investigators have demonstrated increases in serum glutathione peroxidase and erythrocyte and lymphocyte superoxide dismutase.

Silymarin may also protect hepatocyte-lipid membranes. Studies demonstrated that silymarin can inhibit cell lysis as measured by changes in alanine aminotransferase levels when exposing isolated hepatocytes to carbon tetrachloride and galactosamine.

**Toxin Blockade**

Studies demonstrated improvements in cytosol liver and histologic markers in animals receiving silymarin compared with those in controls for an array of hepatotoxins including carbon tetrachloride, galactosamine, thioacetamide, ethanol, and acetaminophen. The mechanism of action is thought to be mediated by competitive inhibition, membrane stabilization, and antioxidant activity. However, in many studies the mechanism was not clearly identified. Silymarin can bind to liver cell membrane receptors to protect cells from toxins. One study demonstrated this effect using the death cap mushroom, Amanita phalloides. The toxins in this fungus are amanitin and phalloidin. Several studies showed that silymarin competes with the toxin for cell membrane receptor sites, thus reducing the effect of the toxin.

**Enhanced Protein Synthesis**

Regeneration of hepatocytes is necessary for hepatic recovery from acute or chronic insults. In chronic injury, fibrosis occurs simultaneously with regeneration; the ultimate outcome is determined by which process dominates. Several studies identified mechanisms through which silybin may facilitate hepatocyte regeneration. In several rat studies, silybin appeared to stimulate ribonucleic acid (RNA) polymerase I and ribosomal RNA. This effect leads to more rapid formation of ribosomes, which in turn increases protein synthesis. The exact mechanism of how RNA polymerase I is stimulated is unclear. One study demonstrated that silymarin binds to a steroid receptor, and it is hypothesized that structural similarity with steroids permits binding. Silymarin then, like steroids, may be able to modulate RNA synthesis. Additionally, one study in rats suggested that silymarin can also enhance deoxyribonucleic acid synthesis and, therefore, possibly enhance hepatocyte regeneration. Thus far, one study demonstrated hepatocyte regeneration in rats with silymarin.

**Antifibrotic Activity**

To date, the evidence for antifibrotic activity comes largely from animal studies. Reportedly, human trials are in progress with Legalon® that are examining antifibrotic activity. According to Madaus, Legalon® administered orally in a rat biliary fibrosis model reduced hepatic collagen accumulation and levels of a serum marker for fibrosis. Another study reportedly slowed down regeneration of procollagen RNA by silymarin in rat livers.
Other Postulated Mechanisms

Milk thistle reportedly reduced leukotriene formation through noncompetitive inhibition of lipoxygenase, thereby suggesting possible anti-inflammatory effects.52

Current Preparations of Milk Thistle

Because silymarin is poorly soluble in water, teas are considered to have a less than 10 percent bioavailability. Since absorption of silymarin from the gastrointestinal tract is only 20 to 50 percent, oral tinctures, or alcohol-extracted preparations, are considered suboptimal, and effective oral therapy is assumed to require concentrated products. A water-soluble derivative of silybinin (silybinin dihemisccinate disodium) is available from Madaus, Germany, and is used parenterally in Europe for deathcap mushroom (Amanita phalloides) poisoning.53

The most common oral formulation is capsules containing powdered seeds or a seed extract. Formulation includes extraction with alcohol, filtration, and evaporation and may also include pressing, heat drying, and blending with other compounds. Some brands may add choline, inositol, tumeric extract, artichoke extract, whole herb powders, dandelion, licorice, curcuma, boldo, iron, or Vitamins A and C. One formulation is combined with kutkin, the roots and rhizome of Picrorhize kurroa, a perennial herb found only in the higher mountains of the northwestern Himalayas. Other concentrated oral formulations include tablets and softgel capsules. Silipide® is the complex of one part silybin and two parts phosphatidycholine from soybean phopholipids (lecithin), for which standardization is expressed as silybin equivalents.

Challenges in Interpreting the Evidence

The primary difficulty in interpreting the available evidence is the quality of study designs and the quality of published reports.9,54 Quality of trials is hampered by heterogeneity in etiologies, chronicity, and severity of liver disease both within and between trials; adequacy of randomization; amount and duration silymarin dosing; assessment of alcohol use during trials; types of controls; and recruitment and sampling strategies. Only placebo-controlled trials permit assessment of the liver’s intrinsic regenerative capacity when the source of injury is removed (e.g., alcohol and resolution of hepatitis). In addition, even if investigators attended to these important issues of study design and methods, there is a very problematic lack of information in many published reports. Much information is lacking on type and homogeneity of liver disease, recruitment settings and methods for study subjects, chronicity and severity of liver disease, dose and duration of treatment with silymarin, whether statistical comparisons are within or between intervention and control groups, exactly what statistical comparisons were done, and the actual results. Few studies report screening subjects for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV), and screening and systematic monitoring for alcohol intake. Few trials adjust for these and other potential confounders; most trials are small, and randomization sometimes did not adequately balance known potential cofounders. Little information is available regarding compliance with milk thistle and placebo and adequacy of blinding. Many of the trials are small, and Type II errors cannot be excluded. Much of the trial data are in languages other than English, raising problems with retrieving the evidence, identifying peer-reviewed journals, and the potential risks of error in translating the information and interpreting the data.9,54
Figure 1. Evidence model: Milk thistle and liver disease

Individuals with:
- Viral hepatitis
  - Acute Hep A
  - Hep B
  - Hep C
  - Chronic Hep A
  - Hep B
  - Hep C
  - Cirrhosis

- Alcoholic liver disease
  - Acute
  - Chronic
  - Cirrhosis

- Toxin- and drug-induced liver disease
  - Acute
  - Chronic
  - Cirrhosis

- Cholestasis
  - Acute
  - Chronic
  - Cirrhosis
  - Liver failure

- Primary hepatic malignancy
  - Pregnancy-related
    - Hepatoma
  - Not pregnancy-related
    - Cholangiocarcinoma

Silybum marianum
- Powdered seeds
- Seeds mash/liquid
- Other preparations

Silybum marianum constituents
- Silymarin complex (silybin + silydianin + silychristin)
- Single agent silybin
- Combined with other compounds (e.g., phosphatidylcholine)

Mechanisms
- Antioxidant
- Protein synthesis
- Toxin blockade through membrane stabilization
- Other activities (e.g., antifibrotic and antiinflammatory)

Effects on pathology and physiology
- Biochemical markers
- Structural changes: Cirrhosis, fatty infiltration
- Enzyme failure: Toxemia

Clinical outcomes
- Overall mortality and morbidity
- Liver mortality and morbidity
- Quality of life
- Other unexpected beneficial effects
- Clinical adverse effects

Other health promoting actions
Chapter 2. Methodology

This section describes methods used to identify key questions; literature search, retrieval, and selection strategies; and processes used for abstracting and analyzing studies.

Expert Input

We owe a major debt of gratitude to the following groups of multidisciplinary experts from around the world who assisted in preparing this report: 10 national advisory panel members and 3 technical experts who helped define the scope and shape the content, 14 peer reviewers representing a variety of backgrounds and viewpoints, 5 scientific authors who provided additional data from their studies, and 12 staff members of the San Antonio Evidence-based Practice Center and the San Antonio Veterans Evidence-based Research, Dissemination, and Implementation Center, a Veterans Affairs Health Service Research and Development Center of Excellence. Their names are listed in the “Appendix C. Contributors” section of this report.

Questions Addressed in Evidence Report

The national advisory and technical expert panels used the evidence model (Figure 1) and a modified Delphi process to identify clinically important questions that the evidence report should address (Table 1). Per the evidence model (see Figure 1), liver disease could be of viral, alcohol, toxin, or malignancy etiologies. The spectrum of level of disease included acute, chronic, cirrhosis (compensated), and liver failure (decompensated cirrhosis or fulminant toxic or viral disease).

Cholestatic liver disease and primary malignancy were included in the evidence model and questions to be addressed because, a priori, we did not know if there would be evidence available for review. The final questions and types of studies deemed appropriate to answer the questions (selection criteria) are given in Table 1.
Table 1. Key questions and selection criteria for evidence
Literature Search and Selection Methods

Sources and Search Methods

English and non-English citations were identified to July 1999 from the electronic databases cited in Table 2; references of pertinent articles and reviews; Madaus, Germany; and technical experts. An update search limited to PubMed was conducted in December 1999. Database searching used maximally sensitive strategies to identify all papers on milk thistle and treatment or prevention of liver disease. Titles, abstracts, and keyword lists of the 11 sources in Table 2 were searched using the following terms that include Latin names for milk thistle and its constituents (“.tw” indicates text word searches, “/” indicates key word searches, and “$” indicates a truncation within a text word). Search strategies are included in Appendix A.

- carduus marianus.tw.
- milkthistle$.tw.
- silydianin$.tw.
- legalon$.tw.
- sily$.tw.
- silymarin$.tw.
- mariendistel.tw.
- silybin$.tw.
- silymarin$/
- milk thistle$.tw.
- silybum marianum.tw.
- silymarin.tw.
- milk-thistle$.tw.
- silybum$.tw.
- silymarin/
- milk-thistle$.tw.
- silychristin$.tw.

After these materials were reviewed and relevant studies obtained and abstracted, an updated search to November 1, 1999, was conducted using MEDLINE and EMBASE.

Selection Processes

At least two independent reviewers scanned the titles and abstracts of all records identified from the search using the selection criteria given in Table 1. For each formulated question, selection criteria specified the types of participants, interventions, control groups, outcomes, and study designs that were deemed appropriate. Figure 2 schematically presents the selection process. Of 1,727 records, reviewers excluded 1,505 with certainty when screening titles and abstracts. Most of these were in vitro studies, involved animals, did not provide primary data regarding effectiveness, were duplicate reports, or did not meet design inclusion criteria. When the full texts of the remaining 215 (7 were unobtainable) were screened, 164 more were excluded for the same reasons. Of the 51 records meeting selection criteria, 33 were prospective trials, and 18 were reports of adverse effects.
Table 2. Electronic sources searched
Figure 2. Selection process
Initially, we planned to limit efficacy evidence to randomized controlled trials (RCTs) comparing milk thistle with placebo, no milk thistle, or another active agent. Ultimately, we included evidence from prospective placebo-controlled trials or cohort studies for several reasons. First, there were scant data, and it was thought that evidence from studies other than randomized trials might provide useful preliminary information. Second, several reportedly “randomized” trials had dissimilar numbers of subjects among the study arms, raising the possibility that they were not randomized and not of significantly different quality than other prospective controlled studies. The search for evidence was not repeated at the point that selection criteria were broadened, because the search had been designed to detect all studies of milk thistle regardless of their design.

**Data Abstraction Process**

Two independent persons with clinical and methodologic expertise abstracted data; they were not blinded either to study titles or to authors’ names. Previous research indicates such blinding does not enhance validity of results, and it is time and labor intensive to prepare fully masked publications. Items related to the internal validity of studies that were assessed included whether the trial was randomized, adequacy of randomization (method and concealment of assignment), whether the trial was single or double blind, whether intervention and control groups were adequately matched, identification of cointerventions such as diet or other medications, and the number of dropouts. Disagreements in abstractions were resolved by consensus. Formal quality scores were not done because of controversy as to how to handle and weight such scores statistically. Elements of study quality are given in the evidence tables. If not known, then no information or “not given” is noted in the evidence tables. After the abstraction training phase, no further reliability assessment was conducted.

One research nurse and one physician with expertise in methodology abstracted studies addressing adverse effects. Items addressing adverse effects that were abstracted included study design (case report, case series, case control, cohort, controlled trial) and type of specific adverse effect. Several explicit criteria aimed at assessing drug adverse effect causality were assessed, including appropriate temporal relationship, lack of apparent alternative causes, known toxic concentrations of the drug at the time of the appearance of the symptom, disappearance of the symptom with drug discontinuation, dose-response relationship, and reappearance of the symptom if the drug was readministered.

**Unpublished Data**

For reports published as abstracts, we excluded those for which we were unable to identify a complete subsequent publication by a repeat search of MEDLINE and EMBASE for any of the abstract authors. When published studies met selection criteria but did not report important design features or outcome data, this unpublished information was requested from the authors.

**Data Analysis Process**

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 or intervention administration, and study designs. Relationships between clinical outcomes, participant characteristics, and methodologic characteristics are presented in evidence tables and graphic summaries such as forest plots.

Primary outcomes in studies were measured with continuous rather than categorical variables. We used the standardized mean differences between treatment and comparison group scores as the effect size measure for each study. Hedges’ $g$ was used to compute the standardized mean difference for each trial:

$$g_i = \frac{\bar{x}_T - \bar{x}_C}{s_{\text{pooled}}}$$

where, for a given trial $i$, $\bar{x}_T$ and $\bar{x}_C$ are the mean clinical outcome scores for the treatment group and comparison group, respectively; $s_{\text{pooled}}$ is the pooled standard deviation for the difference between the two means. $^57$ These estimates were adjusted for between-group differences at baseline and for small sample bias. $^57$ Adjustment for baseline differences was accomplished by calculating an “effect size” at baseline; by definition, it should be zero if study groups were well matched. When a nonzero “effect size” at baseline was found, outcome effect sizes were adjusted by subtracting the baseline effect size.

Published reports seldom provided estimates of $s_{\text{pooled}}$. One of three strategies was used to estimate $s_{\text{pooled}}$ when the authors did not directly provide it. First, the individual group variances were used to estimate $s_{\text{pooled}}$. If these data were not reported, the pooled variance was back-calculated from either the test statistic or the $p$ value for differences at followup. $^58$ If neither was possible, a mean variance derived from studies of similar size was used. Studies in which the pooled variance was calculated using either of the two latter methods were flagged in the event the magnitude of the effect size resulted in the study being identified as a potential outlier in the analysis of heterogeneity.

**Exploratory Meta-Analysis**

Meta-analysis was used as an exploratory tool to help identify patterns of findings. Prospective placebo-controlled randomized trials using albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gammaglutamyl transpeptidase (GGTP), malondialdehyde (MDA), alkaline phosphatase (alk phos), prothrombin time (PT), Child’s score (a score or classification system for chronic liver disease), and histologic and survival outcomes were quantitatively pooled by clinical outcome using meta-analysis. Subgroup analyses were conducted for trials that included patients with the following: chronic alcoholic liver disease, acute viral liver disease, chronic viral liver disease, mixed liver disease (all chronic), cirrhosis, and alcoholic cirrhosis.

We adopted the DerSimonian and Laird random-effects model to estimate the pooled measures of treatment efficacy. $^{59,60}$ If there is no substantial heterogeneity among the trials, the random-effects estimator reduces to the classical fixed-effects estimate. When significant heterogeneity exists, the random-effects model incorporates the statistical heterogeneity into the summary estimate and confidence interval. The random-effects model confidence interval is wider than the fixed-effect model confidence interval, when substantial heterogeneity exists, making the random-effects model more conservative.
Heterogeneity among trials was tested with a standard chi-square test (using a p value greater than 0.1 as evidence of heterogeneity), Galbraith plots, and funnel plots. A Galbraith plot is a graphic method used to complement the statistical assessment of heterogeneity and is particularly useful when the number of studies is small.\textsuperscript{60} The position of each study along the two axes gives an indication of the weight allocated in the meta-analysis. The vertical axis (a Z statistic equal to the effect size divided by its standard error) gives the contribution of each study to the Q (heterogeneity) statistic. Points outside the confidence bounds are those studies that have a major contribution to heterogeneity; in the absence of heterogeneity, all points would be expected to be within the confidence bounds. Funnel plots used Begg’s rank order correlation test.\textsuperscript{61} STATA 6.0\textsuperscript{®} (STATA Corporation\textsuperscript{®}) was used to perform all analyses and produce the graphic output.\textsuperscript{62} Specifically, the meta command was used to compute and graph the random-effects model estimates,\textsuperscript{63} the “galbr” command to assess heterogeneity and produce Galbraith plots,\textsuperscript{62} and the metabias command to examine publication bias.\textsuperscript{64}

Effect sizes were converted to clinical laboratory units to aid in interpreting effect-size standard deviation units. As noted above, the effect-size statistic is calculated by dividing the between-group difference by the pooled standard deviation of the two groups. Since both numerator and denominator are expressed in the original laboratory units (e.g., milligrams per deciliter [mg/dL]), the units cancel out, and the effect size statistic is therefore “unitless.” Effect sizes can be back-converted to a clinical laboratory value expressed in the original unit (e.g., mg/dL) by multiplying the effect-size value by a standard-deviation value. The statistical significance of the values (effect sizes or converted values) does not change; however, the magnitude of the “converted effect” will vary up or down depending on the magnitude of the standard deviation used.

Conversion of effect sizes to clinical laboratory units should not be interpreted as “true” values; conversions are presented for the single purpose of enhancing the interpretation of effect-size standard-deviation units.

Lacking population standard-deviation values (if available, they could be used), the investigator chose to use the “average” standard-deviation value for the pooled studies within each group. Two “averages” were examined: a weighted pooled standard deviation across studies (weighted by sample size) and the median pooled standard deviation. When the two values were substantially different (representing skewness), the median value was chosen. When the values were similar (or when only two studies provided pooled standard deviation estimates), the weighted pooled standard deviation value was used to convert effect sizes. Weighted average standard deviations that were used to convert effect sizes to clinical laboratory units were: albumin (0.74 grams per deciliter [g/dL]), bilirubin (0.32 g/dL), aspartate aminotransferase (44.77 units per liter [U/L]), alanine aminotransferase (36.02 U/L), gammaglutamyl transpeptidase (153.94 U/L), malondialdehyde (6.65 millimoles per milliliter [mmol/mL]), alkaline phosphatase (101.01 U/L), prothrombin time (17.40 seconds), and Child’s score (2.55 units).
<table>
<thead>
<tr>
<th>Questions About Efficacy</th>
<th>Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In adults with alcohol-related liver disease (acute, chronic, cirrhosis, or liver failure), does oral ingestion of milk thistle supplements compared with no supplement, placebo, other oral supplements, or drugs alter physiologic markers of liver function, reduce mortality or morbidity, or improve quality of life?</td>
<td><strong>Study type:</strong> Initially, randomized controlled trial, then changed to any prospective controlled trial.</td>
</tr>
<tr>
<td><strong>Participants:</strong> Humans</td>
<td><strong>Intervention group:</strong> Supplemental milk thistle</td>
</tr>
<tr>
<td><strong>Control group:</strong> Placebo, no supplement, other oral supplements, drugs</td>
<td><strong>Outcomes (physiologic):</strong> Laboratory or histologic assessment of in vivo liver function</td>
</tr>
<tr>
<td><strong>Outcomes (clinical):</strong> Morbidity, mortality, hospitalization, quality of life, symptoms, Child’s score (a score or classification system for chronic liver disease)</td>
<td></td>
</tr>
<tr>
<td>2. In adults with viral hepatitis or its sequel (acute viral hepatitis, chronic active viral hepatitis, cirrhosis, or liver failure), does oral ingestion of milk thistle supplements compared with no supplement, placebo, other oral supplements, or drugs alter physiologic markers of liver function, reduce mortality or morbidity, or improve quality of life?</td>
<td></td>
</tr>
<tr>
<td>3. In adults with toxin- or drug-induced (other than alcohol) liver disease (acute, chronic, cirrhosis, or liver failure), does oral ingestion of milk thistle supplements compared with no supplement, placebo, other oral supplements, or drugs alter physiologic markers of liver function, reduce mortality or morbidity, or improve quality of life?</td>
<td></td>
</tr>
<tr>
<td>4. In adults with cholestasis (pregnancy-related or not pregnancy-related), does oral ingestion of milk thistle supplements compared with no supplement, placebo, other oral supplements, or drugs alter physiologic markers of liver function, reduce mortality or morbidity, or improve quality of life?</td>
<td></td>
</tr>
<tr>
<td>5. In adults with primary hepatic malignancy (hepatoma or cholangiocarcinoma), does oral ingestion of milk thistle supplements compared with no supplement, placebo, other oral supplements, or drugs alter physiologic markers of liver function, reduce mortality or morbidity, or improve quality of life?</td>
<td></td>
</tr>
<tr>
<td>6. Do different preparations vary in effectiveness regarding the above disease states and outcomes?</td>
<td></td>
</tr>
<tr>
<td>Questions About Chemical Profiling</td>
<td>Selection Criteria</td>
</tr>
<tr>
<td>1. What are the constituents of commonly available preparations of silymarin that have been used in studies?</td>
<td><strong>Study type:</strong> Chemical profiling</td>
</tr>
<tr>
<td>Questions About Harms</td>
<td>**Selection Criteria</td>
</tr>
<tr>
<td>1. What are the common symptomatic adverse effects of milk thistle, and what is their frequency?</td>
<td><strong>Study type:</strong> Randomized controlled trial, cohort study, case series study, or case report</td>
</tr>
<tr>
<td><strong>Participants:</strong> Humans</td>
<td><strong>Intervention group:</strong> Supplemental milk thistle</td>
</tr>
<tr>
<td><strong>Control group:</strong> Not required</td>
<td><strong>Outcomes:</strong> Any reported adverse effect</td>
</tr>
<tr>
<td><strong>Outcomes (clinical):</strong> Morbidity, mortality, hospitalization, quality of life, symptoms, Child’s score</td>
<td></td>
</tr>
<tr>
<td>2. What common serious adverse effects of milk thistle have been established for standard doses or large single doses, and what is their frequency?</td>
<td></td>
</tr>
<tr>
<td>3. What uncommon serious adverse effects of milk thistle have been established for standard doses or large single doses, and what is their frequency?</td>
<td></td>
</tr>
<tr>
<td>Electronic Database</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AMED (Alternative and Allied Medicine Database)</td>
<td>This database contains 100,000 references from 400 journals on alternative and complementary medicine going back to 1985.</td>
</tr>
<tr>
<td><em>Searched from 1985 to October 1998</em></td>
<td></td>
</tr>
<tr>
<td>CINAHL (Cumulative Index to Nursing and Allied Health Literature)</td>
<td>This database includes citations from over 500 biomedical and popular sources, including National League of Nursing and American Nurses Association publications, covers publications from 1982 to the present, and is considered the premier nursing database.</td>
</tr>
<tr>
<td><em>Searched from 1984 to July 1999</em></td>
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<tr>
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<td>This database contains over 34,000 references and combines data from MEDLINE, AMED, and other specialist European databases.</td>
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<tr>
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<td>Cochrane Library (<a href="http://www.cochrane.org">http://www.cochrane.org</a>)</td>
<td>These databases contain references of randomized controlled trials and systematic reviews identified from electronic bibliographic sources and hand searching of multiple journals and symposia or meeting proceedings.</td>
</tr>
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<td>DARE (Database of Reviews of Effectiveness) (<a href="http://www.york.ac.uk/inst/crdl/">http://www.york.ac.uk/inst/crdl/</a>)</td>
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<tr>
<td>Dissertation Abstracts</td>
<td>This library indexes doctoral dissertations and masters abstracts from more than 1,000 institutions.</td>
</tr>
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<td><em>Searched from 1961 to December 1998</em></td>
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</tr>
<tr>
<td>EMBASE</td>
<td>This database contains biomedical and pharmaceutical citations and is considered the premier biomedical database in Europe.</td>
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<tr>
<td><em>Searched from 1988 to July 1999</em></td>
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<tr>
<td>MEDLINE (PubMed)</td>
<td>These databases (MEDLINE and PubMed) index almost 4,000 international biomedical journals from 1966 to the present, includes references from Index Medicus, International Nursing Index, and Index to Dental Literature, and is considered the premiere biomedical database in the United States.</td>
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<tr>
<td><em>Searched from 1966 to July 1999</em></td>
<td><em>PubMed searched July 1999 to November 1999</em></td>
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<td>MICROMEDEX contains:</td>
<td>This database provides a major source for drug, poison, and acute care information.</td>
</tr>
<tr>
<td>DRUGDEX Product Index (drug ingredients)</td>
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<td>POISONDEX/IDENTIDEX (toxicology)</td>
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<td>DRUG-REAX (interactive drug interactions)</td>
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<td><em>Searched July 1999</em></td>
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<td>NAPRAERT (Natural Products Alert)</td>
<td>This database contains records from 1650 to the present on natural products, including the pharmacology, biologic activity, taxonomic distribution, ethno-medicine and chemistry of plant, microbial, and animal extracts.</td>
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<td><em>Searched September 1999</em></td>
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<td>This database contains 8,800 references from approximately 300 journals worldwide on toxicology, pharmacology, and therapeutic uses for natural compounds and on isolation of natural compounds from plant material.</td>
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<td>Science Citation Index</td>
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<tr>
<td><em>Searched from January 1990 to March 1999</em></td>
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</tbody>
</table>
Figure 2. Selection process

1,727 total records

1,505 records excluded

7 unobtainable records

215 records retrieved

51 records of primary data included

164 records excluded

18 studies of adverse effects

33 trials
Chapter 3. Results

Overview of the Evidence

Sixteen prospective trials were identified. Fourteen were placebo-controlled, randomized, and single- or double-blind trials (Evidence Table 1). Two were placebo-controlled prospective studies (randomized trial and cohort) with unclear blinding (Evidence Table 2).

