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Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases.
Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003620.
DOI: 10.1002/14651858.CD003620.pub3.

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TABLE OF CONTENTS

[Intervention Review]

Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases

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Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Rambaldi A, Jacobs BP, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003620. DOI: 10.1002/14651858.CD003620.pub3.

ABSTRACT

Background

Alcohol and hepatotoxic viruses cause the majority of liver diseases. Randomised clinical trials have assessed whether extracts of milk thistle, *Silybum marianum (L) Gaertneri*, have any effect in patients with alcoholic and/or hepatitis B or C virus liver diseases.

Objectives

To assess the beneficial and harmful effects of milk thistle or milk thistle constituents versus placebo or no intervention in patients with alcoholic liver disease and/or viral liver diseases (hepatitis B and hepatitis C).

Search methods

TheCochrane Hepato-Biliary Group Controlled Trials Register, *The Cochrane Central Register of Controlled Trials*, *MEDLINE*, *EMBASE*, and full text searches were combined (December 2003). Manufacturers and researchers in the field were contacted.

Selection criteria

Only randomised clinical trials in patients with alcoholic and/or hepatitis B or C virus liver diseases (acute and chronic) were included. Interventions encompassed milk thistle at any dose or duration versus placebo or no intervention. The trials could be double blind, single blind, or unblinded. The trials could be unpublished or published and no language limitations were applied.

Data collection and analysis

The primary outcome measure was mortality. Binary outcomes are reported as relative risks (RR) with 95% confidence interval (CI). Subgroup analyses were performed with regard to methodological quality.

Main results

Thirteen randomised clinical trials assessed milk thistle in 915 patients with alcoholic and/or hepatitis B or C virus liver diseases. The methodological quality was low: only 23% of the trials reported adequate allocation concealment and only 46% were considered adequately double-blinded. Milk thistle versus placebo or no intervention had no significant effect on mortality (RR 0.78, 95% CI 0.53 to 1.15), complications of liver disease (RR 0.95, 95% CI 0.83 to 1.09), or liver histology. Liver-related mortality was significantly reduced by milk thistle in all trials (RR 0.50, 95% CI 0.29 to 0.88), but not in high-quality trials (RR 0.57, 95% CI 0.28 to 1.19). Milk thistle was not associated with a significantly increased risk of adverse events (RR 0.83, 95% CI 0.46 to 1.50).

Authors' conclusions

Our results question the beneficial effects of milk thistle for patients with alcoholic and/or hepatitis B or C virus liver diseases and highlight the lack of high-quality evidence to support this intervention. Adequately conducted and reported randomised clinical trials on milk thistle versus placebo are needed.

PLAIN LANGUAGE SUMMARY

No evidence supporting or refuting milk thistle for alcoholic and/or hepatitis B or C virus liver diseases

Milk thistle (*Silybum marianum (L) Gaertneri)* extracts have been used as medical remedies since the time of ancient Greece. Alcohol and hepatotoxic viruses are the major causes of liver diseases. Several trials have studied the effects of milk thistle for patients with liver diseases. This systematic review could not demonstrate significant effects of milk thistle on mortality or complications of liver diseases in patients with alcoholic and/or hepatitis B or C liver diseases combining all trials or high-quality trials. Low-quality trials suggested beneficial effects. High-quality randomised clinical trials on milk thistle versus placebo are needed.

BACKGROUND

Liver fibrosis and the subsequent development of liver cirrhosis are common reactions to a number of hepatotoxic substances, hepatotropic viruses, autoimmune liver diseases, metabolic liver diseases, etc. Alcohol and hepatotropic viruses cause the majority of liver fibrosis and cirrhosis in the Western World. The attributable risk for symptomatic liver cirrhosis in Italy explained by alcohol consumption, hepatitis B virus, and hepatitis C virus was 98 per cent in men and 67 per cent in women (Corrao 1998a).

Alcohol is the major hepatotoxin (Morgan 1999). Alcohol leads to fatty liver (Rubin 1968) and alcoholic hepatitis, fibrosis, and cirrhosis (Sørensen 1984; Marbet 1987; Morgan 1999). Five-year survival rates in patients with alcoholic cirrhosis who stop drinking are in the order of 50 to 75 per cent; whereas survival rates in patients who continue to drink rarely exceed 40 per cent (Powell 1968). There is no universally accepted therapy for alcoholic liver disease. Meta-analyses and randomised clinical trials have been unable to demonstrate significant effects on mortality of glucocorticosteroids (Christensen 1995; Gluud 2001), anabolic-androgenic steroids (Gluud 1988; Rambaldi 2002a), colchicine (Rambaldi 2001a), propylthiouracil (Rambaldi 2002b), insulin/glucagon (Trinchet 1992), parenteral amino acid supplementation (Mezey 1991), or polyenylphosphatidylcholine (Lieber 2001; Lieber 2003b). S-adenosyl-L-methionine may seem a promising medical intervention for alcoholic liver disease (Mato 1999), but more randomised clinical trials are needed before this treatment can be recommended (Rambaldi 2001b). Liver transplantation may be considered in patients with advanced alcoholic liver disease (Poynard 1994; Lieber 2000).

