Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects

Authors' objectives
Two areas were addressed: efficacy and harm.

Efficacy: to evaluate the efficacy of oral ingestion of milk thistle supplements (silymarin, silybin and silipide) in the treatment of alcohol-related liver disease, viral hepatitis or its sequel, toxin- or drug-induced (other than alcohol) liver disease, cholestasis (pregnancy-related or not), and primary hepatic malignancy. In addition, to evaluate the relative efficacy of different preparations.

Harm: to evaluate the clinical adverse effects of supplemental milk thistle ingestion or contact.

Searching
The following sources were searched from their inception (dates given) to July 1999: AMED, BIOSIS Previews, CINAHL, CISCOM, the Cochrane Library, the Cochrane Controlled Trials Register, DARE, Dissertation Abstracts, EMBASE, MEDLINE, MICROMEDEX, NAPRALERT, Phytodok, and the Science Citation Index. The reference lists were handsearched, and manufacturers and technical experts were contacted. An update search in December 1999 was confined to PubMed. The search terms and strategy were reported in full.

Study selection
Study designs of evaluations included in the review
Efficacy: randomised controlled trials (RCTs), downgraded to prospective controlled trials after the initial search, were included.

Harm: RCTs, cohort studies, case series and case reports were included.

Specific interventions included in the review
Supplemental milk thistle. The eligible controls were placebo, no supplement, other oral supplements, and drugs. Of the 16 placebo-controlled studies subject to meta-analysis, 12 used Legalon. In 8 trials, the dosages were 240 to 800 mg/day and the trial duration ranged from 7 days to 6 years; the dosage and duration were not given in the other 4 studies. Two studies used silymarin (210 and 800 mg) and 2 used silipide (240 mg/day); the treatment duration ranged from 7 to 446 days in 3 studies, but was not reported for the fourth.

Participants included in the review
Humans with liver disease of various aetiologies, e.g. alcoholic and non-alcoholic cirrhosis, alcoholic hepatitis, hepatitis B, hepatitis C, drug-induced liver disease, fatty degeneration.

Outcomes assessed in the review
Efficacy: physiological (laboratory or histological assessment of in vivo liver function) and clinical outcomes were assessed. The clinical outcomes were morbidity, mortality, hospitalisation, quality of life, symptoms, and Child’s score for chronic liver disease. Harm: any reported adverse effect was assessed. The clinical outcomes were morbidity, mortality, hospitalisation, quality of life, symptoms, and Child’s score.

The majority of the accepted papers used laboratory tests as the primary outcome.

How were decisions on the relevance of primary studies made?
At least two independent reviewers scanned the titles and abstracts using pre-specified criteria for each question. The full texts that were retrieved were screened in the same manner.
Assessment of study quality
Validity was assessed. The methodological criteria included adequacy of randomisation, blinding, matching of treatment and control groups, cointerventions, and the number of drop-outs. Study validity was assessed descriptively, without quality scoring or weighting.

Data extraction
Two independent investigators abstracted trial data for each study. The data included adequacy of randomisation, blinding, matching of treatment and control groups, cointerventions, and the number of drop-outs. Any disagreements were resolved by consensus. Another two independent investigators abstracted the data for studies of adverse effects. The data included study design, type of event, and criteria for evaluating causality in drug adverse effects.

Methods of synthesis
How were the studies combined?
The studies were synthesised descriptively, emphasising the methodological characteristics. The effect sizes of primary outcomes were measured as standardised mean differences. These were computed using Hedges’ g, and adjusted for baseline difference and small sample bias (see Other Publications of Related Interest no.1). The pooled effect sizes of treatment efficacy were estimated using a random-effects model (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Multiple exploratory tests of heterogeneity were conducted using chi-squared tests, Galbraith plots and funnel plots. The potential confounders investigated were randomisation, aetiology and the duration of follow-up.