In addition, 16 reports of 17 trials were identified that used nonplacebo controls (Evidence Table 3). The study by Flisiak and Prokopowicz (1997)\(^{65}\) is described in Evidence Table 3 as two separate trials for convenience because it compared silymarin with two different controls (misoprostol and no treatment) and because reported methods did not seem consistent for the two “substudies.” Nonplacebo-controlled trials are not considered further or discussed in detail in evaluating milk thistle’s efficacy because control interventions were diverse and spanned “other hepatoprotective medications,” misoprostol, ursodeoxycholic acid, comparisons with different doses or formulations of silymarin, “traditional therapy and diet,” multivitamins, a 12-component cocktail that included steroids, and no treatment.

Finally, two trials evaluated milk thistle as prophylaxis against hepatotoxic effects of antituberculosis drugs or tacrine (Evidence Table 4). These trials did not meet selection criteria for evaluating milk thistle’s efficacy because patients did not have liver disease at baseline. However, their results are provocative, and they are discussed in this report.

The term “liver function tests,” when used most precisely, refers to laboratory tests of liver function (e.g., bilirubin, albumin, and prothrombin time) and does not include aminotransferases. However, for this report, we will use the more common vernacular interpretation that includes all tests referent to liver status.

Again, interpreting available evidence and meta-analysis is compromised by poor study design and poor reporting of published studies. Across the trials there is heterogeneity in, and lack of information about, the spectrum of liver disease, etiology, severity, and chronicity; preparations and doses of milk thistle; duration of intervention; assessment of compliance; effectiveness of blinding; followups; dropouts; and statistical analyses (see Evidence Tables 1 through 4). Information is scant about screening for alcohol intake, HBV, HCV, and HIV status at baseline, as well as explicit monitoring of alcohol intake during studies. All of these factors can affect the course of liver disease and potential efficacy of milk thistle.

Information on other potential confounders (e.g., comorbidities and severity of liver disease at baseline) is also rarely reported. No information was given regarding whether oral solid dosage formulation used in the trial met any criteria for in vitro dissolution standards. The precision of the available evidence did not measure up to the precision regarding etiology, severity, and chronicity in the a priori evidence questions.

Milk Thistle Preparations and Doses

We will use the term “milk thistle” loosely for summarizing results. By “silymarin,” we mean the extract of seeds, containing silybin, silychristin, and silydianin, which may or may not have been standardized to percent silymarin in the reports of published trials and for which silybin is the primary component. By Silipide\(^{®}\), we mean a silybin-phosphatidylcholine complex, but again studies may not have reported standardization results. Among the 16
placebo-controlled studies, Legalon® (Madaus) was used in 12. Of these 12 studies, the dose varied from 240 to 800 milligrams per day (mg/d) in 8 trials, duration varied from 7 days to 6 years, and neither dose nor duration of Legalon® was given for 4 trials (Figures 3 and 4). Of the remaining 4 of 16 placebo-controlled studies, 2 used silymarin (no further characterization regarding preparation) in doses of 210 and 800 mg, and two used Silipide® at 240 mg/d. Treatment duration for these four trials was 7 to 446 days for three and not given for one (see Figures 3 and 4).

Figure 3. Distribution of durations of therapy for 16 blinded, placebo-controlled studies

![Figure 3](image)

Figure 4. Distribution of doses for 16 placebo-controlled trials

![Figure 4](image)
Among the 17 nonplacebo-controlled trials (Evidence Table 3), five used 420 mg/d of Legalon®, one used 600 mg/d, and two studies used variable dosing from 210 mg/d to 420 mg/d. Preparations for the other nine studies included silymarin, silybin, Silipide®, and Silimarol®. No further information was given, and doses ranged from 140 to 600 mg of silymarin and 10 to 360 mg of silybin; no standardized dose was given for Silimarol®. Over all 17 studies, intervention duration ranged from 14 days to 1 year for 13 and was “variable” or not given for 4 studies.

In the two studies of prophylactic silymarin in conjunction with potentially hepatotoxic antituberculosis drugs or tacrine, an unknown formulation (unknown dose) and silymarin (not further characterized) at 420 mg/d were used. Intervention duration was 56 days and 84 days, respectively (Evidence Table 4).

Milk Thistle and Liver Disease

Milk Thistle and Alcohol-Related Liver Disease

No placebo-controlled studies clearly evaluated subjects with purely acute alcoholic hepatitis. Six randomized, blinded, placebo-controlled studies appear to have evaluated chronic alcoholic liver disease, but the spectrum of disease chronicity and severity varied among the studies or was not clear; two merely described subjects as having “alcoholic liver disease.” Summary Table 1 summarizes these six studies and is from Evidence Tables 1 and 2.

Across these trials, results varied and may be generally confounded by the question of abstinence from alcohol. In one, there was significant improvement in liver function with abstinence from alcohol for patients given silymarin or placebo. However, between silymarin and placebo, there was no difference in the course of liver function as measured by prothrombin time (PT), albumin, bilirubin, gammaglutamyl transpeptidase (GGTP), aspartate aminotransferase (AST), or degree of hepatitis or fibrosis on biopsy. In four trials, at least one parameter of liver function improved significantly with silymarin compared with placebo, but the courses of an equal number or more parameters were not significantly different between silymarin and placebo. One study showed no improvement in overall survival with silymarin but marginally significantly improved survival (p=0.059 by univariate analysis) in HCV-positive patients given silymarin versus placebo. Qualitatively, there does not appear to be a relationship between duration of therapy and improvement in liver function.

Milk Thistle and Chronic Liver Disease of Mixed Etiology

The available evidence did not provide sufficient information to put six studies into any of our a priori etiologic categories of disease. These studies could be characterized as only addressing chronic liver disease of mixed etiologies, including both alcoholic and nonalcoholic disease and without further clarification. Summary Table 2, extracted from Evidence Tables 1 and 2, summarizes these six studies.

Across three studies, at least one parameter showed significant improvement with silymarin compared with placebo, and there was no difference between silymarin and placebo for as many or more parameters. Two studies indicated a possible survival benefit: In one study, survival was significantly improved for patients with Child’s A alcoholic liver disease with silymarin compared with placebo, and in the other study, there was a trend toward improved overall
survival. Again, there is no apparent qualitative relationship between duration of therapy and efficacy of silymarin, but duration was not given or unclear for three of the trials.

In one study, 65 subjects with “chronic persistent hepatitis, etiology unknown” were randomized to receive either Silipide® at 240 mg/d for 3 months or placebo. AST improved significantly in subjects receiving silymarin, but there were no significant differences between the two study groups in the course of alanine aminotransferase (ALT), bilirubin, albumin, and PT.

### Milk Thistle and Viral Liver Disease

One study evaluated silymarin in the setting of acute viral hepatitis. Summary Table 3 summarizes this study and is extracted from Evidence Table 1.

In a blinded study, 59 patients with acute hepatitis A and B were randomized to silymarin at 420 mg/d for 25 days or placebo. No further information on inclusion/exclusion criteria, acuity, or severity was given. The mean age was 37, and 22 percent of subjects were men. Compared with that seen with placebo, improvement in AST and bilirubin was significantly better with silymarin, with a nonsignificant trend toward improvement in ALT. There was no significant difference in the course of alkaline phosphatase.

Two placebo-controlled studies evaluated the efficacy of silymarin in the setting of chronic viral hepatitis (Summary Table 4). Milk thistle was given as Silipide® at 240 mg/d and as Legalon® at 420 mg/d; duration of treatment was 1 week for Silipide® and 1 year for Legalon®. Summary Table 4 summarizes these studies, which are extracted from Evidence Tables 1 and 2.

One randomized, blinded, placebo-controlled trial included 20 patients with biopsy-proven chronic viral hepatitis or with AST and ALT levels greater than twice normal for more than 12 months due to HBV and/or HCV. Patients with portal hypertension, hepatic encephalopathy, ascites, bilirubin or alkaline phosphatase more than twice the normal limit, alcohol consumption exceeding 30 grams per day (g/d), hepatocellular carcinoma, or liver disease associated with collagen vascular disease were excluded. Subjects received placebo or Silipide® at 240 mg/d for 7 days. AST, ALT, and GGTP significantly improved in patients receiving Silipide® compared with placebo. There was no difference between groups in bilirubin, alkaline phosphatase, malondialdehyde (MDA), or albumin.

In the other trial, 24 subjects with chronic viral hepatitis for more than 6 months were randomized to silymarin at 420 mg/d or placebo for 1 year. Exclusion criteria were prior treatment with silymarin, steroids or other toxic drugs, alcohol consumption of more than 80 g/d, or other comorbidities requiring medication. There was a trend toward histologic improvement by liver biopsy in those receiving silymarin compared with placebo.

### Milk Thistle and Cirrhosis

Five randomized and placebo-controlled trials included patients with cirrhosis along with patients with a mixed spectrum of types and severity of liver disease. Four are discussed in the section on chronic alcoholic liver disease, and one is discussed in the section on chronic liver disease of mixed etiologies. Across three trials, at least one parameter of liver function improved in those taking silymarin compared with placebo. Most parameters, however, did not improve. Specifically, none improved in one study, results were not separately
presented for cirrhotic patients in a third study, and in another study, liver function improved equally in placebo and milk thistle arms with abstinence from alcohol.67

Two randomized, blinded, placebo-controlled trials studied patients with alcoholic or nonalcoholic cirrhosis.75,76 Summary Table 5, extracted from Evidence Tables 1 and 2, summarizes these studies. In both studies, silymarin dose was 420 mg/d, but duration of therapy was variable or unclear. The two studies are nearly identical in sample size (n=172, n=170) and relatively similar in exclusion criteria. One showed a nonsignificant trend toward improved survival overall with silymarin, and the other found significantly improved survival in the subgroups with alcoholic liver disease and in patients initially rated as Child’s score A in severity.75,76

Only two randomized, placebo-controlled, blinded trials specifically studied patients with alcoholic cirrhosis.68,71 These studies are summarized in Summary Table 6, which is extracted from Evidence Tables 1 and 2. In these studies, the dose of silymarin was similar (450 mg/d of Legalon® and 420 mg/d of Legalon®); duration of therapy was unclear in one study and 30 days in the other. One reported nonsignificant trends favoring silymarin, compared with placebo, in rates of encephalopathy and upper gastrointestinal bleeding. There was a trend (p=0.059) toward improved survival, compared with placebo, in the subgroup of patients who also had HCV. However, HCV status was determined retrospectively on frozen sera from a convenience sample of patients. There was no apparent benefit of silymarin in aminotransferases, PT, bilirubin, alkaline phosphatase, survival, or rates of other clinical syndromes (i.e., hepatomegaly, splenomegaly, jaundice, and ascites).68 Again, duration of treatment with silymarin was unclear. In the other study, when silymarin was given for 30 days, there was a significant improvement in aminotransferases for patients taking silymarin compared with placebo, but no improvement in bilirubin.71

**Milk Thistle and Toxin-Induced Liver Disease**

Only one study met criteria for evaluating milk thistle’s efficacy in the setting of nonalcohol toxin-induced liver disease.81 Summary Table 7 summarizes this study and is extracted from Evidence Table 1. In randomized, placebo-controlled, blinded trial with factorial design, 60 women were studied who were 40 to 60 years old, had been receiving phenothiazines and/or butyrophenones for 5 or more years, and had increased aminotransferases to more than twice the normal limit. Exclusion criteria included current therapy with other potentially hepatotoxic drugs or other etiologies of liver disease, compromised renal function (blood urea nitrogen exceeding 60 mg/dL or creatinine exceeding 2.5 mg/dL), “cardiac or circulatory insufficiency,” diabetes mellitus, “other important extrahepatic disease,” pregnancy, and alcohol (more than 30 g/d) or opiate abuse. Subjects were treated for 90 days after randomization to the following: (1) placebo and continued psychotropic drugs; (2) silymarin at 800 mg/d and continued psychotropic drugs; (3) silymarin at 800 mg/d and psychotropic drugs discontinued; or (4) placebo and psychotropic drugs discontinued. MDA significantly improved in patients on silymarin and psychotropic drugs compared with women on placebo and psychotropic drugs. However, no difference was found in the course of liver function tests for AST, ALT, or MDA between patients taken off psychotropic drugs and given silymarin or placebo.

Two blinded studies evaluated prophylactic milk thistle in conjunction with hepatotoxic medications—drugs for treating tuberculosis and tacrine for treating Alzheimer’s disease.82,83 Summary Table 8 summarizes these studies and is extracted from Evidence Table 4.
In the study of prophylactic milk thistle during treatment for tuberculosis, 29 subjects with normal liver function tests received antituberculosis drugs plus Hepabene®, a mixture of silymarin and *Fumaria officinalis* alkaloids (two capsules daily, no other information given), and 93 subjects received antituberculosis drugs alone. Proportions receiving various antituberculosis drugs, in the control and silymarin groups respectively, were the following: rifampin (98 percent and 100 percent); isoniazid (99 percent and 97 percent); pyrazinamide (84 percent and 100 percent); ethambutol (50 percent and 38 percent); and streptomycin (37 percent and 14 percent). Initially, AST increased in 49 percent of control subjects and 38 percent of subjects receiving Hepabene®. Similarly, ALT increased in 48 percent of control and 31 percent of those receiving Hepabene®. These differences were statistically significant over the course of 8 weeks; AST then fell in 40 percent of subjects receiving Hepabene®, compared with 19 percent of controls. Similarly, ALT fell in 48 percent of those receiving Hepabene®, compared with 22 percent in controls. Again, these differences were statistically significant.

The second study of prophylactic milk thistle was a randomized, double-blind trial in which 222 patients meeting a priori criteria for Alzheimer’s dementia were randomized to tacrine and silymarin or tacrine with placebo. Patients with prior liver disease were excluded. Silymarin (420 mg/d) was given for 1 week, and then tacrine was added, first at 40 mg/d for 6 weeks, then at 80 mg/d for 6 additional weeks. (Note: Published report states that silymarin [Legalon®] dose was 420 mg/d, but an internal study summary reportedly states dose was 140 mg/d from Madaus.) There were no significant differences in the courses of AST or ALT levels or the rate of side effects during the study. There was no significant difference even though rates appeared lower.

**Milk Thistle and Cholestasis**

No studies met criteria for evaluating efficacy of milk thistle in treating cholestatic liver disease, pregnancy-related or not.

**Milk Thistle and Primary Hepatic Malignancy**

No studies met criteria for evaluating milk thistle efficacy in treating or preventing primary hepatic malignancy (hepatocellular carcinoma or cholangiocarcinoma).

**Effectiveness of Different Preparations of Milk Thistle**

Pharmacokinetic studies indicate that one preparation of oral Silipide® (silybin-phosphatidylcholine complex) has better absorption from the gastrointestinal tract and, as a result, is more bioavailable than a particular preparation of oral silymarin. However, because of variability in different preparation, differences in bioavailability may not be generalizable. No randomized, placebo-controlled trials directly compared a standardized silymarin extract with Silipide® for effectiveness in treating liver disease. One Phase II, dose-response study compared different doses of Silipide® with no treatment, and one nonrandomized study compared silymarin, Silipide®, and “no treatment or placebo control.” Summary Table 9 summarizes the Phase II study of Silipide® and is extracted from Evidence Table 3.
In the Phase II study, 60 subjects with chronic viral or alcoholic hepatitis were randomized to 14 days of Silipide® at 160 mg/d, 240 mg/d, or 360 mg/d or no treatment. AST, GGTP, and bilirubin improved significantly more in subjects receiving 240 mg/d or 360 mg/d, compared with those receiving 160 mg/d. No comparative data and data specific to the control group (no treatment) versus any dose of Silipide® were reported.

Exploratory Meta-Analyses Results

Exploratory meta-analyses proceeded in the following sequence: (1) all 16 placebo-controlled studies (studies in Evidence Tables 1 and 2); (2) the 14 randomized, placebo-controlled trials in Evidence Table 1; and (3) subgroup analyses by etiology of liver disease and duration of followup (≤45 days or 46 to 90 days). Relevant funnel plots, Galbraith plots, and forest plots are given in Appendix B.

Summary Table 10 shows the results for pooling all 16 placebo-controlled trials. Effect size is given both as the standardized mean difference, in standard deviation units, and in converted laboratory values (see preceding Data Analysis Process section). Statistical significance is expressed as the probability that the effect of silymarin is not zero. When one outlier study was removed, there was no significant heterogeneity. Most effect sizes favored silymarin, but effect sizes were small or not statistically significant. Results were similar for pooling only the 14 higher quality trials in Evidence Table 1 (Summary Table 11).

Table 3 shows the variables for which data were available in etiologic subgroups. Tables 4, 5, and 6 show results of these subgroup analyses. Results are similar throughout: Silymarin was generally associated with small favorable, but not statistically significant, effect sizes.

In summary, results of multiple exploratory meta-analyses show either nonsignificant effects or a few statistically significant effects that are small in magnitude. There is no obvious relationship between observed effectiveness and etiology of liver disease or duration of followup. It is possible that clinical heterogeneity in subject populations and small sample sizes may have masked statistically significant effects of milk thistle in different clinical groups. As we conducted multiple exploratory analyses, it is also possible that some of the statistically significant findings occurred by chance.
Insert Table 3 Here
Insert Table 3 Here.
Insert Table 4 Here.
Insert Table 4 Here.
Insert Table 5 Here.
Insert Table 6 Here.
Adverse Effects of Milk Thistle

Overview of Adverse Effect Literature

The adverse effect literature regarding milk thistle is difficult to interpret for many reasons. First, searching for studies that report adverse effects is difficult and, given current indexing systems for electronic databases, probably incomplete. Many studies may mention adverse effects in passing, but they do not use adverse effects as a key index word or in their abstracts. If these studies do not otherwise meet selection criteria in a review, they will be missed. Second, information is frequently missing on whether adverse effects were elicited by voluntary self-report or standardized probes. Third, in some case reports and case series, adverse effects cannot be directly attributed to milk thistle because chance, coincidence, or confounding factors could have been responsible. Fourth, case reports and case series may miss delayed adverse reactions because such associations are more difficult to make than those that occur immediately after administration of an agent. Fifth, although case reports and case series can provide qualitative information about the nature of an adverse effect, they cannot generate estimates of incidence.

Based on identified reports, milk thistle appears to be safe for most people. Seventeen reports of adverse effects possibly due or attributed to milk thistle oral supplements were identified (Evidence Table 5). Data were abstracted from seven randomized clinical trials, six cohort studies, and five case reports. Besides study characteristics, we attempted to abstract data regarding evidence for causality: (1) documentation of improved adverse effect after the milk thistle supplement was discontinued, (2) adverse effect recurrence when rechallenged with the milk thistle formulation, (3) careful search for other causes of the adverse effect, and (4) documentation of a dose-response relationship. None of the 17 reports provided information regarding a possible dose-response relationship. Detailed data are shown in Evidence Table 5. An overall summary of reported adverse effects, by level of evidence, is shown in Summary Table 12.