The progression of liver fibrosis and cirrhosis in alcoholics is enhanced by the presence of hepatitis B and hepatitis C virus (Chang 1994; Corrao 1998b). Interferon or lamivudine are presently the recommended therapy for hepatitis B (Main 1998; Zavaglia 2000; Lok 2001). Ribavirin plus interferon combination therapy is the recommended therapy for chronic hepatitis C whether interferon naive, relapsers, or non-responders (Main 1998; Pianko 2000; Zavaglia 2000; Brok 2005a). These therapies have shown significant benefit in terms of increased survival (Brok 2005a). They are associated with frequent adverse events (De Franceschi 2000; Russo 2000) and are too expensive to be widely used in low-income countries.

Many patients have turned to alternative medicines in hope of identifying substances with less toxicity and better effectiveness. The extracts of milk thistle, *Silybum marianum (L) Gaertneri*, have been used as medical remedies since the time of ancient Greece and the extracts are now widely used as an alternative medication (Flora 1998; Luper 1998; Saller 2001). Silymarin is the collective name for the flavonolignans (silybin or silibinin, silydianin, silychristin) extracted from milk thistle (Luper 1998). These extracts have been shown to protect animals against various hepatotoxins including acetaminophen (Campos 1989; Muriel 1992), radiation (Hakova 1993), iron overload (Szilard 1988), phalloidin (Floersheim 1978; Tuchweber 1979), carbon tetrachloride (Rauen 1971; Rauen 1973; Halim 1997), and thioacetamide (Schriewer 1973). The 'hepatoprotective' actions of milk thistle may include inhibition of lipid peroxide formation, scavenging of free radicals, and changing of the physical properties of cell membranes (Ramellini 1974; Bindoli 1977; Valenzuela 1985; Flora 1998). Milk thistle may also reduce liver fibrogenesis (Boigk 1997; Lieber 2003a).

Based on a questionnaire survey among European hospital-based specialists in gastroenterology/hepatology in 1992, 13 to 18 per cent of the specialists considered using milk thistle for patients with alcoholic fatty liver, alcoholic fibrosis, alcoholic hepatitis, or alcoholic cirrhosis (Gluud 1993). There were significant regional differences; milk thistle was being considered a treatment for alcoholic liver disease mostly in Eastern Europe (Gluud 1993). According to a recent meta-analysis on milk thistle for patients with liver diseases no significant reduction in mortality or improvements in liver histology, or liver function could be demonstrated, but data were too limited to exclude a substantial benefit or harm of milk thistle on mortality (Lawrence 2000; Jacobs 2002). Accordingly, there is insufficient evidence to support or refute recommending this herbal compound to patients for the treatment of liver diseases (Lawrence 2000; Jacobs 2002). However, another meta-analysis (Saller 2001) demonstrated significant effects of milk thistle on some outcomes like liver-related mortality, but data were not conclusive.

This systematic review summarised the data from randomised clinical trials to examine the beneficial and harmful effects of milk thistle or its constituents for alcoholic and/or hepatitis B or C liver diseases. The reasons for including these different aetiologies are the following. First, many trials conducted before the 1980s did not exclude hepatitis B virus and many trials conducted before the 1990s did not exclude hepatitis C virus as an aetiology. Second, alcoholic and viral liver diseases often coexist. Third, alcohol and hepatitis B and/or C constitute the major aetiologies of chronic liver diseases in the Western World (Corrao 1998a).

OBJECTIVES

The objectives were to assess the beneficial and harmful effects of milk thistle or milk thistle constituents versus placebo or no intervention in patients with alcoholic liver disease and/or viral liver diseases (hepatitis B and hepatitis C) based on the results of randomised clinical trials, irrespective of blinding, publication status, or language.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised clinical trials were included. The randomised clinical trials should have used a proper method of randomisation, ie, central randomisation; serially numbered opaque, sealed envelopes; or other description that contains elements convincing of adequate allocation concealment. Trials using quasi-randomisation were excluded. Randomised clinical trials could be double blind, single blind, or unblinded. The randomised clinical trials could be unpublished or published as an article, an abstract, or a letter. No language limitations were applied.

Types of participants

Patients with alcoholic liver cirrhosis, liver fibrosis, hepatitis and/or steatosis as well as patients with viral induced liver disease (hepatitis B and/or hepatitis C) according to the diagnostic work-up used in the individual trial were included. Both acute and chronic

liver disease were included. However, patients with rarer specific forms of liver disease (such as primary biliary cirrhosis, drug induced liver diseases, etc.) were not included as these diseases have different pathogenic mechanisms. Further, we excluded trials on prevention of liver disease, eg, prior to toxic exposure, as well as patients with liver disease of unknown aetiology. The individual patient groups were considered separately as well as collectively in order to estimate the efficacy of milk thistle and milk thistle constituents in specific diagnostic groups and in all groups.

Types of interventions

Administration of milk thistle or any milk thistle constituent at any dose or duration versus placebo or no intervention. The efficacy of milk thistle and milk thistle constituents were evaluated separately as well as collectively. Additional interventions were allowed, as long as both intervention groups received the additional intervention(s).

Types of outcome measures

The following outcome measures were assessed:
(1) Number of patients dying (total number of death and liver-related death) (primary outcome measures).
(2) Development of clinical symptoms and complications (ie, ascites, variceal bleeding, hepatic encephalopathy, etc.), analysed separately and combined.
(3) Liver biochemistry and function.
(4) Liver biopsy findings.
(5) Number and type of adverse event. Adverse event was defined as any untoward medical occurrence that did not have a causal relationship with the treatment. Severe adverse event was defined according to the ICH guidelines (ICH-GCP 1997) as any event that increase mortality; was life-threatening; required inpatient hospitalisation; resulted in a persistent or significant disability; or any important medical event, which might have jeopardised the patient or required intervention to prevent it.