Results of the review
Efficacy: 33 studies with 2,462 participants met the inclusion criteria. Of these, 16 placebo-controlled trials (14 RCTs, 2 with unclear blinding) with 1,431 participants were retained for detailed evaluation and exploratory meta-analysis. Two trials (394 patients), which evaluated milk thistle as a prophylactic against hepatotoxic effects of antituberculosis drugs or tacrine, did not meet the inclusion criteria but were discussed because of their interest.

Harm: 18 studies of adverse effects in 7,963 patients were analysed. There were 7 RCTs, 6 cohort studies and 5 case reports.

Efficacy.
Chronic alcoholic liver disease (6 studies).
Four studies reported significant improvement when compared with placebo in at least one liver function test or histological finding. In 3 studies with multiple outcome measures, at least one outcome measure improved significantly, but there were no differences from placebo for one or more of the other outcome measures in each study. Two studies indicated a possible survival benefit.

Viral hepatitis (3 studies).
The acute viral hepatitis study showed significant improvement in aspartate aminotransferase and bilirubin. Of the 2 studies of chronic viral hepatitis, one showed improvement in aminotransferases but not other laboratory measures, while the other showed a weak trend towards histologic improvement.

Alcoholic or non-alcoholic cirrhosis (2 studies).
One trial showed a trend towards improved survival that was significant only for subgroups with alcoholic cirrhosis or Child's Group A. Another study reported a significant improvement in laboratory measures and survival for some clinical subgroups, but lacked data.

Alcoholic cirrhosis (2 studies).
One study reported weak evidence of an effect on encephalopathy, gastrointestinal bleeding, and in survival for patients with concomitant hepatitis C. Another study reported significant improvements in aminotransferases.

Hepatotoxic drugs (3 studies).

A factorial study of women already receiving treatment with phenothiazines and/or butyrophenones for 5 or more years reported significant improvements in malondialdehyde in patients treated with silymarin as well as usual medication, compared with those assigned to usual medication plus placebo, discontinued medication plus placebo, or silymarin alone. Two blinded trials that did not meet the inclusion criteria were discussed. In one, patients meeting the criteria for Alzheimer’s dementia showed no difference in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels or rate of side-effects when given tacrine with either silymarin or placebo. Another study in patients with normal liver function tests receiving antituberculosis drugs, with or without a mixture of silymarin and Fumaria officinalis alkaloids (Hepabene), reported significant improvements in AST and ALT levels from Hepabene.

No studies of cholestasis or primary hepatic malignancy were found. Overall, the effect sizes mostly favoured silymarin but were non significant, or small in magnitude. No significant heterogeneity was found, but the meta-analysis was hampered by the widely different aetiologies and outcome measures used in the 16 trials.

Adverse effects.

Seventeen reports of adverse effects were identified (e.g. gastro-intestinal upset, headache or skin symptoms), but without definite establishment of drug causality in most cases. In randomised trials reporting adverse effects, the incidence was very similar in the milk thistle and control groups. Serious adverse effects (anaphylaxis or anaphylloid reactions) were found in 3 case reports, but causality was unambiguous in only one.

Authors’ conclusions

The evaluation of all questions was impeded by the quality of the studies or reporting. Preparation, dosage, durations and outcome measures varied among the studies.

Efficacy: the efficacy of any milk thistle preparation was not clearly established in any disease. The disease populations likely to benefit, the optimal formulations of milk thistle, and the duration of therapy, are unknown.

Harm: milk thistle appeared to be safe for most people. The possibility of rare anaphylactic effects requires closer scrutiny.

CRD commentary

This was a well-conducted review of the available literature on milk thistle. The inclusion criteria, literature searches, relevance testing, and data extraction were appropriate. The studies were presented with sufficient detail through a narrative review, and heterogeneity was assessed formally.

The authors’ conclusions and recommendations appear to follow from the findings of the review.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors state that the type, frequency and severity of adverse effects of milk thistle preparations should be quantified. Studies of efficacy in liver disease should include well-conducted RCTs, which are longer and larger, and measure clinical as well as physiological outcomes.

Bibliographic details

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http://www.ahrq.gov/clinic/epcsums/milktsum.htm

**Other publications of related interest**

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.