Common Symptomatic Effects

Gastrointestinal side effects are the most commonly reported adverse effects, in both randomized clinical trials and prospective cohort studies. Overall incidence appears relatively low, and in RCTs there is no apparent difference between treatment and control groups. Skin manifestations of adverse drug effects are also fairly commonly reported, but again overall incidence appears low and no more frequent in groups receiving milk thistle than in control groups. Incidence of headaches also appears low and no different between silymarin and control groups in RCTs.

Common and Uncommon Serious Adverse Effects

Serious adverse effects identified in available evidence for this systematic review were anaphylactoid reactions or anaphylaxis. Available evidence was limited to three case reports. In one case report, a variety of symptoms plus “collapse” was associated with milk thistle, improved after discontinuation of milk thistle, reappeared on rechallenge, but was also associated with potential alternative etiologies. In a second case report of anaphylactic shock, no information was given about associated evidence of causality. A third case report of an
apparent anaphylactoid reaction improved with prednisone and discontinuing silymarin, and there were no apparent alternative possible etiologies.\textsuperscript{95}
Table 3. Outcome measures and followup times for trials of chronic liver disease, chronic liver disease of mixed etiology, and viral liver disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes Measures</th>
<th>Time Point(s)(^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palasciano(^{61})</td>
<td>AST, ALT</td>
<td>30, 90 days</td>
</tr>
<tr>
<td><strong>Chronic alcoholic liver disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmi(^{69})</td>
<td>AST, ALT, Alk phos, GGTP, Histology</td>
<td>28 days</td>
</tr>
<tr>
<td>Lang(^{71})</td>
<td>Bili, AST, ALT, GGTP</td>
<td>30 days</td>
</tr>
<tr>
<td>Trinchet(^{67})</td>
<td>Alb, Bili, AST, GGTP, PT, Histology</td>
<td>90 days</td>
</tr>
<tr>
<td>Feher(^{70})</td>
<td>Alb, Bili, AST, ALT, Alk phos, GGTP, PT, MDA (180 only)</td>
<td>90, 180 days</td>
</tr>
<tr>
<td>Bunout(^{66})</td>
<td>Alb, Bili, AST, Alk phos, GGTP, PT, Child’s score</td>
<td>15 months</td>
</tr>
<tr>
<td>Pares(^{66})</td>
<td>Alb, Bili, AST, ALT, Alk phos, GGTP, PT, Child’s score</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Chronic liver disease, mixed etiologies (alcohol, viral, toxin assumed)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fintelmann(^{73})</td>
<td>AST, ALT, GGPT</td>
<td>1, 3, 7, 10, 14, 21, 28 days(^a)</td>
</tr>
<tr>
<td>Tanasescu(^{74}): Data separately reported for CAH, CPH, HCV</td>
<td>Bili, ALT, Alk phos, GGTP, PT</td>
<td>40 days</td>
</tr>
<tr>
<td>Fintelmann(^{72})</td>
<td>AST, ALT, Alk phos</td>
<td>42 days</td>
</tr>
<tr>
<td>Marcelli(^{77})</td>
<td>Alb, Bili, AST, ALT, PT</td>
<td>90 days</td>
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<tr>
<td>Ferenci(^{75}): No numerical data for chemistries</td>
<td>Survival</td>
<td>41 months</td>
</tr>
<tr>
<td>Benda(^{76}): No numerical data for chemistries</td>
<td>Survival</td>
<td>48 months</td>
</tr>
<tr>
<td><strong>Acute viral hepatitis</strong></td>
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<tr>
<td>Magliulo(^{78})</td>
<td>Bili, AST, ALT, Alk phos, GGTP</td>
<td>1, 3, 5, 7, 9, 14, 21, 28 days(^a)</td>
</tr>
</tbody>
</table>
Table 3. Outcome measures and followup times for trials of chronic liver disease, chronic liver disease of mixed etiology, and viral liver disease (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes Measures</th>
<th>Time Point(s)\textsuperscript{a,b}</th>
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<tbody>
<tr>
<td><strong>Chronic viral hepatitis</strong></td>
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<tr>
<td>Buzelli\textsuperscript{79}</td>
<td>Bili</td>
<td>AST</td>
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<tr>
<td>Kiesewetter\textsuperscript{80}: Reported as improvement, no change, worse</td>
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<td></td>
</tr>
</tbody>
</table>

Note: When there was more than one study, effect sizes were pooled.

\textsuperscript{a}The last time point (7 to 45 days) was selected for pooling as “\leq 45 day” time point.

\textsuperscript{b}Time points for pooling included \leq 45 days and 90 days.

Abbreviations Used: alb = albumin; alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bili = bilirubin; CAH = chronic active hepatitis; CPH = chronic persistence hepatitis; GGTP = gammaglutamyl transpeptidase; HCV = hepatitis C virus; MDA = malondialdehyde; PT = prothrombin time.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Units9 95% CI</th>
<th>p Value&lt;sup&gt;c&lt;/sup&gt; (ES ≠ 0)</th>
<th>Q p Value&lt;sup&gt;c&lt;/sup&gt; (homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.24 (-0.58 to 0.10)</td>
<td>-10.7 (-26.0 to 4.5)</td>
<td>0.16</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.02 (-0.76 to 0.72)</td>
<td>-0.9 (-34.0 to 32.2)</td>
<td>0.96</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.37 (-1.03 to 0.29)</td>
<td>-16.6 (-46.1 to 13.0)</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>0.37 (-0.21 to 0.95)</td>
<td>17.5 (-9.4 to 42.5)</td>
<td>0.21</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.28 (-0.07 to 0.64)</td>
<td>12.5 (-3.1 to 28.7)</td>
<td>0.12</td>
<td>–</td>
</tr>
<tr>
<td>ALT</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.33 (-0.67 to 0.004)</td>
<td>-11.9 (-24.1 to 0.1)</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>-0.39 (-1.05 to 0.27)</td>
<td>-14.0 (-37.8 to 9.7)</td>
<td>0.24</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.28 (-0.93 to 0.38)</td>
<td>-10.1 (-33.5 to 13.7)</td>
<td>0.41</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.33 (-0.03 to 0.68)</td>
<td>11.9 (-1.1 to 24.5)</td>
<td>0.07</td>
<td>–</td>
</tr>
<tr>
<td>GGTP</td>
<td>≤45 days</td>
<td>1</td>
<td>-0.71 (-1.34 to -0.08)</td>
<td>-109.3 (-206.3 to -12.3)</td>
<td>0.03</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.04 (-0.41 to 0.32)</td>
<td>-6.2 (-63.1 to 49.3)</td>
<td>0.81</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.64 (-1.30 to 0.03)</td>
<td>-98.5 (-200.1 to 4.6)</td>
<td>0.06</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.26 (-0.84 to 0.32)</td>
<td>-40.0 (-129.3 to 49.3)</td>
<td>0.38</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.38 (0.02 to 0.73)</td>
<td>58.5 (3.1 to 112.4)</td>
<td>0.04</td>
<td>–</td>
</tr>
<tr>
<td>MDA</td>
<td>180 days</td>
<td>1</td>
<td>-0.81 (-1.49 to -0.13)</td>
<td>-5.4 (-9.9 to -0.9)</td>
<td>0.02</td>
<td>–</td>
</tr>
<tr>
<td>Alkaline Phosphate</td>
<td>≤45 days</td>
<td>1</td>
<td>0.19 (-0.21 to 0.59)</td>
<td>19.2 (-21.2 to 59.6)</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>0.10 (-0.55 to 0.76)</td>
<td>10.1 (-55.6 to 76.8)</td>
<td>0.76</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.34 (-1.00 to 0.31)</td>
<td>-34.3 (-101.0 to 31.3)</td>
<td>0.31</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.05 (-0.63 to 0.53)</td>
<td>-5.0 (-63.6 to 53.5)</td>
<td>0.87</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>-0.08 (-0.43 to 0.27)</td>
<td>-8.1 (-43.3 to 27.3)</td>
<td>0.65</td>
<td>–</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≤45 days</td>
<td>1</td>
<td>-0.30 (-0.92 to 0.32)</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.10 (-0.70 to 0.49)</td>
<td>-0.03 (-0.2 to 0.2)</td>
<td>0.73</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.49 (-1.16 to 0.17)</td>
<td>-0.2 (-0.4 to 0.05)</td>
<td>0.14</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.16 (-0.74 to 0.43)</td>
<td>-0.05 (-0.2 to 0.1)</td>
<td>0.60</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.004 (-0.35 to 0.36)</td>
<td>0.001 (-0.1 to 0.1)</td>
<td>0.98</td>
<td>–</td>
</tr>
<tr>
<td>Albumin</td>
<td>90 days</td>
<td>2</td>
<td>-0.13 (-0.87 to 0.60)</td>
<td>-0.1 (-0.6 to 0.4)</td>
<td>0.72</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>0.19 (-0.47 to 0.84)</td>
<td>0.1 (-0.3 to 0.6)</td>
<td>0.58</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>0.25 (-0.35 to 0.85)</td>
<td>0.2 (-0.2 to 0.6)</td>
<td>0.42</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>-0.23 (-0.59 to 0.12)</td>
<td>-0.2 (-0.4 to 0.09)</td>
<td>0.20</td>
<td>–</td>
</tr>
<tr>
<td>PT</td>
<td>90 days</td>
<td>2</td>
<td>-0.30 (-1.00 to 0.40)</td>
<td>-5.2 (-17.4 to 7.0)</td>
<td>0.40</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>0.47 (-0.20 to 1.13)</td>
<td>8.2 (-3.5 to 19.7)</td>
<td>0.17</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.29 (-0.87 to 0.29)</td>
<td>-5.0 (-15.1 to 5.0)</td>
<td>0.32</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>-0.18 (-0.53 to 0.17)</td>
<td>-3.1 (-9.2 to 3.0)</td>
<td>0.32</td>
<td>–</td>
</tr>
</tbody>
</table>
Table 4. Effect sizes and meta-analysis for chronic alcoholic liver disease (6 studies) (continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time of Follow-Up</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Unitsb 95% CI</th>
<th>p-Valuec (ES ≠ 0)</th>
<th>Q p-Valuec (Homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child's 2.55 score</td>
<td>15 months</td>
<td>1</td>
<td>-0.09 (-0.68 to 0.50)</td>
<td>-0.2 (-1.7 to 1.3)</td>
<td>0.78</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.27 (-0.08 to 0.62)</td>
<td>0.7 (-0.2 to 1.6)</td>
<td>0.13</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: When there was more than one study, effect sizes were pooled.

a Mean pooled standard deviations.
b Standard deviation effect size units are back-converted to clinical effect sizes by standard deviation x effect size.
c All studies refer to combination of chronic alcohol, chronic and acute viral, and chronic mixed etiology unless otherwise noted (the inclusion of one drug study, factorial design); values reported for meta-analytic results; N/A for single study estimates.

Abbreviations Used: ALT = alanine aminotransferase; AST = aspartase aminotranferase; CI = 95% confidence interval; ES = effect size; GGTP = gammaglutamyl transpeptidase; g/dL = grams per deciliter; MDA = malondialdehyde; nmol/ml = nanomoles per milliliter; PT = prothrombin time; SD = standard deviation; U/L = units per liter.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Units 95% CI</th>
<th>p Value&lt;sup&gt;c&lt;/sup&gt; (ES ≠ 0)</th>
<th>Q p Value&lt;sup&gt;c&lt;/sup&gt; (homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST 44.77 U/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.30 (-0.67 to 0.08)</td>
<td>-13.4 (-30.0 to 3.6)</td>
<td>0.12</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>-0.73 (-1.22 to -0.24)</td>
<td>-32.7 (-54.6 to -10.7)</td>
<td>&lt;0.01</td>
<td>–</td>
</tr>
<tr>
<td>ALT 36.02 U/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤45 days</td>
<td>3</td>
<td>-0.13 (-0.42 to 0.17)</td>
<td>-4.7 (-15.1 to 6.1)</td>
<td>0.40</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>-0.90 (-1.56 to -0.24)</td>
<td>-32.4 (-56.2 to -8.6)</td>
<td>0.01</td>
<td>–</td>
</tr>
<tr>
<td>GGTP 153.94 U/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.11 (-0.38 to 0.15)</td>
<td>-16.9 (-58.5 to 23.1)</td>
<td>0.40</td>
<td>0.30</td>
</tr>
<tr>
<td>Alkaline phosphate 101.01 U/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.14 (-0.41 to 0.12)</td>
<td>-14.1 (-41.4 to 12.1)</td>
<td>0.29</td>
<td>0.74</td>
</tr>
<tr>
<td>Bilirubin 0.32 g/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤45 days</td>
<td>1</td>
<td>-0.28 (-0.57 to 0.02)</td>
<td>-0.1 (-0.2 to 0.01)</td>
<td>0.07</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>0.17 (-0.32 to 0.66)</td>
<td>0.05 (-0.1 to 0.2)</td>
<td>0.49</td>
<td>–</td>
</tr>
<tr>
<td>Albumin 0.74 g/dL</td>
<td>90 days</td>
<td>1</td>
<td>0.08 (-0.41 to 0.57)</td>
<td>0.1 (-0.3 to 0.4)</td>
<td>0.75</td>
<td>–</td>
</tr>
<tr>
<td>PT 17.39&lt;sup&gt;a&lt;/sup&gt; seconds</td>
<td>≤45 days</td>
<td>1</td>
<td>0.14 (-0.16 to 0.44)</td>
<td>2.4 (-2.8 to 7.7)</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>0.03 (-0.46 to 0.52)</td>
<td>0.5 (-8.0 to 9.0)</td>
<td>0.91</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: When there was more than one study, effect sizes were pooled.

<sup>a</sup> Mean pooled standard deviations.

<sup>b</sup> Standard deviation effect units are back-converted to clinical effect sizes by standard deviation x effect size.

<sup>c</sup> All studies refer to combination of chronic alcohol, chronic and acute viral, and chronic mixed etiology unless otherwise noted (the inclusion of one drug study, factorial design); values reported for meta-analytic results; N/A for single study estimates.

Abbreviations Used: ALT = alanine aminotranferase; AST = aspartase aminotranferase; CI = 95% confidence interval; ES = effect size; GGTP = gammaglutamyl transpeptidase; PT = prothrombin time; SD = standard deviation; U/L = units per liter.
Table 6. Effect sizes and meta-analysis for viral liver disease, acute and chronic (3 studies)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Units(^b) 95% CI</th>
<th>p Value(^c) (ES ≠ 0)</th>
<th>Q p Value(^c) (homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST 44.77 U/L(^a)</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.17 (-0.70 to 0.36)</td>
<td>-7.6 (-31.3 to 16.1)</td>
<td>0.53</td>
<td>0.31</td>
</tr>
<tr>
<td>ALT 36.02 U/L(^a)</td>
<td>≤45 days</td>
<td>2</td>
<td>0.25 (-1.46 to 1.96)</td>
<td>9.0 (-52.6 to 70.6)</td>
<td>0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GGTP 153.94 U/L(^a)</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.20 (-0.73 to 0.32)</td>
<td>-30.8 (-112.4 to 49.3)</td>
<td>0.44</td>
<td>0.53</td>
</tr>
<tr>
<td>MDA 6.65 nmol/ml(^a)</td>
<td>≤45 days</td>
<td>1</td>
<td>-0.09 (-0.96 to 0.79)</td>
<td>-0.6 (-6.4 to 5.3)</td>
<td>0.85</td>
<td>–</td>
</tr>
<tr>
<td>Alkaline phosphate 101.01 U/L(^a)</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.05 (-0.56 to 0.46)</td>
<td>-5.1 (-56.6 to 46.5)</td>
<td>0.84</td>
<td>0.38</td>
</tr>
<tr>
<td>Bilirubin 0.32 g/dL(^a)</td>
<td>≤45 days</td>
<td>2</td>
<td>-0.25 (-0.83 to 0.33)</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.40</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Note: When there was more than one study, effect sizes were pooled.

\(^a\) Mean pooled standard deviations.

\(^b\) Standard deviation effect size units are back-converted to clinical effect sizes by standard deviation x effect size.

\(^c\) All studies refer to combination of chronic alcohol, chronic and acute viral, and chronic mixed etiology unless otherwise noted (the inclusion of one drug study, factorial design); values reported for meta-analytic results; N/A for single study estimates.

Abbreviations Used: ALT = alanine aminotransferase; AST = aspartase aminotransferase; CI = 95% confidence interval; ES = effect size; GGTP = gammaglutamyl transpeptidase; MDA = malondialdehyde; SD = standard deviation; U/L = units per liter.
Chapter 4. Conclusions

The effectiveness of milk thistle in human liver disease has not been established. This may be because of the scientific quality of study methods or published reports or both. Possible benefit has been shown most frequently, but not consistently, for improvement in aminotransferases, but 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. Mechanisms of action, disease populations likely to benefit, the optimal formulations of milk thistle, and duration of therapy are undefined. Also, little about adverse effects is known. Further study of mechanisms of action and well-designed clinical trials, with detailed reporting of adverse effects and components of potential causality, are needed.
Chapter 5. Future Research

Adverse Effects

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. The most serious potential adverse effects of milk thistle reported thus far are anaphylactoid reactions and anaphylaxis, and available data are extremely limited regarding causality.

Beneficial Effects Regarding Liver Diseases

Studies in humans with physiologic outcomes are limited by unclear study populations, randomization procedures, small sample sizes, variable and sometimes short duration of treatment, unclear blinding for outcome assessment, and unclear or inadequate information about potential confounders. Characteristics of future studies 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 sophisticated considerations regarding study populations 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).

There are several important considerations for study populations and confounders. After correction for baseline risk differences, our meta-analyses found generally adequate statistical homogeneity, despite poorly defined and heterogeneous study populations. Yet, clinical heterogeneity in study populations regarding etiology, chronicity, and severity of liver disease might have masked subgroup differences in outcomes. There are numerous important potential confounders and combinations of confounders that might affect outcomes in individual subjects. These include the following: comorbidities, baseline and ongoing use of alcohol, various combinations of alcoholic and viral liver disease in individual patients, various etiologies of concomitant fatty liver disease, coinfection with HIV and HBV and/or HCV, treatment with antiviral medications for HIV, and use of interferon for HCV. Thus, future research should assess baseline status regarding alcohol, HBV, HCV, and HIV, as well as systematic surveillance for these factors through the duration of studies.

Specific Areas of Research

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. Several specific research directions appear especially relevant at this time. The high prevalence of alcoholic liver disease and the increasing prevalence of HCV liver disease in the United States and high prevalence of HBV infection in
intravenous drug users and in developing countries warrant research focusing on these populations. Effectiveness of milk thistle in cholestatic disease and nonalcohol steatohepatitis has not been studied. Because of provocative data from two small trials, further research is needed regarding prophylactic use of milk thistle in the setting of potentially hepatotoxic medications or as treatment for iatrogenic liver dysfunction.