In addition, any data on quality of life and health economics (eg, costs or length of hospitalisation) were compared.

Search methods for identification of studies

Searches in *The Cochrane Hepato-Biliary Group Controlled Trials Register* (December 2003), *The Cochrane Central Register of Controlled Trials (CENTRAL)* in *The Cochrane Library (*Issue 4 2003), *MEDLINE* (1966 to December 2003), and *EMBASE* (1974 to December 2003) were done entering the search terms 'milk thistle' or 'silymarin' or 'silybin' or 'silibinin' or 'silydianin' or 'silychristin' or commercial names (Legalon®, Silipide®, Realsil®, Carsil®, Siliphos®) and 'liver disease' or 'alcoholic liver disease' or 'viral liver disease' or 'hepatitis B or hepatitis C' (see Table 1).

The *MEDLINE* search was combined with the search strategy of The Cochrane Hepato-Biliary Group (Gluud 2003).

Further trials were identified by reading the reference lists of the identified studies.

The principal authors of the identified trials were approached and inquired about additional randomised clinical trials they might know of.

Pharmaceutical companies involved in the production of milk thistle products were contacted in order to obtain unidentified published or unpublished randomised clinical trials.

Data collection and analysis

The meta-analysis was conducted according to our protocol for the review (Rambaldi 2003) following the recommendations given by The Cochrane Collaboration (Higgins 2005).

Selection of trials for inclusion

Two reviewers (AR and GI) independently selected the trials to be included in the Review according to the prespecified selection criteria. A third opinion plus discussion resolved any disagreement.

Patient characteristics, diagnosis, and treatments

The following items were recorded from the included trials: mean (or median) age, sex ratio, form of liver disease according to the aetiology (acute viral hepatitis B and/or C; chronic viral hepatitis B and/or C; alcoholic liver disease (alcoholic steatosis; alcoholic hepatitis; alcoholic fibrosis; alcoholic cirrhosis; mixed), duration of liver disease, severity of liver disease at entry, alcohol consumption at entry and during the follow-up, type and dose of milk thistle-intervention (route of administration, formulation, frequency, and duration of dosing), type of intervention in the control group as well as any co-interventions. The diagnostic work-up before entry was registered, specifically if hepatitis markers were evaluated and the types of liver diseases that were excluded from the randomised clinical trials. Development of clinical symptoms and complications, liver biochemistry (serum (s)-bilirubin, prothrombin time (PT), s-albumin, s-aspartate aminotransferase (AST), s-alanine aminotransferase (ALT), s-alkaline phosphatases (AP), s-gamma-glutamyl transferase (GGT), liver biopsy findings, alcohol consumption, quality of life, health economics (eg, length of hospital stay, cost of medication, and cost of additional follow-up weighted against any gains in health), and adverse events during follow-up were registered.

Selection and data extraction

All randomised clinical trials considered for inclusion were analysed at least by two authors. All randomised clinical trials had the pertinent data extracted by two authors, who conferred with the reviewers in case disagreements could not be solved. All identified trials were listed and trials excluded from the meta-analysis of the review were identified with the reason for exclusion.

Assessment of methodological quality

The methodological quality of the randomised clinical trials was assessed using individual components of methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001):

Generation of the allocation sequence

The procedure used to create a random sequence ensuring that each participant has a known, unpredictable, and usually equal chance of being assigned to intervention groups. The allocation sequence generation can be classified as
(1) Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice may also be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.

(2) Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
(3) Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. Such studies are known as quasi-randomised studies and were excluded from the review due to the risk of bias.

Allocation concealment
The procedure used to conceal the allocation sequence from the investigators who assign participants to the intervention groups. The allocation concealment can be classified as
(1) Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes. Envelopes should be serially numbered, sealed, and opaque. However, this information is rarely provided, indicating an increased risk of bias. In that case, sealed envelopes may constitute an intermediate category between adequate and unclear.
(2) Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
(3) Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding
Blinding was classified as
(1) Adequate, if the trial was described as double blind and the method of blinding involved identical placebo and active drugs.
(2) Unclear, if the trial was described as double blind, but the method of blinding was not described.
(3) Not performed, if the trial was not double blind.

Follow-up
The reported follow-up was classified as
(1) Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
(2) Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
(3) Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Intention-to-treat analysis
We registered whether the randomised clinical trial reported or not on the use of intention-to-treat analysis (Gluud 2001).

Data on the number of patients with each outcome event by allocated treatment group, irrespective of compliance of follow-up, were sought to allow an intention-to-treat analysis. If the above data were not available in the trial reports, further information was sought by correspondence with the principal investigators.

Statistical methods
All analyses were performed according to the intention-to-treat method, that is, all randomised patients were included. We conducted analyses counting outcomes as reported in the individual trials. Further for patients without clear description of the outcome, we conducted a 'worst-case scenario' analysis regarding dichotomous outcome measures considering patients dropped out or withdrawn as having the outcome (eg, died).

The statistical package (RevMan Analyses 1.0.2) provided by The Cochrane Collaboration was used. We examined all outcomes with both the random-effects model and the fixed-effect model. In case both models reached the same conclusion regarding intervention effect (ie, both non-significant or both significant), only the fixed-effect model results were reported. In case both models reached different conclusions regarding intervention effect (ie, one model found no significant difference and the other a significant difference), the results of both analyses were reported (with fixed or random appended) (DerSimonian 1986; Demets 1987).

Dichotomous data were analysed by calculating the relative risk (RR) and continuous outcomes as weighed mean difference (WMD), both with 95% confidence intervals (CI).

Heterogeneity and funnel plot asymmetry
Heterogeneity in the results of the trials was initially assessed by inspection of graphical presentations and by calculating tests of heterogeneity (chi square and I^2) (Higgins 2003; Alderson 2004). Potential causes for heterogeneity were explored by performing subgroup analyses. The review performed subgroup analyses with regard to the stage (aetiology, acuity) of liver disease, methodological quality of included randomised clinical trials (analysing separately randomised clinical trials with adequate quality components and inadequate quality components (generation of the allocation sequence, allocation concealment, blinding, and follow-up) (Kjaergard 2001), and way (frequency) of administration of milk thistle or milk thistle constituents as well as preparation (formulation), dose and duration of milk thistle or milk thistle constituent treatment. In addition to the assessment of the potential impact of the individual quality components, we stratified the analyses of interventions effects on the major outcome measures into trials having all components adequate, trials with only some of the components adequate, and trials without any of the components adequate.

Due to the risk of chance, statistical findings among the secondary outcome measures were interpreted conservatively.

Funnel plots to identify publication bias and other biases were analysed by regression analyses (Egger 1997; Vickers 1998).

RESULTS

Description of studies

Search results
We identified 1,831 references through electronic searches of *The Cochrane Hepato-Biliary Group Controlled Trials Register* (n = 40), *The Cochrane Library* (n = 75), and *MEDLINE* and *EMBASE* (n = 1,716). Of these, 1,622 were in vitro studies, animal studies, studies unrelated to liver disease, or duplicate reports. Therefore, these studies were excluded.

Among the remaining 209 publications, 67 publications were on patients with alcoholic and/or hepatitis B or C liver diseases treated with milk thistle. Of these 67 publications, 43 had to be excluded for various reasons (see Characteristics of excluded studies). Accordingly, 24 publications could be included. Reading bibliographies identified two further publications, not identified by the electronic searches, on two trials (Salvagnini 1985; Buzzelli 1994), which could be included.

Included trials

Accordingly, 26 publications fulfilled our inclusion criteria. The 26 publications described 13 trials randomising patients with alcoholic and/or hepatitis B or C liver diseases to milk thistle versus placebo or no intervention. The individual randomised clinical trials are described in the table 'Characteristics of included studies'.

Eleven randomised clinical trials were described in full paper articles (Magliulo 1978; Fehér 1988; Ferenci 1989; Trinchet 1989; Láng 1990; Bunout 1992; Buzzelli 1993; Velussi 1997; Pár 2000; Lirussi 2002; Lucena 2002) and two randomised clinical trials in abstracts (Salvagnini 1985; Buzzelli 1994).

The experimental treatment consisted of silymarin orally in 10 randomised clinical trials (Magliulo 1978; Salvagnini 1985; Fehér 1988; Ferenci 1989; Trinchet 1989; Láng 1990; Bunout 1992; Velussi 1997; Parés 1998; Lucena 2002); IdB1016 orally in two randomised clinical trials (Buzzelli 1993; Buzzelli 1994) (IdB1016 is a lipophilic complex with silybin and phosphatidylcholine in a molar ratio of 1:1); and silybin-beta-cyclodextrin, a new formulation containing silybin, in one randomised clinical trial (Lirussi 2002).

The entry criteria in the randomised clinical trials varied, but the inclusion criteria were generally of good quality making it highly likely that all patients did have alcoholic and/or hepatitis B or C virus liver diseases. The randomised clinical trials could be divided into four groups according to etiology:
- 657 patients with alcoholic liver disease, the majority having cirrhosis (Salvagnini 1985; Fehér 1989; Ferenci 1989; Trinchet 1989; Láng 1990; Bunout 1992; Velussi 1997; Lirussi 2002; Lucena 2002);
- 28 patients with acute hepatitis B (Magliulo 1978);
- 10 patients with chronic hepatitis C (Buzzelli 1994);
- patients with alcoholic and/or hepatitis B or C liver diseases (Buzzelli 1993; Par), of which one trial included 20 patients with hepatitis B and hepatitis C (Buzzelli 1993) and the other included 200 patients with alcoholic liver disease with or without HCV antibody positivity (Parés 1998). Anti-HCV antibodies were positive in 29 (13 receiving milk thistle and 16 receiving placebo) of the 75 patients for whom stored sera were available after completion of the trial.

Out of the 915 patients randomised, 364 patients were males (Fehér 1989; Trinchet 1989; Láng 1990; Buzzelli 1993; Buzzelli 1994; Parés 1998; Lucena 2002), while 118 patients were females (Fehér 1989; Trinchet 1989; Láng 1990; Buzzelli 1993; Buzzelli 1994; Parés 1998; Lucena 2002). The sex of the patients was not given for 433 patients (Magliulo 1978; Salvagnini 1985; Ferenci 1989; Bunout 1992; Velussi 1997; Lirussi 2002).