More information is needed about effectiveness of milk thistle for severe acute ingestion of hepatotoxins, such as occupational exposures, acetaminophen overdose, and amanita poisoning. The available data are limited to case reports and small case series in Europe for amanita poisoning and occupational exposures to hepatotoxins. We identified no trials of milk thistle for acetaminophen hepatotoxicity. Because of the low incidence and ethical issues, it is premature to consider randomized clinical trials. However, a systematic review of the evidence at hand and then careful consideration of the feasibility and utility of well-designed case-control or cohort-comparison studies would be useful. Such data could inform the decision regarding trials of n-acetylcysteine with and without milk thistle or treatment for other acute toxic exposures.
References


103. Cavalieri S. [Controlled clinical trial of silymarin in 40 patients]. [Ita]. Gazz Med Ital 1974;133:628-35.


<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| Author: Bunout66  
Year: 1992  
Country: Chile  
Language: Spanish | Study type: RCT/blind  
Intervention/dose/duration: Silymarin (Legalon®)/280 mg daily/446 days  
Control: Placebo  
Outcome measures: AST, GGTP, alk phos, bilirubin, albumin, PT  
Followup interval: Monthly for an average of 15 months  
Assessment time points with results reported: Mean of 15 months | Type: Alcoholic liver disease (inactive cirrhosis, active cirrhosis, cirrhosis with alcoholic hepatitis, alcoholic hepatitis, fibrosis)  
Include: Positive for alcohol history and symptoms of icterus edema, ascites, or encephalopathy or bilirubin exceeding 2 mg/dL; PT exceeding 75 percent control; albumin less than 3 mg/dL  
Exclude: HBV antigen; renal failure; cardiac failure; terminal liver disease  
Acuity/severity: Chronic, cirrhosis, no other information  
Baseline group similarity: Demos, LFTs appear similar | N: 59  
Mean age: 50  
Percent male: 86  
Setting: Specialty clinic | Significant: Albumin  
Not significant: Child’s score, bilirubin, AST, GGTP, alk phos, PT, survival |
| Author: Feher70,99,100  
Year: 1989/1990  
Country: Hungary  
Language: Hungarian | Study type: RCT/blind  
Intervention/dose/duration: Silymarin (Legalon®)/420 mg daily/180 days  
Control: Placebo  
Outcome measures: AST, ALT, GGTP, alk phos, bilirubin, albumin  
Followup interval: 90 and 180 days  
Assessment time points with results reported: 90 and 180 days | Type: Chronic alcoholic liver disease (cirrhosis, reactive fibrosis, fatty degeneration)  
Include: Alcohol intake exceeding 60 g/d in men and 30 g/d in women for 8 ± 4 years; chronic liver disease; no previous corticosteroid or immunosuppressive treatment  
Exclude: Not given  
Acuity/severity: Chronic, no other information  
Baseline group similarity: Demos, LFTs appear similar | N: 36  
Mean age: 46  
Percent male: 75  
Setting: Unclear | Significant: AST, GGTP, MDA  
Not significant: (assumed for all) ALT, alk phos, albumin, PT, survival |
| Author: Lang71  
Year: 1990  
Country: Hungary  
Language: English | Study type: RCT/blind/three arms  
Interventions/dose/duration: Silymarin (Legalon®)/420 mg daily/30 days  
AICA-P/600 mg daily/30 days  
Control: Placebo  
Outcome measures: AST, ALT, GGTP, alk phos, albumin  
Followup interval: 28 days  
Assessment time points with results reported: Weekly for 1 month | Type: Alcoholic cirrhosis  
Include: Alcohol intake exceeding 60 g/d in men and 30 g/d women for more than 6 years; histologic diagnosis of micronodular cirrhosis  
Exclude: Vascular and/or parenchymal decompensation; +HBsAg  
Acuity/severity: Chronic, cirrhosis, no other information  
Baseline group similarity: LFTs appear similar | N: 60  
Mean age: 45  
Percent male: 68  
Setting: Unclear | Significant: AST, ALT, GGTP  
Not significant: Bilirubin |
### Summary Table 1. Placebo-controlled studies of milk thistle for chronic alcoholic liver disease (n = 6) (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Pares, 1998</td>
<td><strong>Study type:</strong> RCT/blind</td>
<td><strong>Type:</strong> Alcoholic cirrhosis (24 percent had superimposed alcohol hepatitis)</td>
<td><strong>N:</strong> 200</td>
<td><strong>Significant:</strong> + Trend: Encephalopathy, UGIB, survival for HCV-positive patients</td>
</tr>
<tr>
<td><strong>Country:</strong> Spain</td>
<td><strong>Intervention/dose/duration:</strong> Silymarin (Legalon®)/450 mg daily/unclear</td>
<td><strong>Include:</strong> Chronic alcoholism defined as alcohol exceeding 80 g/d men and 60 g/d women for more than 5 years; biopsy or laparoscopic proven alcoholic cirrhosis</td>
<td><strong>Mean age:</strong> 50</td>
<td><strong>Not significant:</strong> AST, ALT, GGTP, alk phos, bilirubin, albumin, PT</td>
</tr>
<tr>
<td><strong>Language:</strong> English</td>
<td><strong>Control:</strong> Placebo</td>
<td><strong>Exclude:</strong> If ever received colchicine, malotilate, penicillamine, or corticosteroids; other known etiologies for cirrhosis (i.e., HBV, autoimmunity, primary biliary cirrhosis, or cryptogenic cirrhosis)</td>
<td><strong>Percent male:</strong> 79</td>
<td><strong>Setting:</strong> Diagnosis in hospital then outpatient followup.</td>
</tr>
<tr>
<td></td>
<td><strong>Outcome measures:</strong> AST, ALT, GGTP, alk phos, bilirubin, albumin, PT</td>
<td><strong>Acuity/severity:</strong> Chronic, all cirrhosis, Child's score A/B/C/ 63/114/14</td>
<td><strong>Followup interval:</strong> Every 3 months for 2 years</td>
<td><strong>Note:</strong> Trend was assessed qualitatively only for this review.</td>
</tr>
<tr>
<td></td>
<td><strong>Assessment time points with results reported:</strong> Survival at 5 years; all others at 2 years (assumed)</td>
<td><strong>Baseline group similarity:</strong> Demos, LFTs appear similar</td>
<td><strong>Assessment time points with results reported:</strong> Survival at 5 years; all others at 2 years (assumed)</td>
<td></td>
</tr>
<tr>
<td><strong>Author:</strong> Salmi, 1982</td>
<td><strong>Study type:</strong> RCT/blind</td>
<td><strong>Type:</strong> Alcoholic liver disease</td>
<td><strong>N:</strong> 97</td>
<td><strong>Significant:</strong> AST, ALT, histology</td>
</tr>
<tr>
<td><strong>Country:</strong> Finland</td>
<td><strong>Intervention/dose/duration:</strong> Silymarin (Legalon®)/420 mg daily/28 days</td>
<td><strong>Include:</strong> Increased AST and ALT for more than 1 month despite order to abstain from alcohol</td>
<td><strong>Mean age:</strong> 37</td>
<td><strong>Not significant:</strong> Alk phos, bilirubin</td>
</tr>
<tr>
<td><strong>Language:</strong> English</td>
<td><strong>Control:</strong> Placebo</td>
<td><strong>Exclude:</strong> Not given</td>
<td><strong>Percent male:</strong> 86</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Outcome measures:</strong> AST, ALT, alk phos, bilirubin, histology</td>
<td><strong>Acuity/severity:</strong> No other information</td>
<td><strong>Setting:</strong> Hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Followup interval:</strong> Day 28</td>
<td><strong>Baseline group similarity:</strong> Aminotransferase levels reported as similar but lower in controls</td>
<td><strong>Assessment time points with results reported:</strong> 28 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Assessment time points with results reported:</strong> 28 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Author:</strong> Trinchet, 1989</td>
<td><strong>Study type:</strong> RCT/blind</td>
<td><strong>Type:</strong> Alcoholic hepatitis (50 percent with cirrhosis)</td>
<td><strong>N:</strong> 116</td>
<td><strong>Significant:</strong> Both silymarin and placebo better with alcohol abstinence</td>
</tr>
<tr>
<td><strong>Country:</strong> France</td>
<td><strong>Intervention/dose/duration:</strong> Silymarin (Legalon®)/420 mg daily/ 90 days</td>
<td><strong>Include:</strong> Biopsy-proven alcoholic hepatitis with or without cirrhosis</td>
<td><strong>Mean age:</strong> 51</td>
<td><strong>Not significant:</strong> PT, albumin, bilirubin, GGTP, AST, histology (hepatitis, fibrosis)</td>
</tr>
<tr>
<td><strong>Language:</strong> French</td>
<td><strong>Control:</strong> Placebo</td>
<td><strong>Exclude:</strong> Hepatic encephalopathy; contraindications to liver biopsy; hepatocellular cancer; ascites resistant to diuretics; platelets less than 100,000 per mm; PT less than 50 percent; other diseases limiting survival</td>
<td><strong>Percent male:</strong> 67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Outcome measures:</strong> AST, GGTP, bilirubin, albumin, PT, histology</td>
<td><strong>Acuity/severity:</strong> 58/116 with cirrhosis; no other information</td>
<td><strong>Setting:</strong> Unclear</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Followup interval:</strong> 90 days</td>
<td><strong>Baseline group similarity:</strong> Demos, LFTs appear similar</td>
<td><strong>Assessment time points with results reported:</strong> 90 days</td>
<td></td>
</tr>
</tbody>
</table>

*Results not necessarily reported for all.

Abbreviations Used: AICA-P = amino imidazol carboxamid phosphate; alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartase aminotransferase; demos = demographic variables; GGTP = gammaglutamyl transpeptidase; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function test; MDA = malondialdehyde; PT = prothrombin time; RCT = randomized controlled trial; UGIB = upper gastrointestinal bleed.
## Summary Table 2. Placebo-controlled studies of milk thistle for chronic liver disease, mixed etiologies (n = 6)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Fintelmann⁷³  
**Year:** 1980  
**Country:** Germany  
**Language:** German | Study type: RCT/blind  
**Intervention/dose/duration:** Silymarin(Legalon®)/not given/not given  
**Control:** Placebo  
**Outcome measures:** AST, ALT, GGTP, alk phos, bilirubin  
**Followup interval:** Days 1, 3, 7, 10, 14, 21, 28  
**Assessment time points with results reported:** Had to read off graphs, but all followups | **Type:** Toxic liver disease, any etiology (usually alcohol)  
**Include:** Clinical and laboratory evidence of toxic liver damage  
**Exclude:** Not given  
**Acuity/severity:** No other information  
**Baseline group similarity:** No information except age and gender “similar” | N: 66  
Mean age: Not given  
Percent male: Not given  
Setting: Unclear | Significant: ALT, GGTP  
Not significant: AST, bilirubin, alk phos |
| **Author:** Fintelmann⁷²  
**Year:** 1970  
**Country:** Germany  
**Language:** German | Study type: Cohort with comparison group/blinding unclear  
**Intervention/dose/duration:** Silymarin (Legalon®)/6 tablets daily/42 days  
**Control:** Placebo  
**Outcome measures:** Bilirubin, alk phos, AST, ALT  
**Followup interval:** 42 days  
**Assessment time points with results reported:** 42 days | **Type:** Alcoholic liver disease, also other causes of fatty liver (pure parenchymal fatty degeneration, fatty degeneration and reactive inflammation, cirrhosis transformation in progress)  
**Include:** Biopsy-proven fatty liver, including early cirrhosis without portal hypertension, assignment stratified by diabetes mellitus, obesity, alcohol intake  
**Exclude:** Not given  
**Acuity/severity:** All degrees of fatty liver including early cirrhosis without portal hypertension  
**Baseline group similarity:** LFTs appear similar | N: 50  
Mean age: Not given  
Percent male: Not given  
Setting: Unclear | Significant: AST (categorical)  
Not significant: AST (continuous), ALT, alk phos |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Tanasescu  
**Year:** 1988  
**Country:** Romania  
**Language:** English | **Study type:** RCT, randomization stratified by type of disease: CPH, CAH, HCV/blind  
**Intervention/dose/duration:** Silymarin (Silimarina®)/210 mg silybin equivalents daily/ 40 days  
**Control:** Placebo  
**Outcome measures:** ALT, GGTP, bilirubin, alk phos, PT  
**Followup interval:** 40 days  
**Assessment time points with results reported:** 40 days | **Type:** CPH, CAH, hepatic cirrhosis, etiology not given  
**Include:** Diagnosis based on hepatic biopsy; clinical and laboratory data on CAH and CPH patients; some hepatic cirrhosis patients did not have hepatic biopsy; medium forms of disease; both sexes; 20 to 60 years old; basic disease from 1 to 10 years  
**Exclude:** Not given  
**Acuity/severity:** Chronic, no other information  
**Baseline group similarity:** Age, LFTs appear similar | **N:** 177  
**Mean age:** 53  
**Percent male:** 47  
**Setting:** Hospital | **CAH**  
**CHP**  
**HCV**  
**Significant:**  
**Trend:**  
**Not significant:** ALT, GGTP, bilirubin, alk phos, PT |
| **Author:** Ferenci  
**Year:** 1989  
**Country:** Austria  
**Language:** English | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon®)/420 mg daily/ mean 41 months, range 2 to 6 years  
**Control:** Placebo  
**Outcome measures:** AST, ALT, GGTP, alk phos, bilirubin, albumin, PT  
**Followup interval:** 4 years  
**Assessment time points with results reported:** 2 and 4 to 5.5 years for survival | **Type:** Alcoholic and nonalcoholic cirrhosis; cirrhosis with alcoholic hepatitis  
**Include:** Diagnosis of cirrhosis within 2 years before entering study  
**Exclude:** End-stage liver disease; known malignancies; primary biliary cirrhosis; immunosuppressive therapy  
**Acuity/severity:** Chronic, cirrhosis, Child’s score A/B/C 89/69/12  
**Baseline group similarity:** Demos, LFTs appear similar | **N:** 170  
**Mean age:** 57  
**Percent male:** 72  
**Setting:** Primary care/community clinic, specialty clinic, hospital | **Survival**  
**A:**  
**B:**  
**C:**  
**Significant:** Survival (alcohol disease, Child’s score A)  
**Not significant:** (No data given; reported only as not significant) AST, ALT, GGTP, bilirubin, survival (nonalcohol disease, Child’s score B and C)  
**Correspondence from Ferenci, Oct. 10, 1999:** Length of treatment was variable. All patients were treated for 2 years (original primary endpoint) and were continued on the same therapy until the last patient that entered completed 2 years of therapy. Mortality was 27/83 in placebo group and 20/83 in silymarin group. |
| **Author:** Benda  
**Year:** 1980  
**Country:** Germany  
**Language:** German | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon®)/420 mg daily/ Unclear  
**Control:** Placebo MVI  
**Outcome measures:** Survival  
**Followup interval:** 4 years  
**Assessment time points with results reported:** 4 years | **Type:** Alcoholic and nonalcoholic cirrhosis  
**Include:** Biopsy-proven cirrhosis  
**Exclude:** Moribund; poor compliance; immunosuppressive treatment in the past year; prednisone in past 6 months; D-penicillamine in past 3 months; primary biliary cirrhosis; Wilson’s disease  
**Acuity/severity:** Chronic, cirrhosis, no other information  
**Baseline group similarity:** No information | **N:** 172  
**Mean age:** Not given  
**Percent male:** Not given  
**Setting:** Unclear | **Survival**  
**A:**  
**B:**  
**C:**  
**Significant:** Survival  
**Not significant:** |

Note: Trend was assessed qualitatively only for this review.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author: Marcelli</td>
<td>Study type: RCT/blinding unclear</td>
<td>Type: CPH, etiology unknown</td>
<td>N: 65</td>
<td>Significant: AST, ALT</td>
</tr>
<tr>
<td>Year: 1992</td>
<td>Intervention/dose/duration: Silipide®/240 mg daily/90 days</td>
<td>Include: Biopsy confirmed CPH, ALT, or AST 1.5 or greater than 2 times normal limits in past year</td>
<td>Mean age: 48</td>
<td>Not significant: Bilirubin, albumin, PT</td>
</tr>
<tr>
<td>Country: Italy</td>
<td>Control: Placebo</td>
<td>Exclude: Other forms of liver disease (non-CPH) or decompensated disease; treatment with interferon antivirals, immunosuppressants, or immunomodulators within past 6 months</td>
<td>Percent male: 71</td>
<td>Setting: Specialty clinic</td>
</tr>
</tbody>
</table>
| Language: English | Outcome measures: AST, ALT, bilirubin, albumin, PT | Acuity/severity: Chronic, no other information | Baseline group similarity: Demos appear similar; higher AST and ALT in Silipide® group |}

*aResults not necessarily reported for all. Abbreviations used: alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAH = chronic active hepatitis; CPH = chronic persistent hepatitis; demos = demographic variables; GGTP = gammaglutamyl transpeptidase; HCV = hepatitis C virus; LFT = liver function test; MVI = multivitamin; PT = prothrombin time; RCT = randomized controlled trial.*
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Magliulo, 78<sup>a</sup>  
**Year:** 1978  
**Country:** Italy  
**Language:** German | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon®)/420 mg daily/25 days  
**Control:** Placebo  
**Outcome measures:** AST, ALT, GGTP, alk phos, bilirubin, PT  
**Followup interval:** 1, 3, 5, 7, 9, 14, 21, 28 days  
**Assessment time points with results reported:** All followup | **Type:** Viral HAV and HBV  
**Include:** Acute HAV and HBV patients  
**Exclude:** Not given  
**Acuity/severity:** Acute, no other information  
**Baseline group similarity:** LFTs appear similar | **N:** 59  
**Mean age:** 37  
**Percent male:** 22  
**Setting:** Hospital | **Significant:** AST, bilirubin  
**+ Trend:** ALT  
**Not significant:** Alk phos  
**Note:** Trend was assessed qualitatively only for this review. |

<sup>a</sup>Results not necessarily reported for all. Abbreviations used: alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGTP = gammaglutamyl transpeptidase; HAV = hepatitis A virus; HBV = hepatitis B virus; LFT = liver function test; PT = prothrombin time; RCT = randomized controlled trial.
### Summary Table 4. Placebo-controlled studies of milk thistle for chronic viral hepatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Buzelli<sup>79</sup>  
**Year:** 1993  
**Country:** Italy  
**Language:** English | Study type: RCT/blind  
Intervention/dose/duration: Silipide®/240 mg silybin equivalents daily/7 days  
Control: Placebo  
Outcome measures<sup>a</sup>: AST, ALT, GGTP, MDA, alk phos, bilirubin, albumin  
Followup interval: 7 days  
Assessment time points with results reported: 7 days | Type: Chronic active hepatitis due to HBV and/or HCV  
Include: Biopsy-proven CAH, AST, and/or ALT greater than twice normal limits for more than 12 months; age 30 to 70 years old  
Exclude: Portal hypertension; hepatic encephalopathy, ascites, hepatocellular cancer, pruritus, icterus bilirubin, and alk phos more than twofold reference values; drug addiction and ANA, AMA, and ASMA; alcohol exceeding 30 g/d; malabsorption syndromes; cardiovascular, renal, or endocrine disorders; pregnancy; any drug treatment 3 months before beginning trial  
Acuity/severity: Chronic, AST or ALT greater than twice normal limits  
Baseline group similarity: Demos, LFTs appear similar | N: 20  
Mean age: 53  
Percent male: 30  
Setting: Hospital  
Significant: AST, ALT, GGTP  
Not significant: Bilirubin, alk phos, MDA, albumin |
| **Author:** Kiesewetter<sup>80</sup>  
**Year:** 1977  
**Country:** Austria  
**Language:** German | Study type: RCT/quasi  
Intervention/dose/duration: Silymarin (Legalon®)/420 mg daily/365 days  
Control: Placebo  
Outcome measures<sup>b</sup>: Histology  
Followup interval: 14, 30, 60 days then every 90 days to 1 year  
Assessment time points with results reported: One, combined/90 to 360 days | Type: Viral hepatitis (CPH and CAH)  
Include: CPH or CAH for more than 6 months; other medications for liver discontinued for 2 weeks or more  
Exclude: Disease less than 6 months; previous treatment with silymarin, steroids, or other cytotoxic drugs; alcohol exceeding 80 g/d or exceeding alcohol intake by laboratory values than patients’ statement; other comorbidities requiring medications  
Acuity/severity: Chronic, no other information  
Baseline group similarity: Demos, similar, no information on LFTs | N: 24  
Mean age: 53  
Percent male: 50  
Setting: Hospital  
Significant: + Trend: Improvement in liver biopsy  
Not significant: Note: Trend was assessed qualitatively only for this review. |

<sup>a</sup>Results not necessarily reported for all. Abbreviations used: alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = antismooth muscle antibody; AST = aspartase aminotransferase; CAH = chronic active hepatitis; CPH = chronic persistent hepatitis; demos = demographic variables; GGTP = gammaglutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function test; MDA = malondialdehyde; RCT = randomized controlled trial.
**Summary Table 5. Placebo-controlled studies of milk thistle and cirrhosis due to alcohol or other etiologies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Benda<sup>76</sup>  
**Year:** 1980  
**Country:** Germany  
**Language:** German | Study type: RCT/blind  
*Intervention/dose/duration:* Silymarin (Legalon<sup>®</sup>)/420 mg daily/ Unclear  
*Control:* Placebo MVI  
*Outcome measures:* Survival  
*Followup interval:* 4 years  
*Assessment time points with results reported:* 4 years | Type: Alcoholic and nonalcoholic cirrhosis  
*Include:* Biopsy-proven cirrhosis  
*Exclude:* Moribund; poor compliance; immunosuppressive treatment in the past year; Prednisone in past 6 months; D-Penicillamine in past 3 months; primary biliary cirrhosis; Wilson’s disease  
*Acuity/severity:* Chronic, cirrhosis, no other information  
*Baseline group similarity:* No information | N: 172  
*Mean age:* Not given  
*Percent male:* Not given  
*Setting:* Unclear | Significant:  
+ Trend: Survival  
Not significant:  
Note: Trend was assessed qualitatively only for this review. |

| **Author:** Ferenci<sup>75</sup>  
**Year:** 1989  
**Country:** Austria  
**Language:** English | Study type: RCT/blind  
*Intervention/dose/duration:* Silymarin (Legalon<sup>®</sup>)/420 mg daily/ mean 41 months, range 2 to 6 years  
*Control:* Placebo  
*Outcome measures:* AST, ALT, GGTP, alk phos, bilirubin, albumin, PT  
*Followup interval:* 4 years  
*Assessment time points with results reported:* 2 and 4 to 5.5 years for survival | Type: Alcoholic and nonalcoholic cirrhosis; cirrhosis with alcoholic hepatitis  
*Include:* Diagnosis of cirrhosis within 2 years before entering study  
*Exclude:* End-stage liver disease; known malignancies; primary biliary cirrhosis; immunosuppressive therapy  
*Acuity/severity:* Chronic, cirrhosis, Child’s score A/B/C 89/69/12  
*Baseline group similarity:* Demos, LFTs appear similar | N: 170  
*Mean age:* 57  
*Percent male:* 72  
*Setting:* Primary care/community clinic, specialty clinic, hospital | Significant: Survival (alcohol disease, Child’s score A)  
Not significant: (No data given; reported only as not significant) AST, ALT, GGTP, bilirubin, survival (nonalcohol disease, Child’s score B and C)  
Correspondence from Ferenci, Oct. 10, 1999: Length of treatment was variable. All patients were treated for 2 years (original primary endpoint) and were continued on the same therapy until the last patient that entered completed 2 years of therapy. Mortality was 27/83 in placebo group and 20/83 in silymarin group. |

<sup>a</sup>Results not necessarily reported for all. Abbreviations used: alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartase aminotransferase; demos = demographic variables; GGTP = gammaglutamyl transpeptidase; LFT = liver function test; MVI = multivitamin; PT = prothrombin time; RCT = randomized controlled trial.
### Summary Table 6. Placebo-controlled studies of milk thistle and alcoholic cirrhosis (other etiologies of cirrhosis excluded)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Pares&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;<strong>Year:</strong> 1998&lt;br&gt;<strong>Country:</strong> Spain&lt;br&gt;<strong>Language:</strong> English</td>
<td><strong>Study type:</strong> RCT/blind&lt;br&gt;<strong>Intervention/dose/duration:</strong> Silymarin (Legalon&lt;sup&gt;b&lt;/sup&gt;)&lt;br&gt;450 mg daily/unclear</td>
<td><strong>Type:</strong> Alcoholic cirrhosis (24 percent had superimposed alcohol hepatitis)&lt;br&gt;<strong>Include:</strong> Chronic alcoholism defined as alcohol exceeding 80 g/d men and 60 g/d women for more than 5 years; biopsy or laparoscopic proven alcoholic cirrhosis&lt;br&gt;<strong>Exclude:</strong> If ever received colchicine, malotilate, penicillamine, or corticosteroids; life expectancy less than 6 months; drug addicted or pregnant; other known etiologies for cirrhosis (i.e., HBV, autoimmunity, primary biliary cirrhosis, or cryptogenic cirrhosis)&lt;br&gt;<strong>Acuity/severity:</strong> Chronic, all cirrhosis, Child’s score A/B/C 63/114/14&lt;br&gt;<strong>Baseline group similarity:</strong> Demos, LFTs appear similar</td>
<td><strong>N:</strong> 200&lt;br&gt;<strong>Mean age:</strong> 50&lt;br&gt;<strong>Percent male:</strong> 79&lt;br&gt;<strong>Setting:</strong> Diagnosis in hospital then outpatient followup.</td>
<td><strong>Significant:</strong>&lt;br&gt;+ Trend: Encephalopathy, UGIB, survival for HCV-positive patients&lt;br&gt;<strong>Not significant:</strong> AST, ALT, GGTP, PT, bilirubin, alk phos, hepatomegaly, splenomegaly, jaundice, ascites, survival&lt;br&gt;<strong>Note:</strong> Trend was assessed qualitatively only for this review.</td>
</tr>
<tr>
<td><strong>Author:</strong> Lang&lt;sup&gt;71&lt;/sup&gt;&lt;br&gt;<strong>Year:</strong> 1990&lt;br&gt;<strong>Country:</strong> Hungary&lt;br&gt;<strong>Language:</strong> English</td>
<td><strong>Study type:</strong> RCT/blind/three arms&lt;br&gt;<strong>Interventions/dose/duration:</strong> Silymarin (Legalon&lt;sup&gt;b&lt;/sup&gt;)&lt;br&gt;420 mg daily/30 days&lt;br&gt;AICA-P/600 mg daily/30 days</td>
<td><strong>Type:</strong> Alcoholic cirrhosis&lt;br&gt;<strong>Include:</strong> Alcohol intake exceeding 60 g/d in men and 30 g/d women for more than 6 years; histologic diagnosis of micronodular cirrhosis&lt;br&gt;<strong>Exclude:</strong> Vascular and/or parenchymal decompensation; +HBsAg&lt;br&gt;<strong>Acuity/severity:</strong> Chronic, cirrhosis, no other information&lt;br&gt;<strong>Baseline group similarity:</strong> LFTs appear similar</td>
<td><strong>N:</strong> 60&lt;br&gt;<strong>Mean age:</strong> 45&lt;br&gt;<strong>Percent male:</strong> 68&lt;br&gt;<strong>Setting:</strong> Unclear</td>
<td><strong>Significant:</strong> AST, ALT, GGTP&lt;br&gt;<strong>Not significant:</strong> Bilirubin</td>
</tr>
</tbody>
</table>

<sup>a</sup>Results not necessarily reported for all. Abbreviations used: AICA-P = aminoimidazol carboxamid phosphate; alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; demos = demographic variables; GGTP = gammaglutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function test; PT = prothrombin time; RCT = randomized controlled trial; UGIB = upper gastrointestinal bleed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Palasciano<sup>81</sup>  
**Year:** 1994  
**Country:** Italy  
**Language:** English | **Study type:** RCT/blind, factorial design  
**Intervention/dose/duration:** Silymarin and psychotropic drugs/800 mg silymarin daily/90 days  
Silymarin and psychotropic drugs discontinued/800 mg daily/90 days  
**Control:** Placebo and no psychotropic drugs discontinued  
Placebo and psychotropic drugs/ not given/90 days  
**Outcome measures:** AST, ALT, MDA  
**Followup interval:** Day 15, 30, 60, 90, 120  
**Assessment time points with results reported:** 30, 60, 90, and 120 days for MDA; 30 and 90 for AST and ALT | **Type:** Drug-induced liver disease (some patients were HBV-positive)  
**Include:** Women 40 to 60 years old; hospitalized; phenothiazines and/or butyrophenones for 5 years; AST or ALT greater than twice normal limits  
**Exclude:** Current therapy with other drugs that could influence progress of hepatopathy; other hepatopathies (alcohol, viral, autoimmune, hemochromatosis, Wilson’s disease, porphyria cutanea tarda, primary or secondary hepatic neoplasia); BUN exceeding 60 mg/dL and/or creatinine exceeding 2.5 mg/dL; cardiac and circulatory insufficiency; diabetes mellitus; other important extrahepatic diseases; verified or presumed pregnancy; alcohol (more than 30 g/d) or opiate abuse  
**Acuity/severity:** Chronic; AST or ALT greater than two times the normal limit  
**Baseline group similarity:** Demos similar; LFTs variable | **N:** 60  
**Mean age:** 52  
**Percent male:** 0  
**Setting:** Hospital | **Significant:** MDA for psychotropic drugs with silymarin versus placebo  
**Not significant:** AST, ALT, MDA for psychotropic drugs discontinued, silymarin versus placebo |

<sup>a</sup>Results not necessarily reported for all. Abbreviations used: ALT = alanine aminotransferase; AST = aspartase aminotransferase; BUN = blood urea nitrogen; demos = demographic variables; HBV = hepatitis B virus; LFT = liver function test; MDA = malondialdehyde; RCT = randomized controlled trial.
## Summary Table 8. Prophylactic milk thistle with hepatotoxic drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author**: Magula<sup>82</sup>  
**Year**: 1996  
**Country**: Slovak  
**Language**: Slovak | **Study type**: RCT/not blinded/prophylaxis  
Intervention/dose/duration: tuberculosis treatment and Hepabene<sup>®</sup> (Silymarin and *Fumaria officinalis* alkaloids)/2 capsules daily/8 weeks  
**Control**: Tuberculosis medications alone  
**Outcome measures**: AST, ALT, bilirubin, “liver injury,” interruption of tuberculosis medications  
**Followup interval**: Every 2 weeks for 8 weeks  
**Assessment time points with results reported**: 8 weeks (56 days) | **Type**: Drug-induced liver disease  
**Include**: Patients requiring tuberculosis treatment; normal LFTs at baseline  
**Exclude**: Not given  
**Acuity/severity**: No disease at baseline | **N**: 172 (92 tuberculosis medications alone; 29 tuberculosis medications plus silymarin)  
**Mean age**: 50  
**Percent male**: 60  
**Setting**: Unclear | **Significant**: AST, ALT  
**Not significant**: |
| **Author**: Allain<sup>83</sup>  
**Year**: 1999  
**Country**: France  
**Language**: English | **Study type**: RCT/blind/prophylaxis  
Intervention/dose/duration: Silymarin/420 mg daily/84 days  
**Control**: Placebo  
**Outcome measures**: AST, ALT  
**Followup interval**: 8 times over 15 weeks  
**Assessment time points with results reported**: 8 times over 15 weeks | **Type**: Drug-(Tacrine-) induced liver disease  
**Include**: Patient over 50 years old; mild to moderate Alzheimer’s disease; Tacrine treatment  
**Exclude**: Past history hepatic disorder (cirrhosis, increased bilirubin, AST, and/or ALT)  
**Acuity/severity**: No disease at baseline | **N**: 222  
**Mean age**: Approximately 74  
**Percent male**: 39  
**Setting**: Specialty clinic | **Significant**:  
**Not significant**: AST, ALT |

<sup>8</sup>Results not necessarily reported for all. Abbreviations used: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver function test; RCT = randomized controlled trial.
## Summary Table 9. Phase II study of Silipide®

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Vailati</td>
<td>Study type: RCT/not blind/Phase II study</td>
<td>Type: Viral and alcoholic hepatitis</td>
<td>N: 60</td>
<td>Significant: AST, GGTP, bilirubin for 240 or 360 mg versus 160 mg</td>
</tr>
<tr>
<td><strong>Year:</strong> 1993</td>
<td>Intervention/dose/duration: Silymarin (Silipide®)/160 mg silybin equivalents daily/14 days</td>
<td>Include: Biopsy-proven chronic hepatitis (viral or alcoholic); AST and ALT 1.5 or greater than 2 times normal limits and biopsy within 1 year</td>
<td>Mean age: 50</td>
<td>Not significant:</td>
</tr>
<tr>
<td><strong>Country:</strong> Italy</td>
<td>Silymarin (Silipide®)/240 mg silybin equivalents daily/14 days</td>
<td>Exclude: Other forms of liver disease; decompensated liver disease; treatment with interferon, antivirals, immunosuppressants, or immunodulators for 6 months or less</td>
<td>Percent male: 62</td>
<td></td>
</tr>
<tr>
<td><strong>Language:</strong> English</td>
<td>Silymarin (Silipide®)/360 mg silybin equivalents daily/14 days</td>
<td>Acuity/severity: Chronic, no other information</td>
<td>Setting: Outpatient clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control: No treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outcome measures*: AST, GGTP, bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Followup interval: 7, 14 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assessment time points with results reported: 7, 14 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aResults not necessarily reported for all. Abbreviations used: ALT = alanine aminotransferase; AST = aspartase aminotransferase; GGTP = gammaglutamyl transpeptidase; RCT = randomized controlled trial.
### Summary Table 10. Effect sizes and meta-analyses of 16 placebo-controlled trials (Evidence Tables 1 and 2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Units 95% CI</th>
<th>p Value(^c) (ES ≠ 0)</th>
<th>Q p Value(^c) (homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AST without drug study</strong></td>
<td>≤45 days</td>
<td>6</td>
<td>−0.25 (−0.47 to −0.02)</td>
<td>−11.2 (−21.0 to −0.9)</td>
<td>0.03</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>3</td>
<td>−0.27 (−0.96 to 0.42)</td>
<td>−12.1 (−4.30 to 89.5)</td>
<td>0.44</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>90 days without outlier</td>
<td>2</td>
<td>−0.02 (−0.76 to 0.72)</td>
<td>−0.9 (−34.0 to 32.2)</td>
<td>0.96</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>−0.37 (−1.03 to 0.29)</td>
<td>−16.6 (−46.1 to 13.0)</td>
<td>0.27</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>0.37 (−0.21 to 0.95)</td>
<td>17.5 (−9.4 to 42.5)</td>
<td>0.21</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.28 (−0.07 to 0.63)</td>
<td>12.5 (−3.1 to 28.2)</td>
<td>0.12</td>
<td>−</td>
</tr>
<tr>
<td><strong>AST with drug study</strong></td>
<td>≤45 days</td>
<td>8</td>
<td>−0.21 (−0.42 to −0.004)</td>
<td>−9.4 (−18.8 to −0.2)</td>
<td>0.046</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>5</td>
<td>−0.30 (−0.73 to 0.13)</td>
<td>−13.4 (−32.7 to 5.8)</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>90 days without outlier</td>
<td>4</td>
<td>−0.53 (−0.85 to −0.22)</td>
<td>−23.7 (−38.0 to −9.8)</td>
<td>0.001</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>ALT without drug study</strong></td>
<td>≤45 days</td>
<td>7</td>
<td>−0.09 (−0.45 to 0.28)</td>
<td>−3.2 (−16.2 to 10.1)</td>
<td>0.64</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>≤45 days without outlier</td>
<td>6</td>
<td>−0.22 (−0.42 to −0.03)</td>
<td>−7.9 (−15.1 to −1.1)</td>
<td>0.03</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>−0.65 (−1.15 to −0.15)</td>
<td>−23.4 (−41.4 to −5.4)</td>
<td>0.01</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>−0.28 (−0.94 to 0.38)</td>
<td>−10.1 (−33.9 to 13.7)</td>
<td>0.41</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.33 (−0.02 to 0.68)</td>
<td>11.9 (−0.7 to 24.5)</td>
<td>0.07</td>
<td>−</td>
</tr>
<tr>
<td><strong>ALT with drug study</strong></td>
<td>≤45 days</td>
<td>9</td>
<td>−0.07 (−0.37 to 0.23)</td>
<td>−2.5 (−13.3 to 8.3)</td>
<td>0.66</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>≤45 days without outlier</td>
<td>8</td>
<td>−0.19 (−0.37 to −0.01)</td>
<td>−6.8 (−13.3 to −0.4)</td>
<td>0.04</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>4</td>
<td>−0.48 (−0.83 to −0.14)</td>
<td>−17.3 (−29.9 to −5.0)</td>
<td>0.01</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>GGTP</strong></td>
<td>≤45 days</td>
<td>5</td>
<td>−0.21 (−0.45 to 0.02)</td>
<td>−32.3 (−69.3 to 3.1)</td>
<td>0.08</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>−0.04 (−0.41 to 0.32)</td>
<td>−6.2 (−63.1 to 49.3)</td>
<td>0.81</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>−0.64 (−1.30 to 0.02)</td>
<td>−98.5 (−200.1 to 3.1)</td>
<td>0.06</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>−0.26 (−0.84 to 0.32)</td>
<td>−40.0 (−129.3 to 49.3)</td>
<td>0.38</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.38 (0.02 to 0.73)</td>
<td>58.5 (3.1 to 112.4)</td>
<td>0.04</td>
<td>−</td>
</tr>
<tr>
<td><strong>MDA 6.65 nmol/ml</strong></td>
<td>≤45 days</td>
<td>1</td>
<td>−0.09 (−0.96 to 0.79)</td>
<td>−0.6 (−6.4 to 5.3)</td>
<td>0.85</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>−0.81 (−1.49 to −1.13)</td>
<td>−5.3 (−9.9 to −7.5)</td>
<td>0.02</td>
<td>−</td>
</tr>
<tr>
<td><strong>Alkaline phosphate</strong></td>
<td>≤45 days</td>
<td>5</td>
<td>−0.04 (−0.25 to 0.16)</td>
<td>−4.0 (−25.3 to 16.2)</td>
<td>0.68</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>0.10 (−0.55 to 0.76)</td>
<td>10.1 (−55.6 to 76.8)</td>
<td>0.76</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>−0.34 (−1.00 to 0.34)</td>
<td>−34.3 (−101.0 to 34.3)</td>
<td>0.31</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>−0.05 (−0.63 to 0.53)</td>
<td>−5.0 (−63.6 to 53.5)</td>
<td>0.87</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>−0.08 (−0.43 to 0.27)</td>
<td>−8.1 (−43.4 to 27.3)</td>
<td>0.66</td>
<td>−</td>
</tr>
</tbody>
</table>
Summary Table 10. Effect sizes and meta-analyses of 16 placebo-controlled trials (Evidence Tables 1 and 2) (continued)

<table>
<thead>
<tr>
<th>Outcomea</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Unitsb 95% CI</th>
<th>p Valuec (ES ≠ 0)</th>
<th>Q p Valuec (homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin 0.32 g/dLa</td>
<td>≤45 days</td>
<td>4</td>
<td>−0.28 (−0.52 to −0.03)</td>
<td>−0.1 (−0.2 to −0.01)</td>
<td>0.03</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>3</td>
<td>0.02 (−0.33 to 0.37)</td>
<td>0.01 (−0.1 to 0.1)</td>
<td>0.91</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>−0.49 (−1.15 to 0.17)</td>
<td>−0.2 (−0.4 to 0.05)</td>
<td>0.15</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>−0.16 (−0.74 to 0.43)</td>
<td>−0.05 (−0.2 to 0.1)</td>
<td>0.60</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.00 (−0.35 to 0.36)</td>
<td>0.0 (−0.1 to 0.1)</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Albumin 0.74 g/dLa</td>
<td>90 days</td>
<td>3</td>
<td>−0.08 (−0.53 to 0.38)</td>
<td>−0.05 (−0.4 to 0.3)</td>
<td>0.74</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>0.19 (−0.46 to 0.84)</td>
<td>0.1 (−0.3 to 0.6)</td>
<td>0.57</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>0.25 (−0.35 to 0.85)</td>
<td>0.2 (−0.2 to 0.6)</td>
<td>0.42</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>−0.23 (−0.58 to 0.12)</td>
<td>−0.2 (−0.4 to 0.1)</td>
<td>0.20</td>
<td>–</td>
</tr>
<tr>
<td>PT 17.39s seconds</td>
<td>≤45 days</td>
<td>1</td>
<td>0.14 (−0.16 to 0.44)</td>
<td>2.4 (−2.8 to 7.7)</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>3</td>
<td>−0.19 (−0.67 to 0.28)</td>
<td>−3.3 (−11.6 to 4.9)</td>
<td>0.42</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>0.47 (−0.20 to 1.14)</td>
<td>8.2 (−3.5 to 19.8)</td>
<td>0.17</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>−0.29 (−0.87 to 0.29)</td>
<td>−5.0 (−15.1 to 5.0)</td>
<td>0.32</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>−0.18 (−0.53 to 0.17)</td>
<td>−3.1 (−9.2 to 3.0)</td>
<td>0.31</td>
<td>–</td>
</tr>
<tr>
<td>Child’s 2.55 score</td>
<td>15 months</td>
<td>1</td>
<td>−0.09 (−0.68 to 0.50)</td>
<td>−0.2 (−1.7 to 1.3)</td>
<td>0.78</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.27 (−0.08 to 0.62)</td>
<td>0.7 (−0.2 to 1.6)</td>
<td>0.13</td>
<td>–</td>
</tr>
</tbody>
</table>

When there was more than one study, effect sizes were pooled.

a Mean pooled standard deviations.

b Standard deviation effect size units are back-converted to clinical effect sizes by standard deviation x effect size.

c All studies refer to combination of chronic alcohol, chronic and acute viral, and chronic mixed etiology unless otherwise noted (the inclusion of one drug study, factorial design); values reported for meta-analytic results; N/A for single study estimates.

Abbreviations used: ALT = alanine aminotranferase; AST = aspartase aminotranferase; CI = 95% confidence interval; ES = effect size; GGTP = gammaglutamyl transpeptidase; MDA = malondialdehyde; PT = prothrombin time; SD = standard deviation; U/L = units per liter.
Summary Table 11. Effect sizes and meta-analyses of 14 randomized, placebo-controlled trials of higher methodological quality (Evidence Table 1)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Units 95% CI</th>
<th>p Value (ES ≠ 0)</th>
<th>Q p Value (Homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST without drug study 44.77 U/L</td>
<td>≤45 days</td>
<td>5</td>
<td>-0.27 (-0.52 to -0.03)</td>
<td>-12.1 (-23.3 to -1.3)</td>
<td>0.03</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.02 (-0.76 to 0.72)</td>
<td>-0.9 (-34.0 to 32.2)</td>
<td>0.96</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.37 (-1.03 to 0.29)</td>
<td>-16.6 (-46.1 to 13.0)</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>0.37 (-0.21 to 0.95)</td>
<td>17.5 (-9.4 to 42.5)</td>
<td>0.21</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.28 (-0.07 to 0.63)</td>
<td>12.5 (-3.1 to 28.2)</td>
<td>0.12</td>
<td>–</td>
</tr>
<tr>
<td>AST with drug study 44.77 U/L</td>
<td>≤45 days</td>
<td>7</td>
<td>-0.23 (-0.46 to -0.004)</td>
<td>-10.3 (-20.6 to -0.2)</td>
<td>0.046</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>4</td>
<td>-0.15 (-0.58 to 0.27)</td>
<td>-1.8 (-18.4 to 14.8)</td>
<td>0.48</td>
<td>0.14</td>
</tr>
<tr>
<td>ALT without drug study 36.02 U/L</td>
<td>≤45 days</td>
<td>6</td>
<td>-0.14 (-0.55 to 0.28)</td>
<td>-5.0 (-19.8 to 10.1)</td>
<td>0.52</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>-0.39 (-1.05 to 0.27)</td>
<td>-14.0 (-37.8 to 9.7)</td>
<td>0.24</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.28 (-0.94 to 0.38)</td>
<td>-10.1 (-33.9 to 13.7)</td>
<td>0.41</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.33 (-0.02 to 0.68)</td>
<td>11.9 (-0.7 to 24.5)</td>
<td>0.07</td>
<td>–</td>
</tr>
<tr>
<td>ALT with drug study 36.02 U/L</td>
<td>≤45 days</td>
<td>8</td>
<td>-0.10 (-0.43 to 0.23)</td>
<td>-3.6 (-15.5 to 8.3)</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>GGTP 153.94 U/L</td>
<td>≤45 days</td>
<td>5</td>
<td>-0.21 (-0.45 to 0.02)</td>
<td>-32.3 (-69.3 to 3.1)</td>
<td>0.08</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.04 (-0.41 to 0.32)</td>
<td>-6.2 (-63.1 to 49.3)</td>
<td>0.81</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.64 (-1.30 to 0.02)</td>
<td>-98.5 (-200.1 to 3.1)</td>
<td>0.06</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.26 (-0.84 to 0.32)</td>
<td>-40.0 (-129.3 to 49.3)</td>
<td>0.38</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.38 (0.02 to 0.73)</td>
<td>58.5 (3.1 to 112.4)</td>
<td>0.04</td>
<td>–</td>
</tr>
<tr>
<td>MDA 6.65 nmol/ml</td>
<td>≤45 days</td>
<td>1</td>
<td>-0.09 (-0.96 to 0.79)</td>
<td>-0.6 (-6.4 to 5.3)</td>
<td>0.85</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.81 (-0.149 to -1.13)</td>
<td>-5.4 (-9.9 to -7.5)</td>
<td>0.02</td>
<td>–</td>
</tr>
<tr>
<td>Alkaline Phosphate 101.01 U/L</td>
<td>≤45 days</td>
<td>4</td>
<td>-0.04 (-0.26 to 0.17)</td>
<td>-4.0 (-26.3 to 17.2)</td>
<td>0.70</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>1</td>
<td>0.10 (-0.55 to 0.76)</td>
<td>10.1 (-55.6 to 76.8)</td>
<td>0.76</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.34 (-1.00 to 0.34)</td>
<td>-34.3 (-101.0 to 34.3)</td>
<td>0.31</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.05 (-0.63 to 0.53)</td>
<td>-5.0 (-63.6 to 53.5)</td>
<td>0.87</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>-0.08 (-0.43 to 0.27)</td>
<td>-8.1 (-43.4 to 27.3)</td>
<td>0.66</td>
<td>–</td>
</tr>
<tr>
<td>Bilirubin 0.32 g/dL</td>
<td>≤45 days</td>
<td>4</td>
<td>-0.28 (-0.52 to -0.03)</td>
<td>-0.1 (-0.2 to -0.01)</td>
<td>0.03</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.10 (-0.70 to 0.49)</td>
<td>-0.03 (-0.2 to 0.2)</td>
<td>0.73</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>-0.49 (-1.15 to 0.17)</td>
<td>-0.2 (-0.4 to 0.05)</td>
<td>0.15</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.16 (-0.74 to 0.43)</td>
<td>-0.05 (-0.2 to 0.1)</td>
<td>0.60</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.00 (-0.35 to 0.36)</td>
<td>0.0 (-0.1 to 0.1)</td>
<td>1.00</td>
<td>–</td>
</tr>
</tbody>
</table>
### Summary Table 11. Effect sizes and meta-analyses of 14 randomized, placebo-controlled trials of higher methodological quality (Evidence Table 1) (continued)