All the randomised clinical trials compared milk thistle versus placebo, except one that compared milk thistle versus no intervention (Velussi 1997). The median duration of treatment was six months and varied from seven days (Buzzelli 1993) to 41 months (Ferenci 1989).

Excluded studies
A total of 33 studies, described in 43 publications, were excluded mainly because they were observational studies or case series (Characteristics of excluded studies).

Two of the excluded studies were randomised clinical trials on milk thistle (Fintelmann 1980; Salmi 1982). The aetiology was toxic liver disease in the Fintelmann trial (Fintelmann 1980) mostly due to alcoholic liver disease. The aetiology in the Salmi trial (Salmi 1982) was also mostly due to alcohol problems (the majority 81% in the milk thistle arm and 76% in the placebo arm admitted previous alcohol consumption). These trials were excluded in the main analyses, but included in an explorative sensitivity analysis.

We were unable to obtain three studies, which were excluded (Berenguer 1977; Dittrich 1980; Conti 1989) .

Risk of bias in included studies

Only one (Trinchet 1989) of the 13 randomised clinical trials provided a sample size estimation, which was based on liver histology.

The method to generate the allocation sequence was considered adequate in six (46.2%) of the trials (Ferenci 1989; Trinchet 1989; Bunout 1992; Parés 1998; Lirussi 2002; Lucena 2002).

Only three (23.1%) of the trials described adequate allocation concealment (Trinchet 1989; Parés 1998; Lucena 2002).

All but one (7.7%) of the trials (Velussi 1997) were described as double blinded. However, only six (46.2%) trials (Ferenci 1989; Trinchet 1989; Buzzelli 1993; Parés 1998; Lirussi 2002; Lucena 2002) described the use of placebo with identical presentation in the control arm.

There was a fair description of follow-up and withdrawals/drop-outs in 12 (92.3%) trials (Magliulo 1978; Fehér 1989; Ferenci 1989; Trinchet 1989; Láng 1990; Bunout 1992; Buzzelli 1993; Buzzelli 1994; Velussi 1997; Parés 1998; Lirussi 2002; Lucena 2002).

None of the randomised clinical trials stated that they used an intention-to-treat method to evaluate their data. All the randomised clinical trials but three (Bunout 1992; Lirussi 2002; Lucena 2002) presumably used intention-to-treat analysis.

Effects of interventions

Mortality

Combining the results of the 13 randomised clinical trials demonstrated no significant effect of milk thistle versus placebo/no intervention on mortality (RR 0.78, 95% confidence interval (CI) 0.53 to 1.15). There was no significant heterogeneity. In the milk thistle group 36/456 (7.9%) patients died versus 45/459 (9.8%) patients in the control group (Comparison 01-01).

Subgroup analyses stratifying the trials according to the single methodological quality components (generation of the allocation sequence, allocation concealment, blinding, and follow-up) did not demonstrate significant differences regarding the effect of milk thistle on mortality between trials with and without adequate methodology components (Comparison 01-02, 01-03, 01-04, 01-05).

Subgroup analysis stratifying the trials into trials having all methodological components adequate, trials with some of the components adequate, and trials without any of the components adequate did not demonstrate significant differences regarding the effect of milk thistle on mortality: trials having all components adequate (RR 0.95, 95% CI 0.55 to 1.65); trials having some components adequate (RR 0.62, 95% CI 0.35 to 1.08) (test of interaction z = -1.06; P = 0.29); trial without any of components adequate (not estimable since no events happened in this group) (Comparison 01-06).

Milk thistle did not significantly influence mortality in the trials with a treatment duration less than six months (RR 0.35; 95% CI 0.04 to 3.22) or in the trials with a duration of treatment of at least six months (RR 0.81, 95% CI 0.54 to 1.20) (Comparison 01-07).

Milk thistle did not significantly influence mortality in the trials including patients with chronic liver disease (RR 0.72, 95% CI 0.48 to 1.09); the RR in the trials including patients with acute liver disease was not estimable since no events occurred in this group (Comparison 01-08).

The RR of death of the randomised clinical trials evaluating silymarin (Legalon®) was 0.72 (95% CI 0.48 to 1.09); the RRs of the randomised clinical trials evaluating Silipide® or silybin-beta cyclodextrin were not estimable since no events occurred in these groups (Comparison 01-09).

A worst-case scenario analysis (all patients who dropped-out or were withdrawn were considered dead) did not change the estimate of no significant effect of milk thistle on mortality (RR 1.09; 95% CI 0.75 to 1.58) (Comparison 01-10).

In patients with alcoholic liver disease (Salvagnini 1985; Fehér 1989; Ferenci 1989; Trinchet 1989; Bunout 1992; Láng 1990; Velussi 1997; Lirussi 2002; Lucena 2002), a significant effect of milk thistle on mortality was demonstrated (RR 0.58, 95% CI 0.34 to 0.98; P = 0.04). There was no significant heterogeneity. In the milk thistle group 16/325 (4.9%) patients died versus 28/332 (8.4%) in the control group (Comparison 01-01). However, focusing only on high-quality trials (Trinchet 1989; Lucena 2002) milk thistle had no significant effect on mortality (RR 0.34, 95% CI 0.06 to 2.11) (Comparison 01-11).