<table>
<thead>
<tr>
<th>Outcomea</th>
<th>Time of Followup</th>
<th>No. of Studies</th>
<th>Effect Size (SD units) 95% CI</th>
<th>Effect Size, Clinical Unitsb 95% CI</th>
<th>p Value&lt;sup&gt;c&lt;/sup&gt; (ES ≠ 0)</th>
<th>Q p Value&lt;sup&gt;c&lt;/sup&gt; (Homogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumin 0.74 g/dL</strong></td>
<td>90 days</td>
<td>2</td>
<td>-0.13 (−0.87 to 0.60)</td>
<td>-0.1 (−0.6 to 0.4)</td>
<td>0.72</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>0.19 (−0.46 to 0.84)</td>
<td>0.1 (−0.3 to 0.6)</td>
<td>0.57</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>0.25 (−0.35 to 0.85)</td>
<td>0.2 (−0.2 to 0.6)</td>
<td>0.42</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>-0.23 (−0.58 to 0.12)</td>
<td>-0.2 (−0.4 to 0.1)</td>
<td>0.20</td>
<td>–</td>
</tr>
<tr>
<td><strong>PT 17.39&lt;sup&gt;a&lt;/sup&gt; seconds</strong></td>
<td>≤45 days</td>
<td>1</td>
<td>0.14 (−0.16 to 0.44)</td>
<td>2.4 (−2.8 to 7.7)</td>
<td>0.35</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>2</td>
<td>-0.30 (−1.00 to 0.40)</td>
<td>-5.2 (−17.4 to 7.0)</td>
<td>0.40</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1</td>
<td>0.47 (−0.20 to 1.14)</td>
<td>8.2 (−3.5 to 19.8)</td>
<td>0.17</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15 months</td>
<td>1</td>
<td>-0.29 (−0.87 to 0.29)</td>
<td>-5.0 (−15.1 to 5.0)</td>
<td>0.32</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>-0.18 (−0.53 to 0.17)</td>
<td>-3.1 (−9.2 to 3.0)</td>
<td>0.31</td>
<td>–</td>
</tr>
<tr>
<td><strong>Child’s 2.55 score</strong></td>
<td>15 months</td>
<td>1</td>
<td>-0.09 (−0.68 to 0.50)</td>
<td>-0.2 (−1.7 to 1.3)</td>
<td>0.76</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>0.27 (−0.08 to 0.62)</td>
<td>0.7 (−0.2 to 1.6)</td>
<td>0.13</td>
<td>–</td>
</tr>
</tbody>
</table>

When there was more than one study, effect sizes were pooled.

* Mean pooled standard deviations.

* Standard deviation effect size units are back-converted to clinical effect sizes by standard deviation x effect size.

* All studies refer to combination of chronic alcohol, chronic and acute viral, and chronic mixed etiology unless otherwise noted (the inclusion of one drug study, factorial design); values reported for meta-analytic results; N/A for single study estimates.

Abbreviations used: ALT = alanine aminotransferase; AST = aspartase aminotranferase; CI = 95% confidence interval; ES = effect size; GGTP = gammaglutamyl transpeptidase; MDA = malondialdehyde; PT = prothrombin time; SD = standard deviation; U/L = units per liter.
<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible/probable anaphylaxis</td>
<td>Three case reports</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Four RCTs: silymarin ≤ control</td>
</tr>
<tr>
<td>Nausea, diarrhea, upset stomach, epigastric discomfort, heartburn, dyspepsia, flatulence, meteorism, “uneasiness” of stomach, vomiting, anorexia, change in bowel movement, “gastric intolerance,” abdominal fullness or pain</td>
<td>Five cohort studies: 0.3%, &lt;2%, 5%, 6%, 8%</td>
</tr>
<tr>
<td></td>
<td>11 occurrences/975 patients</td>
</tr>
<tr>
<td></td>
<td>9 occurrences/2,169 patients</td>
</tr>
<tr>
<td>Headache</td>
<td>Three RCTs: silymarin ≤ control</td>
</tr>
<tr>
<td></td>
<td>Two cohort studies: 0.04%, 0.04%</td>
</tr>
<tr>
<td>Skin:</td>
<td>Two RCTs: silymarin ≤ control</td>
</tr>
<tr>
<td>Itching, pruritus</td>
<td>Three cohort studies:</td>
</tr>
<tr>
<td></td>
<td>2 occurrences/2,637 patients</td>
</tr>
<tr>
<td></td>
<td>2 occurrences/975 patients</td>
</tr>
<tr>
<td></td>
<td>2 occurrences/2,169 patients</td>
</tr>
<tr>
<td>Exanthem, urticaria, skin rash, eczema</td>
<td>Two RCTs: silymarin ≤ control</td>
</tr>
<tr>
<td></td>
<td>Two cohort studies:</td>
</tr>
<tr>
<td></td>
<td>2 occurrences/975 patients</td>
</tr>
<tr>
<td></td>
<td>1 occurrence/2,169 patients</td>
</tr>
<tr>
<td>Other:</td>
<td>Cohort study: 0.3%</td>
</tr>
<tr>
<td>Decreased energy, discomfort, indisposition, decreased energy, restlessness</td>
<td>1 occurrence/975 patients</td>
</tr>
<tr>
<td></td>
<td>1 occurrence/2,169 patients</td>
</tr>
<tr>
<td>Asthenia, malaise, irritability</td>
<td>One RCT: silymarin ≤ control</td>
</tr>
<tr>
<td>Insomnia</td>
<td>One RCT: silymarin ≤ control</td>
</tr>
<tr>
<td>Arthalgia</td>
<td>One RCT: silymarin ≤ control</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td>One case report</td>
</tr>
<tr>
<td>Impotence</td>
<td>One RCT: 1/29 silymarin, 0/31 control</td>
</tr>
</tbody>
</table>

Frequency of adverse effects was sometimes reported as the following: (1) percent of subjects, (2) number of subjects, or (3) number of occurrences of adverse effects in a group of subjects without detail about subjects who may have had more than one adverse effect.

RCT = randomized controlled trial.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silimarlin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Benda&lt;br&gt;<strong>Year:</strong> 1980&lt;br&gt;<strong>Country:</strong> Germany&lt;br&gt;<strong>Language:</strong> German</td>
<td><strong>Study type:</strong> RCT/blind&lt;br&gt;<strong>Intervention/dose/duration:</strong> Silymarin (Legalon®)/420 mg daily/Unclear&lt;br&gt;<strong>Control:</strong> Placebo MVI&lt;br&gt;<strong>Outcome measures</strong>: Survival&lt;br&gt;<strong>Followup interval:</strong> 4 years&lt;br&gt;<strong>Assessment time points with results reported:</strong> 4 years</td>
<td><strong>Type:</strong> Alcoholic and nonalcoholic cirrhosis&lt;br&gt;<strong>Include:</strong> Biopsy-proven cirrhosis&lt;br&gt;<strong>Exclude:</strong> Moribund; poor compliance; immunosuppressive treatment in the past year; Prednisone in past 6 months; D-Penicillamine in past 3 months; primary biliary cirrhosis; Wilson’s disease&lt;br&gt;<strong>Acuity/severity:</strong> Chronic, cirrhosis, no other information&lt;br&gt;<strong>Baseline group similarity:</strong> No information</td>
<td><strong>N:</strong> 172&lt;br&gt;<strong>Mean age:</strong> Not given&lt;br&gt;<strong>Percent male:</strong> Not given&lt;br&gt;<strong>Setting:</strong> Unclear</td>
<td><strong>Significant:</strong>&lt;br&gt;<strong>+ Trend:</strong> Survival&lt;br&gt;<strong>Not significant:</strong>&lt;br&gt;<strong>Note:</strong> Trend was assessed qualitatively only for this review.</td>
</tr>
<tr>
<td><strong>Author:</strong> Bunout&lt;br&gt;<strong>Year:</strong> 1992&lt;br&gt;<strong>Country:</strong> Chile&lt;br&gt;<strong>Language:</strong> Spanish</td>
<td><strong>Study type:</strong> RCT/blind&lt;br&gt;<strong>Intervention/dose/duration:</strong> Silymarin (Legalon®)/280 mg daily/446 days&lt;br&gt;<strong>Control:</strong> Placebo&lt;br&gt;<strong>Outcome measures</strong>: AST, GGTP, alk phos, bilirubin, albumin, PT&lt;br&gt;<strong>Followup interval:</strong> Monthly for an average of 15 months&lt;br&gt;<strong>Assessment time points with results reported:</strong> Mean of 15 months</td>
<td><strong>Type:</strong> Alcoholic liver disease (inactive cirrhosis, active cirrhosis, cirrhosis with alcoholic hepatitis, alcoholic hepatitis, fibrosis)&lt;br&gt;<strong>Include:</strong> Positive for alcohol history and symptoms of icterus edema, ascites, or encephalopathy or total bilirubin exceeding 2 mg/dL; PT exceeding 75 percent control; albumin less than 3 mg/dL&lt;br&gt;<strong>Exclude:</strong> HBV antigen; renal failure; cardiac failure; terminal liver disease&lt;br&gt;<strong>Acuity/severity:</strong> Chronic, cirrhosis, no other information&lt;br&gt;<strong>Baseline group similarity:</strong> Demos, LFTs appear similar</td>
<td><strong>N:</strong> 59&lt;br&gt;<strong>Mean age:</strong> 50&lt;br&gt;<strong>Percent male:</strong> 86&lt;br&gt;<strong>Setting:</strong> Specialty clinic</td>
<td><strong>Significant:</strong> Albumin&lt;br&gt;<strong>Not significant:</strong> Child’s score, bilirubin, AST, GGTP, alk phos, PT</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Milk thistle for treatment of liver disease: Placebo-controlled, randomized, blinded trials (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Buzelli<sup>79</sup>  
**Year:** 1993  
**Country:** Italy  
**Language:** English | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silipide®/240 mg silybin equivalents daily/7 days  
**Control:** Placebo  
**Outcome measures:** AST, ALT, GGTP, MDA, alk phos, bilirubin, albumin  
**Followup interval:** 7 days  
**Assessment time points with results reported:** 7 days | **Type:** Chronic active hepatitis due to HBV and/or HCV  
**Include:** Biopsy-proven CAH, AST, and/or ALT greater than twice normal limits for more than 12 months; age 30 to 70 years old  
**Exclude:** Portal hypertension; hepatic encephalopathy, ascites, hepatocellular cancer, pruritus, icterus bilirubin, and alk phos more than two-fold reference values; drug addiction and ANA, AMA, and ASMA; alcohol exceeding 30 g/d; malabsorption syndromes; cardiovascular, renal, or endocrine disorders; pregnancy; any drug treatment 3 months before beginning trial  
**Acuity/severity:** Chronic, AST or ALT greater than twice normal limits  
**Baseline group similarity:** Demos, LFTs appear similar | **N:** 20  
**Mean age:** 53  
**Percent male:** 30  
**Setting:** Hospital |
| **Significant:** AST, ALT, GGTP  
**Not significant:** Bilirubin, alk phos, MDA, albumin |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Feher<sup>70,99,100</sup>  
**Year:** 1989/1990  
**Country:** Hungary  
**Language:** Hungarian | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon<sup>®</sup>)/420 mg daily/180 days  
**Control:** Placebo  
**Outcome measures<sup>a</sup>:** AST, ALT, GGTP, alk phos, bilirubin, albumin  
**Followup interval:** 90 and 180 days  
**Assessment time points with results reported:** 90 and 180 days | **Type:** Chronic alcoholic liver disease (cirrhosis, reactive fibrosis, fatty degeneration)  
**Include:** Alcohol intake exceeding 60 g/d in men and 30 g/d in women for 8 ± 4 years; chronic liver disease; no previous corticosteroid or immunosuppressive treatment  
**Exclude:** Not given  
**Acuity/severity:** Chronic, no other information  
**Baseline group similarity:** Demos, LFTs appear similar | **N:** 36  
**Mean age:** 46  
**Percent male:** 75  
**Setting:** Unclear | **Significant:** AST, GGTP, MDA  
**Not significant:** (Assumed for all) ALT, alk phos, albumin, PT |
| **Author:** Ferenci<sup>75</sup>  
**Year:** 1989  
**Country:** Austria  
**Language:** English | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon<sup>®</sup>)/420 mg daily/ mean 41 months, range 2 to 6 years  
**Control:** Placebo  
**Outcome measures<sup>a</sup>:** AST, ALT, GGTP, alk phos, bilirubin, albumin, PT  
**Followup interval:** 4 years  
**Assessment time points with results reported:** 2 and 4 to 5.5 years for survival | **Type:** Alcoholic and nonalcoholic cirrhosis; cirrhosis with alcoholic hepatitis  
**Include:** Diagnosis of cirrhosis within 2 years before entering study  
**Exclude:** End-stage liver disease; known malignancies; primary biliary cirrhosis; immunosuppressive therapy  
**Acuity/severity:** Chronic, cirrhosis, Child’s score A/B/C 89/69/12  
**Baseline group similarity:** Demos, LFTs appear similar | **N:** 170  
**Mean age:** 57  
**Percent male:** 72  
**Setting:** Primary care/community clinic, specialty clinic, hospital | **Significant:** Survival (alcohol disease, Child’s score A)  
**Not significant:** (No data given; reported only as not significant) AST, ALT, GGTP, bilirubin, survival (non-alcohol disease, Child’s score B and C)  
**Correspondence from Ferenci, October 10, 1999:** Length of treatment was variable. All patients were treated for 2 years (original primary end point) and were continued on the same therapy until the last patient that entered completed 2 years of therapy. Mortality was 27/83 in placebo group and 20/83 in silymarin group. |
Evidence Table 1. Milk thistle for treatment of liver disease: Placebo-controlled, randomized, blinded trials (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Fintelmann<sup>73</sup>  
**Year:** 1980  
**Country:** Germany  
**Language:** German | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon<sup>®</sup>)/not given/not given  
**Control:** Placebo  
**Outcome measures<sup>a</sup>:** AST, ALT, GGTP, alk phos, bilirubin  
**Followup interval:** Days 1, 3, 7, 10, 14, 21, 28  
**Assessment time points with results reported:** Had to read off graphs, but all followups | **Type:** Toxic liver disease, any etiology (usually alcohol)  
**Include:** Clinical and laboratory evidence of toxic liver damage  
**Exclude:** Not given  
**Acuity/severity:** No other information  
**Baseline group similarity:** No information except age and gender “similar” | N: 66  
**Mean age:** Not given  
**Percent male:** Not given  
**Setting:** Unclear | Significant: ALT, GGTP  
**Not significant:** AST, bilirubin, alk phos |
| **Author:** Kiesewetter<sup>80</sup>  
**Year:** 1977  
**Country:** Austria  
**Language:** German | **Study type:** RCT/quasi  
**Intervention/dose/duration:** Silymarin (Legalon<sup>®</sup>)/420 mg daily/365 days  
**Control:** Placebo  
**Outcome measures<sup>a</sup>:** Histologic findings  
**Followup interval:** 14, 30, 60 days then every 90 days to 1 year  
**Assessment time points with results reported:** One, combined/90 to 360 days | **Type:** Viral hepatitis (CPH and CAH)  
**Include:** CPH or CAH for more than 6 months; other medications for liver discontinued for 2 weeks or more  
**Exclude:** Disease less than 6 months; previous treatment with silymarin, steroids, or other cytotoxic drugs; alcohol exceeding 80 g/d or exceeding alcohol intake by laboratory values than patients’ statement; other comorbidities requiring medications  
**Acuity/severity:** Chronic, no other information  
**Baseline group similarity:** Demos, similar, no information on LFTs | N: 24  
**Mean age:** 53  
**Percent male:** 50  
**Setting:** Hospital | Significant:  
+ Trend: Improvement in liver biopsy  
**Not significant:**  
**Note:** Trend was assessed qualitatively only for this review. |
### Evidence Table 1. Milk thistle for treatment of liver disease: Placebo-controlled, randomized, blinded trials (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Lang(^7)</td>
<td><strong>Study type:</strong> RCT/blind/three arms</td>
<td>Type: Alcoholic cirrhosis</td>
<td>N: 60</td>
<td>Significant: AST, ALT, GGTP</td>
</tr>
<tr>
<td><strong>Year:</strong> 1990</td>
<td><strong>Interventions/dose/duration:</strong> Silymarin (Legalon(^6))/420 mg daily/30 days</td>
<td>Include: Alcohol intake exceeding 60 g/d in men and 30 g/d women for more than 6 years; histologic diagnosis of micronodular cirrhosis</td>
<td>Mean age: 45</td>
<td>Not significant: Bilirubin</td>
</tr>
<tr>
<td><strong>Country:</strong> Hungary</td>
<td><strong>Control:</strong> Placebo</td>
<td>Exclude: Vascular and/or parenchymal decompensation; +HBsAg</td>
<td>Percent male: 68</td>
<td></td>
</tr>
<tr>
<td><strong>Language:</strong> English</td>
<td><strong>Outcome measures:</strong> AST, ALT, GGTP, alk phos, albumin</td>
<td>Acuity/severity: Chronic, cirrhosis, no other information</td>
<td>Setting: Unclear</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Followup interval:</strong> 28 days</td>
<td>Baseline group similarity: LFTs appear similar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Assessment time points with results reported:</strong> Weekly for 1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Magliulo(^7)</td>
<td><strong>Study type:</strong> RCT/blind</td>
<td>Type: Viral HAV and HBV</td>
<td>N: 59</td>
<td>Significant: AST, bilirubin</td>
</tr>
<tr>
<td><strong>Year:</strong> 1978</td>
<td><strong>Intervention/dose/duration:</strong> Silymarin (Legalon(^6))/420 mg daily/25 days</td>
<td>Include: Acute HAV and HBV patients</td>
<td>Mean age: 37</td>
<td>+ Trend: ALT</td>
</tr>
<tr>
<td><strong>Country:</strong> Italy</td>
<td><strong>Control:</strong> Placebo</td>
<td>Exclude: Not given</td>
<td>Percent male: 22</td>
<td>Not significant: Alk phos</td>
</tr>
<tr>
<td><strong>Language:</strong> German</td>
<td><strong>Outcome measures:</strong> AST, ALT, GGTP, alk phos, bilirubin, PT</td>
<td>Acuity/severity: Acute, no other information</td>
<td>Setting: Hospital</td>
<td>Note: Trend was assessed qualitatively only for this review.</td>
</tr>
<tr>
<td></td>
<td><strong>Followup interval:</strong> 1, 3, 5, 7, 9, 14, 21, 28 days</td>
<td>Baseline group similarity: LFTs appear similar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Assessment time points with results reported:</strong> All followup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Liver Disease</td>
<td>Subject Characteristics</td>
<td>Outcomes (favoring silymarin unless otherwise noted)</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------------</td>
<td>--------------------------</td>
<td>---------------------------------------------------</td>
</tr>
</tbody>
</table>
| Author: Palasciano<sup>81</sup>  
Year: 1994  
Country: Italy  
Language: English | Study type: RCT/blind, factorial design  
Intervention/dose/duration: Silymarin and psychotropic drugs/800 mg silymarin daily/90 days  
Silymarin and psychotropic drugs discontinued/800 mg daily/90 days  
Control: Placebo and no psychotropic drugs discontinued  
Placebo and psychotropic drugs/ not given/90 days  
Outcome measures<sup>8</sup>: AST, ALT, MDA  
Followup interval: Day 15, 30, 60, 90, 120  
Assessment time points with results reported: 30, 60, 90, and 120 days for MDA; 30 and 90 for AST and ALT | Type: Drug-induced liver disease (some patients were HBV-positive)  
Include: Women 40 to 60 years old; hospitalized; phenothiazines and/or butyrophenones for 5 years; AST or ALT greater than twice normal limits  
Exclude: Current therapy with other drugs that could influence progress of hepatopathy; other hepatopathies (alcohol, viral, autoimmune, hemochromatosis, Wilson’s disease, porphyria cutanea tarda, primary or secondary hepatic neoplasia); BUN exceeding 60 mg/dL and/or creatinine exceeding 2.5 mg/dL; cardiac and circulatory insufficiency; diabetes mellitus; other important extrahepatic diseases; verified or presumed pregnancy; alcohol (more than 30 g/d) or opiate abuse  
Acuity/severity: Chronic; AST or ALT greater than two times the normal limit  
Baseline group similarity: Demos similar; LFTs variable | N: 60  
Mean age: 52  
Percent male: 0  
Setting: Hospital  
Significant: MDA for psychotropic drugs with silymarin versus placebo  
Not significant: AST, ALT, MDA for psychotropic drugs discontinued, silymarin versus placebo |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| Author: Pares<sup>68</sup>  
Year: 1998  
Country: Spain  
Language: English | Study type: RCT/blind  
Intervention/dose/duration: Silymarin (Legalon®)/450 mg daily/unclear  
Control: Placebo  
Outcome measures<sup>a</sup>: AST, ALT, GGTP, alk phos, bilirubin, albumin, PT  
Followup interval: Every 3 months for 2 years  
Assessment time points with results reported: Survival at 5 years; all others at 2 years (assumed) | Type: Alcoholic cirrhosis (24 percent had superimposed alcohol hepatitis)  
Include: Chronic alcoholism defined as alcohol exceeding 80 g/d men and 60 g/d women for more than 5 years; biopsy or laparoscopic proven alcoholic cirrhosis  
Exclude: If ever received colchicine, malotilate, penicillamine, or corticosteroids; life expectancy less than 6 months; drug addicted or pregnant; other known etiologies for cirrhosis (i.e., HBV, autoimmune, primary biliary cirrhosis, or cryptogenic cirrhosis)  
Acuity/severity: Chronic, all cirrhosis, Child’s score A/B/C/63/114/14  
Baseline group similarity: Demos, LFTs appear similar | N: 200  
Mean age: 50  
Percent male: 79  
Setting: Diagnosis in hospital then outpatient followup. | Significant:  
+ Trend: Encephalopathy, UGIB, survival for HCV-positive patients  
Not significant: AST, ALT, GGTP, PT, bilirubin, alk phos, hepatomegaly, splenomegaly, jaundice, ascites, survival  
Note: Trend was assessed qualitatively only for this review. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| Author: Salmi<sup>89</sup>  
Year: 1982  
Country: Finland  
Language: English | Study type: RCT/blind  
Intervention/dose/duration: Silymarin (Legalon®)/420 mg daily/28 days  
Control: Placebo  
Outcome measures<sup>a</sup>: AST, ALT, alk phos, bilirubin, histologic findings  
Followup interval: Day 28  
Assessment time points with results reported: 28 days | Type: Alcoholic liver disease  
Include: Increased AST and ALT for more than 1 month despite order to abstain from alcohol  
Exclude: Not given  
Acuity/severity: No other information  
Baseline group similarity: Aminotransferase levels reported as similar but lower in controls | N: 97  
Mean age: 37  
Percent male: 86  
Setting: Hospital | Significant: AST, ALT, histology  
Not significant: Alk phos, bilirubin |
| Author: Tanasescu<sup>74</sup>  
Year: 1988  
Country: Romania  
Language: English | Study type: RCT, randomization stratified by type of disease: CPH, CAH, HCV/blind  
Intervention/dose/duration: Silymarin (Silimarina®)/210 mg silybin equivalents daily/40 days  
Control: Placebo  
Outcome measures<sup>a</sup>: ALT, GGTP, bilirubin, alk phos, PT  
Followup interval: 40 days  
Assessment time points with results reported: 40 days | Type: CPH, CAH, hepatic cirrhosis, etiology not given  
Include: Diagnosis based on hepatic biopsy; clinical and laboratory data on CAH and CPH patients; some hepatic cirrhosis patients did not have hepatic biopsy; medium forms of disease; both sexes; 20 to 60 years old; basic disease from 1 to 10 years  
Exclude: Not given  
Acuity/severity: Chronic, no other information  
Baseline group similarity: Age, LFTs appear similar | N: 177  
Mean age: 53  
Percent male: 47  
Setting: Hospital | CAH  
Significant: AL  
Not significant: ALT, GGTP, bilirubin, alk phos, PT  
Note: Trend was assessed qualitatively only for this review.
## Evidence Table 1. Milk thistle for treatment of liver disease: Placebo-controlled, randomized, blinded trials (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Subject Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Trinchet<sup>67</sup>  
**Year:** 1989  
**Country:** France  
**Language:** French | **Study type:** RCT/blind  
**Intervention/dose/duration:** Silymarin (Legalon<sup>®</sup>)/420 mg daily/90 days  
**Control:** Placebo  
**Outcome measures**: AST, GGTP, bilirubin, albumin, PT, histology  
**Followup interval:** 90 days  
**Assessment time points with results reported:** 90 days | **Type:** Alcoholic hepatitis (50 percent with cirrhosis)  
**Include:** Biopsy-proven alcoholic hepatitis with or without cirrhosis  
**Exclude:** Hepatic encephalopathy; contraindications to liver biopsy; hepatocellular cancer; ascites resistant to diuretics; platelets less than 100,000 per mm; PT less than 50 percent; other diseases limiting survival  
**Acuity/severity:** 58/116 with cirrhosis; no other information  
**Baseline group similarity:** Demos, LFTs appear similar | N: 116  
Mean age: 51  
Percent male: 67%  
Setting: Unclear | **Significant:** Both silymarin and placebo better with alcohol abstinence  
**Not significant:** PT, albumin, bilirubin, GGTP, AST, histologic findings (hepatitis, fibrosis) |

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<sup>6</sup> Results not necessarily reported for all.

Alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = antismooth muscle antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CAH = chronic active hepatitis; CPH = chronic persistent hepatitis; demos = demographic variables; GGTP = gammaglutamyl transpeptidase; HAV = hepatitis A virus; HbsAg = Hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function test; MDA = malondialdehyde; MVI = multivitamin; PT = prothrombin time; RCT = randomized controlled trial; UGIB = upper gastrointestinal bleed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Fintelmann&lt;sup&gt;72&lt;/sup&gt;</td>
<td><strong>Study type:</strong> Cohort with comparison group/blinding unclear</td>
<td><strong>Type:</strong> Alcoholic liver disease, also other causes of fatty liver (pure parenchymal fatty degeneration, fatty degeneration and reactive inflammation, cirrhosis transformation in progress)</td>
<td>N: 50</td>
<td>Significant: AST (categorical)</td>
</tr>
<tr>
<td><strong>Year:</strong> 1970</td>
<td><strong>Intervention/dose/duration:</strong> Silymarin (Legalon®)/6 tablets daily/42 days</td>
<td><strong>Include:</strong> Biopsy-proven fatty liver, including early cirrhosis without portal hypertension, assignment stratified by diabetes mellitus, obesity, alcohol intake</td>
<td>Mean age: Not given</td>
<td>Not significant: AST (continuous), ALT, alk phos</td>
</tr>
<tr>
<td><strong>Country:</strong> Germany</td>
<td><strong>Control:</strong> Placebo</td>
<td><strong>Exclude:</strong> Not given</td>
<td>Percent male: Not given</td>
<td></td>
</tr>
<tr>
<td><strong>Language:</strong> German</td>
<td><strong>Outcome measures</strong>: Bilirubin, alk phos, AST, ALT</td>
<td><strong>Acuity/severity:</strong> All degrees of fatty liver including early cirrhosis without portal hypertension</td>
<td>Setting: Unclear</td>
<td></td>
</tr>
<tr>
<td><strong>Followup interval:</strong> 42 days</td>
<td><strong>Assessment time points with results reported:</strong> 42 days</td>
<td><strong>Baseline group similarity:</strong> LFTs appear similar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Author:</strong> Marcelli&lt;sup&gt;77&lt;/sup&gt;</td>
<td><strong>Study type:</strong> RCT/blinding unclear</td>
<td><strong>Type:</strong> CPH, etiology unknown</td>
<td>N: 65</td>
<td>Significant: AST, ALT</td>
</tr>
<tr>
<td><strong>Year:</strong> 1992</td>
<td><strong>Intervention/dose/duration:</strong> Silipide®/240 mg daily/90 days</td>
<td><strong>Include:</strong> Biopsy confirmed CPH, ALT, or AST 1.5 or greater than 2 times normal limits in past year</td>
<td>Mean age: 48</td>
<td>Not significant: Bilirubin, albumin, PT</td>
</tr>
<tr>
<td><strong>Country:</strong> Italy</td>
<td><strong>Control:</strong> Placebo</td>
<td><strong>Exclude:</strong> Other forms of liver disease (non-CPH) or decompensated disease; treatment with interferon antivirals, immunosuppressants, or immunomodulators within past 6 months</td>
<td>Percent male: 71</td>
<td></td>
</tr>
<tr>
<td><strong>Language:</strong> English</td>
<td><strong>Outcome measures</strong>: AST, ALT, bilirubin, albumin, PT</td>
<td><strong>Acuity/severity:</strong> Chronic, no other information</td>
<td>Setting: Specialty clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Followup interval:</strong> 90 days</td>
<td><strong>Baseline group similarity:</strong> Demos appear similar; higher AST and ALT in Silipide® group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Assessment time points with results reported:</strong> 90 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Results not necessarily reported for all.

alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartase aminotransferase; CPH = chronic persistent hepatitis; Demos = demographic variables; LFT = liver function test; PT = prothrombin time; RCT = randomized controlled trial.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Boari<sup>101</sup>  
**Year:** 1981  
**Country:** Italy  
**Language:** Italian |  
**Study type:** RCT unclear/blinding unclear  
**Intervention/dose/duration:** Silymarin/420 mg daily/15 to 20 days  
**Control:** Vitamin B complex/not given/15 to 20 days  
**Outcome measures:** AST, ALT, GGTP, alk phos, bilirubin  
**Followup interval:** 20 days  
**Assessment time points with results reported:** 20 days |  
**Type:** Toxic hepatopathy caused by various substances (mostly solvents, paints, and glues); mostly suffering from chronic or subacute forms  
**Include:** Not given  
**Exclude:** Not given  
**Acuity/severity:** Chronic, cirrhosis, liver failure, other, no other information |  
**N:** 55  
**Mean age:** 36  
**Percent male:** 60  
**Setting:** Hospital |  
**Significant:** AST, ALT, GGTP, alk phos  
**Not significant:** Bilirubin |
| **Author:** Bode<sup>102</sup>  
**Year:** 1977  
**Country:** Germany  
**Language:** German |  
**Study type:** RCT (quasi/odd-even birthdate)/not blind  
**Intervention/dose/duration:** Silymarin (Legalon®)/420 mg daily/35 days  
**Control:** No treatment  
**Outcome measures:** AST, ALT, GGTP, alk phos, bilirubin, PT  
**Followup interval:** 10, 25, 35 days  
**Assessment time points with results reported:** 35 days |  
**Type:** Viral hepatitis  
**Include:** Patients with viral hepatitis  
**Exclude:** Jaundice exceeding 8 days  
**Acuity/severity:** Acute, no other information |  
**N:** 151  
**Mean age:** Not given  
**Percent male:** 48  
**Setting:** Unclear |  
**Significant:** AST, bilirubin, ALT, alk phos  
**Not significant:** AST, ALT, GGTP, alk phos |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author**: Cavalieri<sup>103</sup>  
**Year**: 1974  
**Country**: Italy  
**Language**: Italian | **Study type**: RCT  
unclear/blinding unclear  
**Intervention/dose/duration**: Silymarin (Legalon®)/420 mg daily/variable  
**Control**: “Traditional treatment”: a 12-component cocktail including vitamin and steroids  
**Outcome measures**:<sup>a</sup> AST, ALT, GGTP, alk phos, bilirubin, PT  
**Followup interval**: 7, 14, 28 days  
**Assessment time points with results reported**: 7, 14, 28 days | **Type**: Acute hepatitis  
(posttransfusion, contagious, presumably parenteral, and sporadic)  
**Include**: Not given  
**Exclude**: Not given  
**Acuity/severity**: Acute, no other information | **N**: 40  
**Mean age**: 29  
**Percent male**: 45  
**Setting**: Hospital | Significant: AST at weeks 1, 2, and 3; ALT at week 2; alk phos at week 1; albumin at week 1  
Not significant: AST at week 4; ALT at weeks 1, 3, and 4; PT and albumin at weeks 2 and 3 |
| **Author**: Del Dotto<sup>104</sup>  
**Year**: 1982  
**Country**: Italy  
**Language**: Italian | **Study type**: RCT  
unclear/blinding unclear  
**Intervention/dose/duration**: Silymarin (Legalon®)/420 mg daily/90 days  
**Control**: Vitamin B complex  
**Outcome measures**:<sup>a</sup> AST, ALT, GGTP, PT, bilirubin, albumin, alk phos  
**Followup interval**: 30, 60, 90 days  
**Assessment time points with results reported**: 30, 60, 90 days | **Type**: Alcoholic liver disease  
**Include**: Patients with alcoholic liver disease  
**Exclude**: Not given  
**Acuity/severity**: Chronic, no other information | **N**: 42  
**Mean age**: 53  
**Percent male**: 74  
**Setting**: Specialty clinic | Significant: AST, ALT, GGTP, PT, bilirubin, albumin, alk phos  
Not significant: AST, ALT, GGTP, PT, bilirubin, albumin, alk phos |
### Evidence Table 3. Milk thistle for treatment of liver disease: Studies without placebo controls (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** DeMartisis[^105]  
**Year:** 1980  
**Country:** Italy  
**Language:** Italian | Study type: RCT unclear/blinding unclear  
Intervention/dose/duration: Silymarin, traditional therapy, and diet/400 mg daily/45 to 90 days  
Control: Traditional therapy + diet  
Outcome measures[^a]: Bilirubin  
Followup interval: 90 days  
Assessment time points with results reported: 90 days | Type: Chronic hepatitis and cirrhosis  
Include: Macrocytic anemia and hemolytic syndrome  
Exclude: Lab values indicating the presence of cholestasis (alk phos, GGTP) dyslipidemia, or diabetes  
Acuity/severity: Chronic, no other information | N: 45  
Mean age: Not given  
Percent male: Not given  
Setting: Unclear | Significant:  
Not significant: Indirect bilirubin |
## Evidence Table 3. Milk thistle for treatment of liver disease: Studies without placebo controls (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Language</th>
<th>Study type</th>
<th>Intervention/dose/duration</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Followup interval</th>
<th>Setting</th>
<th>N</th>
<th>Mean age</th>
<th>Percent male</th>
<th>Acuity/severity</th>
<th>Significant</th>
<th>Not significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeMartiis</td>
<td>1980</td>
<td>Italy</td>
<td>Italian</td>
<td>RCT</td>
<td>Vitamin B12, folic acid, uridine-5, and difosfoglucone/600 mg daily/not given</td>
<td>Vitamin B12, folic acid, uridine-5, and difosfoglucone/not given</td>
<td>Alk phos, bilirubin</td>
<td>Unclear</td>
<td>Not given</td>
<td>91</td>
<td>56</td>
<td>71</td>
<td>Chronic hepatopathies (diagnoses include chronic hepatitis, hepatic cirrhosis, and hepatic neoplasm)</td>
<td>All CE or EC Patients</td>
<td>All others All others</td>
</tr>
<tr>
<td>Fintelmann</td>
<td>1973</td>
<td>Germany</td>
<td>German</td>
<td>RCT</td>
<td>Silymarin (Legalon®)/210 or 420 mg daily/preoperative and 8 days postoperative</td>
<td>No treatment</td>
<td>AST, ALT, alk phos, bilirubin</td>
<td>1, 2, 3 days</td>
<td>Hospital</td>
<td>63</td>
<td>Not given</td>
<td>6</td>
<td>Cholestasis, not pregnancy related</td>
<td>All others</td>
<td>AST, ALT, bilirubin, alk phos</td>
</tr>
</tbody>
</table>

Note: Trend was assessed qualitatively only for this review.
### Evidence Table 3. Milk thistle for treatment of liver disease: Studies without placebo controls (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Flisiak</td>
<td><strong>Year:</strong> 1997</td>
<td><strong>Country:</strong> Poland</td>
<td><strong>Language:</strong> English</td>
<td><strong>Study type:</strong> RCT/not blind</td>
</tr>
<tr>
<td><strong>Correspondence from Flisiak, November 2, 1999:</strong> Study was not placebo controlled; subjects were blinded, but providers and outcome assessors were not blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author:</strong> Flisiak</td>
<td><strong>Year:</strong> 1997</td>
<td><strong>Country:</strong> Poland</td>
<td><strong>Language:</strong> English</td>
<td><strong>Study type:</strong> Cohort with comparison group/not blind</td>
</tr>
<tr>
<td><strong>Correspondence from Flisiak, November 2, 1999:</strong> Study was not placebo controlled; subjects were blinded, but providers and outcome assessors were not blinded</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Liver Disease</td>
<td>Patient Characteristics</td>
<td>Outcomes (favoring silymarin unless otherwise noted)</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Author:</strong> Lirussi</td>
<td><strong>Study type:</strong> RCT/blinding unclear</td>
<td><strong>Type:</strong> Compensated active cirrhosis (HCV, alcoholic with or without HCV, HBsAg)</td>
<td><strong>N:</strong> 23</td>
<td><strong>Significant:</strong> Not significant: AST, ALT, GGTP, bilirubin, alk phos</td>
</tr>
<tr>
<td><strong>Year:</strong> 1995</td>
<td><strong>Intervention/dose/duration:</strong> UDCA/600 mg daily/180 days Silymarin (Legalon®)/420 mg/180 days Combination therapy UDCA and silymarin/600 mg UDCA and 420 mg silymarin/6 months</td>
<td><strong>Include:</strong> Biopsy-proven compensated cirrhosis; AST and ALT 2 to 10 times normal limits</td>
<td><strong>Mean age:</strong> 58</td>
<td><strong>Percent male:</strong> 36</td>
</tr>
<tr>
<td><strong>Country:</strong> Italy</td>
<td><strong>Exclude:</strong> Not given</td>
<td><strong>Acuity/severity:</strong> No other information</td>
<td><strong>Setting:</strong> Unclear</td>
<td><strong>Phase 1:</strong> Cross-over</td>
</tr>
<tr>
<td><strong>Language:</strong> English</td>
<td><strong>Outcome measures:</strong> AST, ALT, GGTP, alk phos, bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Followup interval:</strong> 90, 180, 210, 300, 395 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Assessment time points with results reported:</strong> 90, 180 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Study:</strong> RCT unclear/blinding unclear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Author:</strong> Roveda</td>
<td><strong>Intervention/dose/duration:</strong> Silymarin/140 or 280 mg daily or silybin/70 or 140 mg daily/90 days</td>
<td><strong>Type:</strong> Organic and functional diseases of liver parenchyma</td>
<td><strong>N:</strong> 51</td>
<td><strong>Significant:</strong> Hepatomegaly, gastric burning, pain on palpation</td>
</tr>
<tr>
<td><strong>Year:</strong> 1991</td>
<td><strong>Outcome measures:</strong> AST, ALT, GGTP, alk phos, bilirubin</td>
<td><strong>Include:</strong> Not given</td>
<td></td>
<td><strong>Percent male:</strong> 41</td>
</tr>
<tr>
<td><strong>Country:</strong> Italy</td>
<td><strong>Followup interval:</strong> 90 days</td>
<td><strong>Exclude:</strong> Not given</td>
<td></td>
<td><strong>Setting:</strong> Not given</td>
</tr>
<tr>
<td><strong>Language:</strong> Italian</td>
<td><strong>Assessment time points with results reported:</strong> 90 days</td>
<td><strong>Acuity/severity:</strong> No other information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Liver Disease</td>
<td>Patient Characteristics</td>
<td>Outcomes (favoring silymarin unless otherwise noted)</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------------</td>
<td>--------------------------</td>
<td>---------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Author:** Saba¹¹⁰  
**Year:** 1979  
**Country:** Italy  
**Language:** Italian | **Study type:** RCT/blinding unclear  
**Intervention/dose/duration:** Silymarin/420 mg daily/not given  
**Control:** MVI + choline + methionin  
**Outcome measures:** AST, ALT, alk phos, bilirubin  
**Followup interval:** Unclear  
**Assessment time points with results reported:** Unclear | **Type:** Acute viral hepatitis  
**Include:** Onset in 15 days or fewer; hospitalized 4 days or fewer of onset of jaundice; no previous episodes of jaundice  
**Exclude:** More than 100 g of alcohol per day for 15 days or fewer of disease onset  
**Acuity/severity:** Acute, no other information | **N:** 38  
**Mean age:** 36  
**Percent male:** 53  
**Setting:** Not given | Significant: Time to normalization for direct bilirubin, AST, ALT, alk phos  
Not significant: Time to normalization for total bilirubin |
| **Author:** Schopen¹¹¹  
**Year:** 1970  
**Country:** Germany  
**Language:** German | **Study type:** RCT/blinding unclear  
**Intervention/dose/duration:** Silymarin (Legalon®)/1 tablet = 35 mg (dose varied from 6 tablets daily to 9 tablets daily and, in rare cases, 12 tablets daily/mean 45 days  
**Control:** Other hepatoprotective medicines but not silymarin  
**Outcome measures:** AST, ALT, alk phos, bilirubin, albumin, PT  
**Followup interval:** 45 days  
**Assessment time points with results reported:** Mean 45 days | **Type:** Alcoholic-, toxin-, and drug-induced liver disease and fatty liver secondary to diabetes mellitus; cholestasis (not pregnancy related)  
**Include:** Patients with microscopic changes of moderately severe to severe localized fatty deposits or diffuse steatosis; 51 toxic metabolic changes with fatty liver and some with cholestasis (patients with alcohol abuse, some diabetes mellitus); 13 diabetes mellitus; 8 poisoning; 2 aflatoxin; 1 mercury; 5 chronic barbiturate abuse  
**Exclude:** Not given  
**Acuity/severity:** No other information | **N:** 72  
**Mean age:** Not given  
**Percent male:** Not given  
**Setting:** Unclear | Significant: AST, ALT  
Not significant: |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Szilard¹¹²  
**Year:** 1988  
**Country:** Hungary  
**Language:** English  
  | Study type: Cohort/not blind  
  Intervention/dose/duration: Silymarin (Legalon®) 420 mg daily/30 days  
  Control: No treatment  
  Outcome measures*: AST, ALT, GGTP  
  Followup interval: 30 days  
  Assessment time points with results reported: 28 days  
  | Type: Toxic hepatopathy caused by organic solvents (toluene and xylene)  
  Include: Hepatomegaly, increased AST and ALT levels, lymphocytosis, decreased platelet counts attributable to toluene and/or xylene  
  Exclude: Alcoholics  
  Acuity/Severity: No other information  
  Baseline group similarity: Demos, LFTs, appear similar except higher GGTP in treatment group  
  | N: 49 (Legalon® = 30; no treatment = 19)  
  Mean age: Not given  
  Percent male: 100  
  Setting: Workplace  
  | Significant: AST, ALT  
  Not significant: GGTP |
| **Author:** Tkacz¹¹³  
**Year:** 1983  
**Country:** Poland  
**Language:** Polish  
  | Study type: RCT unclear/blinding unclear  
  Intervention/dose/duration: Silimarol® (and vitamins B and C)/6 pills daily/21 days  
  Control: Vitamins B and C and cocarboxylase  
  Outcome measures*: ALT, alk phos, bilirubin, PT  
  Followup interval: 21 days  
  Assessment time points with results reported: 21 days  
  | Type: Viral hepatitis  
  Include: Abnormal LFTs  
  Exclude: Not given  
  Acuity/Severity: No other information  
  | N: 87  
  Mean age: Not given  
  Percent male: Not given  
  Setting: Unclear  
  | Significant:  
  Not significant: ALT, PT, bilirubin, length of stay |
Evidence Table 3. Milk thistle for treatment of liver disease: Studies without placebo controls (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author: Vailati</td>
<td>Study type: RCT/not blind/phase 2 study</td>
<td>Type: Viral and alcoholic hepatitis</td>
<td>N: 60</td>
<td>Significant: AST, GGTP, bilirubin for 240 or 360 mg versus 160 mg</td>
</tr>
<tr>
<td>Year: 1993</td>
<td>Intervention/dose/duration:</td>
<td>Include: Biopsy-proven chronic hepatitis (viral or alcoholic); AST and ALT 1.5 or greater than 2 times normal limits and biopsy within 1 year</td>
<td>Mean age: 50</td>
<td>Not significant:</td>
</tr>
<tr>
<td>Country: Italy</td>
<td>Silymarin (Silipide®)/160 mg silybin equivalents daily/14 days</td>
<td>Exclude: Other forms of liver disease; decompensated liver disease; treatment with interferon, antivirals, immunosuppressants, or immunodulators for 6 months or fewer</td>
<td>Percent male: 62</td>
<td></td>
</tr>
<tr>
<td>Language: English</td>
<td>Silymarin (Silipide®)/240 mg silybin equivalents daily/14 days</td>
<td>Acuity/severity: Chronic, no other information</td>
<td>Setting: Outpatient clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silymarin (Silipide®)/360 mg silybin equivalents daily/14 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control: No treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outcome measures*: AST, GGTP, bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Followup interval: 7, 14 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assessment time points with results reported: 7, 14 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3. Milk thistle for treatment of liver disease: Studies without placebo controls (continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
</table>
| **Author:** Velussi¹¹⁴,¹¹⁵  
**Year:** 1993, 1997  
**Country:** Italy  
**Language:** English | **Study type:** RCT/not blind  
**Intervention/dose/duration:** Silymarin (Legalon®)/600 mg daily/365 days  
**Control:** No treatment  
**Outcome measures**: MDA, AST, ALT GGTP, alk phos, bilirubin  
**Followup interval:** 90, 180, 270, 365 days  
**Assessment time points with results reported:** 90, 180, 270, 365 days | **Type:** Diabetics with alcoholic cirrhosis  
**Include:** Age 45 to 70 years; NIDDM with alcoholic liver cirrhosis; BMI more than 29 kg/m²; diabetes for 5 or more years treated with insulin only; stable insulin therapy for 2 or more years; increased endogenous insulin secretion; negative for HAV, HBV, and HCV; not addicted to alcohol for 2 or more years before study; no variceal esophagus bleeding; positive liver biopsy for cirrhosis 4 or fewer years before enrollment  
**Exclude:** Not given  
**Acuity/severity:** Chronic, no other information | **N:** 60  
**Mean age:** Not given  
**Percent male:** Not given  
**Setting:** Specialty clinic | **Significant:** MDA  
**Not significant:** GGTP, bilirubin, alk phos |