In patients with alcoholic liver disease including patients with HCV antibody positivity (Parés 1998) milk thistle demonstrated no significant effect on mortality RR (1.11, 95% CI 0.62 to 1.99). In the milk thistle group 20/103 (19.4%) patients died versus 17/97 (17.5%) in the control group (Comparison 01-01).

In a worst-case scenario analysis in patients with alcoholic liver disease, milk thistle was without significant effect on mortality (RR 1.09, 95% CI 0.75 to 1.58) (Comparison 01-10).

In patients with hepatitis B (Magliulo 1978) none of the patients died out of the 13 in the milk thistle and 15 in the control group (Comparison 01-01).

In patients with hepatitis C (Buzzelli 1994) none of the patients died out of the five in the milk thistle and five in the control group (Comparison 01-01).

In patients with hepatitis B and hepatitis C (Buzzelli 1993) none of the patients died out of the 10 in the milk thistle and 10 in the control group (Comparison 01-01).

Exploratory analysis adding two excluded randomised clinical trials (Fintelmann 1980; Salmi 1982) because they treated patients with other liver diseases than alcoholic liver disease, hepatitis B, and/or hepatitis C did not change the estimate significantly (RR 0.78, 95% CI 0.53 to 1.15) (Comparison 01-12). In the milk thistle group 36/540 (6.7%) patients died versus 45/545 (8.3%) patients in the control group as no deaths occurred in the two added trials.

Liver-related mortality

Among the 13 trials, only four reported liver-related mortality (Ferenci 1989; Trinchet 1989; Parés 1998; Lucena 2002). Three of the trials included patients with alcoholic liver disease and the Pares trial included patients with alcoholic liver disease or alcoholic liver disease with HCV antibody positivity. These trials found a significant effect of milk thistle on liver-related mortality (RR 0.50, 95% CI 0.29 to 0.88; P = 0.02). There was no significant heterogeneity. In the milk thistle group, 16/422 (3.8%) patients died versus 31/422 (7.3%) patients in the control group (Comparison 02-01).

Subgroup analysis demonstrated no significant effect of milk thistle on liver-related mortality in the trials having all four methodological components adequate (RR 0.57, 95% CI 0.28 to 1.19) whereas milk thistle significantly decreased mortality in the trials having only one or more components adequate (RR 0.41, 95% CI 0.17 to 0.97). This effect was based on only one trial with less than 100 patients randomised (Ferenci 1989). There was no significant difference between the two estimates (z = 0.57). The effect of milk thistle on liver-related deaths in the trials with no adequate methodological component was not estimable due to no deaths (Comparison 02-02).

A worst-case scenario analysis of patients with alcoholic liver disease (all patients who dropped-out or were withdrawn were considered dead) changed the estimate to no significant effect of milk thistle on liver-related mortality (RR 0.81, 95% CI 0.58 to 1.13) (Comparison 02-03).

Liver-related complications

Milk thistle did not significantly affect the incidence of patients with ascites (RR 0.88, 95% CI 0.65 to 1.20), hepatic encephalopathy (RR 1.09, 95% CI 0.55 to 2.16), or gastro-intestinal bleeding (RR 0.84, 95% CI 0.53 to 1.34) (Parés 1998) (Comparison 03-01, 03-02, 03-02). None of the randomised clinical trials reported hepato-renal syndrome as an outcome measure. Combining the results of two trials (Parés 1998; Lucena 2002) demonstrated no significant effect of milk thistle on the combined complications (RR 0.95, 95% CI 0.83 to 1.09). In the milk thistle group the total number of complications were 85/133 (63.3%) versus 84/127 (66.1%) in the control group (Comparison 03-04).

Liver biochemistry

Milk thistle significantly decreased s-bilirubin concentration and GGT activity in both fixed effect and random effects analyses when all trials are considered:

- s-bilirubin (µmol/L): WMD -4.68 (95% CI -7.72 to -1.64; P < 0.05) (fixed effect model). There was no significant heterogeneity (Comparison 03-07);
- GGT (U/L): WMD -26.80 (95% CI -32.86 to -20.73; P < 0.05) (fixed effect model). There was significant heterogeneity (I^2 = 68%) (Comparison 03-10).

When focusing on high-quality trials only, no significant beneficial effects of milk thistle on s-bilirubin or GGT activity were found (data not shown).

Milk thistle also showed a significant beneficial effect on some of the other biochemical measures when analysed by the fixed effect model, but not by the random effects model:

- AST (U/I): WMD -7.55 (95% CI -12.10 to -2.99; P < 0.05) (fixed effect model). There was significant heterogeneity (I^2 = 81%) (Comparison 03-08);

- AST (U/l): WMD -3.78 (95% CI -15.76 to 8.20) (random effects model) (Comparison 03-08);
- ALT (U/L): WMD -6.35 (95% CI -10.26 to -2.44; P < 0.05) (fixed effect model). There was significant heterogeneity (I^2 = 67%) (Comparison 03-09);
- ALT (U/L): WMD -3.96 (95% CI -12.59 to 4.68) (random effects model) (Comparison 03-09).

When focusing on high-quality trials only, no significant beneficial effects of milk thistle on AST or ALT activity were found (data not shown).

Milk thistle did not significantly influence:
- prothrombin time (%): WMD -2.77 (95% CI -6.42 to 0.88) (fixed effect model). There was no significant heterogeneity (Comparison 03-05);
- s-albumin (g/L): WMD 0.15 (95% CI -1.35 to 1.65) (fixed effect model). There was significant heterogeneity (I^2 = 67%) (Comparison 03-06);
- AP (U/l): WMD 0.58 (95% CI -13.65 to 14.80) (fixed effect model). There was no significant heterogeneity (Comparison 03-11).

Liver histology

There were no significant effects of milk thistle on hepatitis or fibrosis of liver biopsy findings in the only trial reporting this outcome (Trinchet 1989):
- liver biopsy change (hepatitis): WMD -0.10 (95% CI -0.85 to 0.65) (Comparison 03-12);
- liver biopsy change (fibrosis): WMD 0.00 (95% CI -13.65 to 14.80) (Comparison 03-13).

Adverse events

In the milk thistle group 0/456 patients had serious adverse events versus 0/459 patient in the control group (Comparison 04-01).

Milk thistle had no significant effect on the occurrence of non-serious adverse events (RR 0.83, 95% CI 0.46 to 1.50). In the milk thistle group, 16/456 (3.5%) patients had non-serious adverse events versus 20/459 (4.4%) patients in the control group (Comparison 04-02). The adverse events observed in the milk thistle group encompassed impotence (one patient), pruritus (four patients), cephalea (three patients), and nausea and epigastric discomfort (one patient). The authors did not report the type of adverse event in seven patients. The adverse events observed in the control group encompassed pruritus (11 patients), cephalea (four patients), and nausea and epigastric discomfort (one patient). The authors did not report the type of adverse events in four patients.

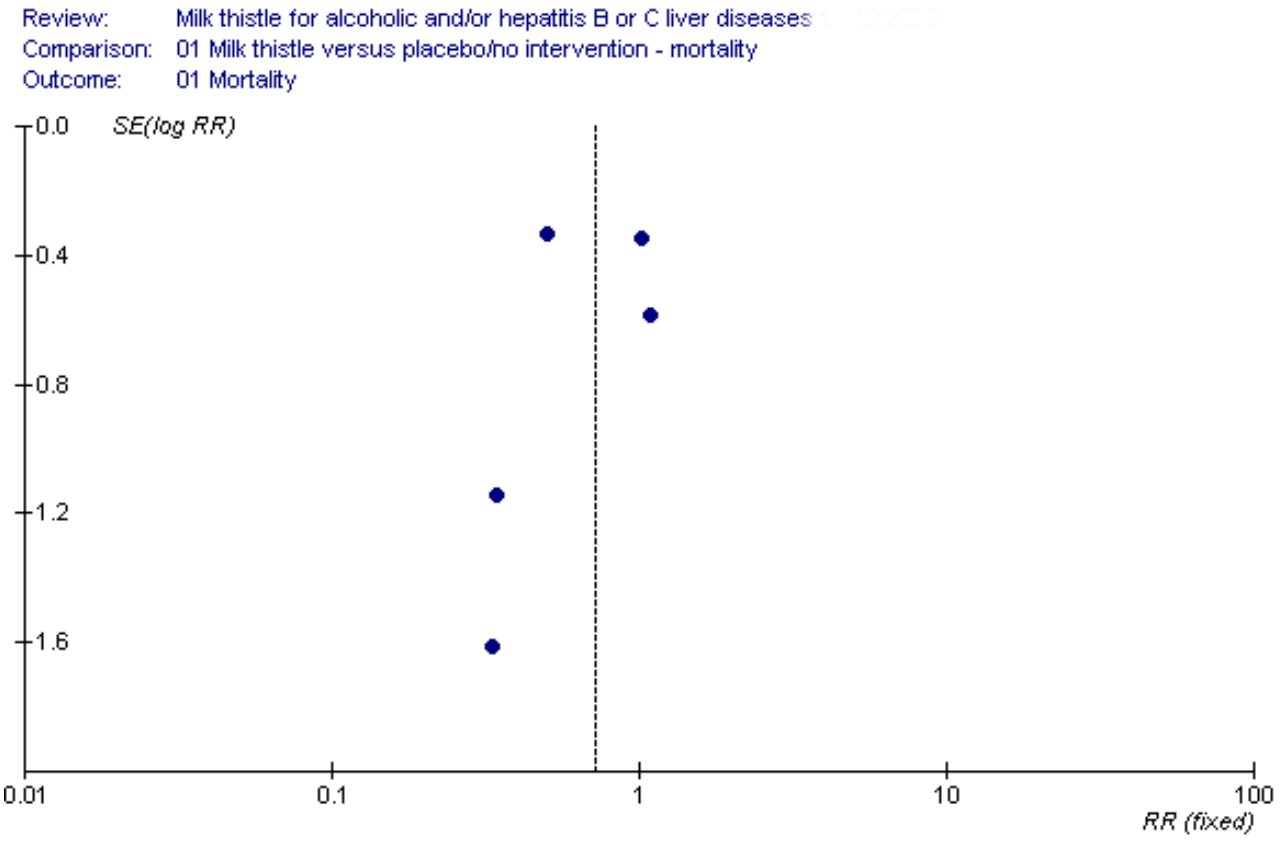
Quality of life and health economics

None of the randomised clinical trials reported quality of life or health economics outcomes.