¹Results not necessarily reported for all.

alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CE = cirrosi epatica; Demos = demographic variables; EC = epatite cronica; GGTP = gammaglutamyl transpeptidase; HAV = hepatitis A virus; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; LFT = liver function test; MDA = malondialdehyde; MVI = multivitamin; NIDDM = noninsulin dependent diabetes; PT = prothrombin time; RCT = randomized controlled trial; UDCA = ursodeoxycholic acid.
### Evidence Table 4. Milk thistle for prophylaxis against liver disease: Ineligible (normal liver function at study entry) but provocative studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Liver Disease</th>
<th>Patient Characteristics</th>
<th>Outcomes (favoring silymarin unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allain</strong></td>
<td>Study type: RCT/blind/prophylaxis</td>
<td>Type: Drug- (Tacrine-)induced liver disease</td>
<td>N: 222</td>
<td>Significant:</td>
</tr>
<tr>
<td>Year: 1999</td>
<td>Intervention/dose/duration: Silymarin/420 mg daily/84 days</td>
<td>Include: Patient over 50 years old; mild to moderate Alzheimer’s disease; Tacrine treatment</td>
<td>Mean age: Approximately 74</td>
<td>AST, ALT</td>
</tr>
<tr>
<td>Country: France</td>
<td>Control: Placebo</td>
<td>Exclude: Past history hepatic disorder (cirrhosis, increased bilirubin, AST, and/or ALT)</td>
<td>Percent male: 39</td>
<td></td>
</tr>
<tr>
<td>Language: English</td>
<td>Outcome measures: AST, ALT</td>
<td>Acuity/severity: No disease at baseline</td>
<td>Setting: Specialty clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Followup interval: 8 times over 15 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assessment time points with results reported: 8 times over 15 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Magula</strong></td>
<td>Study type: RCT/not blinded/prophylaxis</td>
<td>Type: Drug-induced liver disease</td>
<td>N: 172 (92 tuberculosis medications alone; 29 tuberculosis medications plus silymarin)</td>
<td></td>
</tr>
<tr>
<td>Year: 1996</td>
<td>Intervention/dose/duration: Tuberculosis treatment and Hepabene® (Silymarin and Fumaria officinalis alkaloids)/2 capsules daily/8 weeks</td>
<td>Include: Patients requiring tuberculosis treatment; normal LFTs at baseline</td>
<td>Mean age: 50</td>
<td><strong>Significant:</strong> AST, ALT</td>
</tr>
<tr>
<td>Country:</td>
<td>Control: Tuberculosis medications alone</td>
<td>Exclude: Not given</td>
<td>Percent male: 60</td>
<td>Not significant:</td>
</tr>
<tr>
<td>Language: Slovak</td>
<td>Outcome measures: AST, ALT, bilirubin, “liver injury,” interruption of tuberculosis medications</td>
<td>Acuity/severity: No disease at baseline</td>
<td>Setting: Unclear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Followup interval: Every 2 weeks for 8 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assessment time points with results reported: 8 weeks (56 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aResults not necessarily reported for all.

ALT = alanine aminotransferase; AST = aspartase aminotransferase; LFT = liver function test; RCT = randomized controlled trial.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adverse Effect</th>
<th>Study N</th>
<th>Study Design</th>
<th>Type</th>
<th>Amount</th>
<th>Improved after discontinued?</th>
<th>Rechallenged?</th>
<th>Alternative causes possible?</th>
<th>Dose-response?</th>
</tr>
</thead>
</table>
| Bunout, 1992<sup>66</sup> | Control: Pruritus, Headache  
Treatment: Pruritus, Headache | 11/34 4/34 | RCT | Placebo  
Silymarin (Legalon<sup>®</sup>) | 280 mg/d | Yes, in one patient  
Not discontinued | No | Not given | Not given |
| Ferenci, 1989<sup>75</sup> | Control: Nausea, epigastric discomfort  
Treatment: Nausea, epigastric discomfort | 2/83 2/87 | RCT | Placebo  
Silymarin (Legalon<sup>®</sup>) | 420 mg/d | Yes  
Yes | No | Not given | Not given |
| Pares, 1998<sup>68</sup> | Control: 4 Urticaria, pruritus, arthralgia, headache  
Treatment: 7 Urticaria, pruritus, arthralgia, headache | Total n: 11/200 | RCT | Placebo  
Silymarin (Legalon<sup>®</sup>) | 450 mg/d | Yes, 2 patients in treatment and 1 patient in control | No | Not given | Not given |
| Vailati, 1993<sup>55</sup> | Treatment: Nausea, heartburn  
Dyspepsia  
Postprandial nausea, meteorism | 3/20 1/20 2/20 | RCT | Silipide<sup>®</sup>  
Silipide<sup>®</sup> | 160 mg/d  
240 mg/d  
360 mg/d | Yes  
Yes | No | Not given | Not given  
Not given | Not given  
Not given
### Evidence Table 5. Milk thistle for treatment of liver disease: Adverse effects (continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adverse Effect</th>
<th>Study N</th>
<th>Study Design</th>
<th>Type</th>
<th>Amount</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Andrade, 1998</strong>&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Control:</td>
<td>0/31</td>
<td>RCT</td>
<td>Silymarin</td>
<td>450 mg/d</td>
<td>Not given</td>
</tr>
<tr>
<td>Treatment: Impotence</td>
<td></td>
<td>1/29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marcelli, 1992</strong>&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Control: Nausea, dyspepsia, heartburn, skin rash</td>
<td>5/34</td>
<td>RCT</td>
<td>Placebo</td>
<td></td>
<td>Not discontinued</td>
</tr>
<tr>
<td>Treatment: Nausea, heartburn, transient headache</td>
<td></td>
<td>3/31</td>
<td></td>
<td>Silipide®</td>
<td>240 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>Allain, 1999</strong>&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Control: Frequency ADE occurred&lt;sup&gt;b&lt;/sup&gt;: Diarrhea 5 (10.1%)</td>
<td>112</td>
<td>RCT</td>
<td>Placebo and Tacrine</td>
<td></td>
<td>Not given</td>
</tr>
<tr>
<td>Vomiting 10 (8.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea 10 (6.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia 7 (5.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability 6 (5.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia 6 (4.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia 5 (3.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise 3 (3.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis 7 (5.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment: Frequency ADE occurred&lt;sup&gt;b&lt;/sup&gt;: Diarrhea 8 (8.1%)</td>
<td></td>
<td>110</td>
<td></td>
<td>Silymarin and Tacrine</td>
<td>420 mg/d</td>
<td>Not given</td>
</tr>
<tr>
<td>Vomiting 6 (4.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea 10 (10.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia 9 (8.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability 5 (4.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia 5 (4.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis 7 (5.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Adverse Effect</td>
<td>Study N</td>
<td>Study Design</td>
<td>Type</td>
<td>Amount</td>
<td>Improved after discontinued?</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>---------</td>
<td>--------------</td>
<td>------</td>
<td>--------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Studlar, 1985&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Temporary uneasiness of stomach</td>
<td>2/34</td>
<td>Prospective cohort</td>
<td>Silibene&lt;sup&gt;®&lt;/sup&gt; (a silymarin-containing drug)</td>
<td>280 mg/d</td>
<td>Not discontinued</td>
</tr>
<tr>
<td>Albrecht,&lt;sup&gt;a&lt;/sup&gt; 1992&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Treatment: (in 0.8% of patients): Mild diarrhea Nausea Upset stomach Itching Exanthem Headache Decreased energy and discomfort NOS</td>
<td>4/2,637 3/2,637 2/2,637 2/2,637 1/2,637 1/2,637 7/2,637</td>
<td>Prospective cohort</td>
<td>Silymarin (Legalon&lt;sup&gt;®&lt;/sup&gt;) 70 mg</td>
<td>3.8±1.48 tablets per day 267.4±103.6 mg 1 to 9 tablets 55.2 percent 1 tablet tid 28.3 percent 2 tablets tid</td>
<td>Not given</td>
</tr>
<tr>
<td>Marena, 1991&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Gastrointestinal: Mostly upset stomach Control: Silipide&lt;sup&gt;®&lt;/sup&gt;</td>
<td>6/117 12/232</td>
<td>Cohort&lt;sup&gt;c&lt;/sup&gt; Placebo Commercial extract Silipide&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Not given</td>
</tr>
<tr>
<td>Grungreiff, 1995&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Frequency ADE occurred:&lt;sup&gt;b&lt;/sup&gt; Changes in BM 4 Diarrhea 4 Dizziness/circulatory problems 4 Nausea/vomiting 2 Itching 2 Eczemas 2 Indisposition 1 Flatulence 1</td>
<td>16/975 (12 patients reported 1 adverse effect and 4 patients reported 2 adverse effects)</td>
<td>Cohort&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Silymarin</td>
<td>280 to 420 mg/d</td>
<td>Not given</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Adverse Effect</td>
<td>Study N</td>
<td>Study Design</td>
<td>Type</td>
<td>Amount</td>
<td>Improved after discontinued?</td>
</tr>
<tr>
<td>--------------</td>
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<td>--------------</td>
<td>------</td>
<td>--------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Frerick, 1990&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Frequency ADE occurred&lt;sup&gt;b&lt;/sup&gt;: Mild diarrhea 4; Nausea 3; Gastric intolerance 2; Itching 2; Eczema 1; Diffuse headaches 1; Decreased energy/restlessness 1; No specifics 7</td>
<td>2,169</td>
<td>Cohort&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Silymarin</td>
<td>1,210 patients received 210 mg/d; 583 patients received 420 mg/d; 376 patients received 70 to 630 mg/d</td>
<td>Not given</td>
</tr>
<tr>
<td>Schuppan, 1998&lt;sup&gt;52&lt;/sup&gt;</td>
<td>12 ADEs occurred, but not specifically noted; examples were diarrhea, flatulence, abdominal fullness or pain, nausea, vomiting, and dizziness</td>
<td>20/998</td>
<td>Cohort&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Silymarin</td>
<td>280 to 420 mg/d</td>
<td>Not given</td>
</tr>
<tr>
<td>Anonymous, 1972&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Sweating, nausea, colicky abdominal pain, fluid diarrhea, weakness, and collapse</td>
<td>1</td>
<td>Case report</td>
<td>Microgenics Herbals M.T. Vegicaps&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 capsule</td>
<td>Yes</td>
</tr>
<tr>
<td>Geier, 1990&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Anaphylactic shock: facial edema, oral mucosa swelling, marked respiratory distress, bronchospasm, and decrease blood pressure</td>
<td>1</td>
<td>Case report</td>
<td>Silybum marianum tea</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>Mironets, 1990&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Urticaria, fever, laryngeal edema</td>
<td>1</td>
<td>Case report</td>
<td>Carsil&lt;sup&gt;®&lt;/sup&gt;</td>
<td>3 pills per day, no dosage given</td>
<td>Yes, and Tx Prednisone</td>
</tr>
<tr>
<td>Wollemann, 1987&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Rhinoconjunctivitis</td>
<td>1</td>
<td>Case report</td>
<td>Silybum marianum</td>
<td>Contact with seeds</td>
<td>Not given</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Adverse Effect</td>
<td>Study N</td>
<td>Study Design</td>
<td>Milk Thistle Exposure</td>
<td>Questions</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>---------</td>
<td>--------------</td>
<td>-----------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>DeSmet, 1996</td>
<td>Jaundice, increase LFTs</td>
<td>1</td>
<td>Case report</td>
<td>Multiherbal tablets with unknown amount of milk thistle</td>
<td>Improved after discontinued?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

---

a. The study by Albrecht is an extension of the study by Frerick and includes the same patients. 

b. Unit of reporting was ADE, not patient.

c. Unclear if cohort was prospective or retrospective.

ADE = adverse drug effects; BM = bowel movement; LFT = liver function test; NOS = not otherwise specified; RCT = randomized controlled trial; tid = three times daily.
Bibliography


Bonkovsky HL. Therapy of hepatitis C: Other options. Hepatology 1997;26:143S-151S.


Cavalieri S. [Controlled clinical trial of silymarin in 40 patients]. [Ita]. Gazz Med Ital 1974;133:628-35.


Chevrel B. Legalon in the treatment of alcoholic or non-alcoholic chronic liver diseases. Med Chir Dig 1994;23:475-81.


Denneny C. Personal communication from Cathi Denneny, Dec 1999.


Gluud C. “Negative trials” are positive! J Hepatol 1998;28:731-3.


Grieve M. A modern herbal: The medicinal, culinary, cosmetic and economic properties, cultivation, and folklore of herbs, grasses, fungi, shrubs, and trees with all their modern scientific uses. Darien (CT): Hafner Publishing Company; 1931.


Halama P. Chronic hepatopathies due to anticonvulsant agents. Therapiewoche 1984;34:2267-74.


Perhaps not everyone knows that... Ann Oncol 1997;8:721-2.


Sanders D, Kennedy N, McKendrick MW. Monitoring the safety of herbal remedies. Herbal remedies have a heterogeneous nature. BMJ 1995;311:1569.


Appendix A. Milk Thistle Search Strategies

All papers MEDLINE

Date: 18-Jun-1999

Name: sily1, sily2, sily3, sily3a, sily4 (SAVED AS SILYMEDL)

Database: Medline <1966 to present>

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All papers EMBASE

Date: 18-Jun-1999

Name: silyem1

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Figure 1-1. Aspartate aminotransferase, less drug study, <45 days
Begg's funnel plot with pseudo 95% confidence limits

Figure 1-2. Aspartate aminotransferase, less drug study, <45 days
Figure 1-3. Aspartate aminotransferase, less drug study, <45 days

- Buzelli 1993
- telmann 1970
- telmann 1980
- Lang 1990
- Madlulo 1978
- Salmi 1982
- Combined

Effect Size

Figure 1-4. Aspartate aminotransferase, less drug study, 90 days
Begg’s funnel plot with pseudo 95% confidence limits

- Trinchet 1989
- Marcelli 1992
Figure 1-5. Aspartate aminotransferase, less drug study, 90 days

Figure 1-6a. Aspartate aminotransferase, less drug study, 90 days
Figure 1-6b. Aspartate aminotransferase, less drug study, less outlier, 90 days

Figure 1-7. Aspartate aminotransferase, < 45 days
Begg's funnel plot with pseudo 95% confidence limits
Figure 1-8. Aspartate aminotransferase, < 45 days

Figure 1-9. Aspartate aminotransferase, < 45 days
Figure 1-10. Aspartate aminotransferase, 90 days
Begg's funnel plot with pseudo 95% confidence limits

Figure 1-11. Aspartate aminotransferase, 90 days
Figure 1-12a. Aspartate aminotransferase, 90 days

Figure 1-12b. Aspartate aminotransferase, less outlier, 90 days
Figure 1-13. Alanine aminotransferase, less drug study, <45 days
Begg’s funnel plot with pseudo 95% confidence limits

Figure 1-14. Alanine aminotransferase, less drug study, <45 days
Figure 1-15a. Alanine aminotransferase, less drug study, <45 days

- Buzelli 1993
- Fintelmann 1970
- Fintelmann 1980
- Lang 1990
- Magliulo 1978
- Salmi 1982
- Tanasescu 1988
- Combined

Effect Size

Figure 1-15b. Alanine aminotransferase, less drug study, less outlier, <45 days

- Buzelli 1993
- Fintelmann 1970
- Fintelmann 1980
- Lang 1990
- Salmi 1982
- Tanasescu 1988
- Combined

Effect Size
**Figure 1-16.** Alanine aminotransferase, less drug study, 90 days
Begg's funnel plot with pseudo 95% confidence limits

Effect Size vs. Standard Error

**Figure 1-17.** Alanine aminotransferase, less drug study, 90 days
Z Statistic vs. Inverse of Standard Error
Figure 1-18. Alanine aminotransferase, less drug study, 90 days

Figure 1-19. Alanine aminotransferase, <45 days
Begg’s funnel plot with pseudo 95% confidence limits

Magliulo 1978
Figure 1-20. Alanine aminotransferase, <45 days

Figure 1-21a. Alanine aminotransferase, <45 days
Figure 1-21b. Alanine aminotransferase, less outlier, <45 days

Figure 1-22. Alanine aminotransferase, 90 days
Begg’s funnel plot with pseudo 95% confidence limits
Figure 1-25. Gammaglutamyl transpeptidase, <45 days
Begg's funnel plot with pseudo 95% confidence limits

![Begg's funnel plot with pseudo 95% confidence limits](image)

Figure 1-26. Gammaglutamyl transpeptidase, <45 days

![Z Statistic vs. Inverse of Standard Error](image)
Figure 1-27. Gammaglutamyl transpeptidase, <45 days

Figure 1-28. Gammaglutamyl transpeptidase, 90 days
Begg’s funnel plot with pseudo 95% confidence limits
Figure 1-29. Gammaglutamyl transpeptidase, 90 days

Figure 1-30. Gammaglutamyl transpeptidase, 90 days
Figure 1-31. Alkaline phosphatase, <45 days
Begg’s funnel plot with pseudo 95% confidence limits

Figure 1-32. Alkaline phosphatase, <45 days
Figure 1-33. Alkaline phosphatase, <45 days

- Buzelli 1993
- Fintelmann 1970
- Magluto 1978
- Salmi 1982
- Tanasescu 1988
- Combined

Effect Size

-1 -0.5 0 0.5 1 1.5

Figure 1-34. Bilirubin, <45 days
Begg's funnel plot with pseudo 95% confidence limits

Effect Size

-1 0 1

Standard Error

0 0.2 0.4 0.6
Figure 1-37. Bilirubin, 90 days
Begg's funnel plot with pseudo 95% confidence limits

Figure 1-38. Bilirubin, 90 days
Figure 1-39. Bilirubin, 90 days

Figure 1-40. Albumin, 90 days
Begg's funnel plot with pseudo 95% confidence limits
Figure 1-43. Prothrombin time, 90 days
Begg’s funnel plot with pseudo 95% confidence limits

Figure 1-44. Prothrombin time, 90 days
Figure 1-45. Prothrombin time, 90 days

Feher 1990
Marcelli 1992
Trinchet 1989
Combined

Effect Size

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## Appendix D. Acronyms

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