Funnel plot asymmetry

Additional Figure 1 shows a funnel plot of the five trials reporting on mortality. From a visual inspection one gets the impression that the smaller the trial the larger the intervention effect. Due to the paucity of mortality in a number of the randomised clinical trials we did not try to analyse for funnel plot asymmetry.

Figure 1. Funnel plot of five trials on milk thistle for liver diseases



DISCUSSION

We found no significant effect of milk thistle on overall mortality when all trials were combined or in high-quality trials. We observed a potential beneficial effects of milk thistle on mortality in patients with alcoholic liver disease, but this effect could not be demonstrated in high-quality trials. We also observed a potential beneficial effect of milk thistle on liver-related deaths, but again this effect could not be demonstrated in high-quality trials. Further, we found benefit of milk thistle on some biochemical liver tests, but these observations could not be confirmed in high-quality trials. As the methodological quality of the majority of the trials was low, bias and/or random errors may explain some or all of our positive findings.

Our observations mainly confirm two recent meta-analyses on milk thistle for patients with liver disease of any cause, ie, no significant beneficial effect of milk thistle (Lawrence 2000; Jacobs 2002). This is in spite of the fact, that the present systematic review included five more randomised clinical trials (Salvagnini 1985; Buzzelli 1994; Velussi 1997; Lirussi 2002; Lucena 2002) and did not use data from quasi-randomised clinical trials (Jacobs 2002), which may significantly bias estimates of interventions effects (Kjaergard 2003; Kunz 2002).

We observed a statistically significant reduction in mortality in the patients with alcoholic liver disease and a significant reduction in liver-related mortality among all patients. We found no significant effect of milk thistle on mortality in patients with alcoholic liver disease or on liver-related mortality when we focused on high-quality trials. It has previously been demonstrated that the effects of many interventions are significantly overestimated in low-quality trials (Schulz 1995; Moher 1998; Kjaergard 2001). Further, these effects could neither be confirmed in a subgroup analysis including patients with alcoholic liver disease coinfected by HCV nor in a worst-case scenario analysis. Therefore our findings are not robust enough to form a fundament for therapeutic recommendations. On the positive side, milk thistle did not differ significantly from placebo/no intervention regarding adverse events.

The observation that overall mortality is no different but liver-related mortality seems to improve improved appears to be a mutual contradiction. One of the reasons could be that some of the trials did not report liver-related mortality.

We found a significant beneficial effect of milk thistle in improving bilirubin and s-gamma-glutamyl transferase. For the remainder of our analysis on liver biochemistry markers, milk thistle either had effects that were dependent on the method of meta-analysis (fixed effect or random effects) or had no significant effects. Focusing on high-quality trials, no significant effects could be demonstrated. In all circumstances, the effects of milk thistle were not dramatic.

This systematic review has a number of potential limitations. First, the small sample size limits the power of our meta-analyses. The confidence interval for the pooled estimate is sufficiently wide, which means that a substantial benefit or harm cannot be excluded. Evidence shows how much effects of medical intervention may change over time. Ioannidis and Lau (Ioannidis 2001) applied 'recursive cumulative meta-analyses' of randomised clinical trials to evaluate the relative change in the pooled treatment effect over time for 60 medical interventions within pregnancy/perinatal medicine and cardiology. With 500 accumulated patients, the pooled relative risk may change by about 0.6- to 1.7-fold in the immediate future. When 2000 patients have been randomised, the pooled relative risk may change by 0.7- to 1.3-fold. At present, only about 1000 patients with alcoholic liver disease and/or hepatitis B and C have been randomised to milk thistle versus placebo or no intervention. Second, we chose to include only alcoholic liver disease and viral liver disease in the review. The major reason is that viral and alcohol-related liver disease frequently coexist in the same patient. Several trials were old and did not check for viral liver disease in patients with suspected alcoholic liver disease. Further, hepatitis B or C marker positivity was not an exclusion criterion for the entry of the patient in one of the trials on patients with alcoholic liver disease (Parés 1998). Other liver diseases like non-alcoholic liver disease and toxic liver diseases should be considered in other reviews.

Among the randomised clinical trials reporting adverse drug events, milk thistle appeared safe and well-tolerated. We recognise it is difficult to interpret the risk of adverse events from the literature for several reasons (Gluud 2002). Events may be missed since search terms related to adverse events are often not indexed, and causality is difficult to discern when events are published in a case report or case series. However, considering that among the excluded studies there were some randomised clinical trials considering unspecified form of liver diseases like the one of Tanasescu et al (Tanasescu 1988) with 180 patients, milk thistle seems to be well tolerated, although adverse events are reported in the literature (Geier 1990; Vailati 1993).

If milk thistle does not work for alcoholic liver diseases, which drug therapy can we offer these patients for their liver disease? Meta-analyses and randomised clinical trials have been unable to demonstrate significant beneficial effects of colchicine (Rambaldi 2001a), anabolic-androgenic steroids (Rambaldi 2002a), propylthiouracil (Rambaldi 2002b), glucocorticosteroids (Christensen 1995; Gluud 2001), insulin/glucagon (Trinchet 1992), parenteral amino acid supplementation (Mezey 1991), amlodipine (Bird 1998), and polyenylphosphatidylcholine (Lieber 2001; Lieber 2003b) for alcoholic liver disease. A recent trial has demonstrated that ursodeoxycholic acid is detrimental in patients with alcoholic liver disease (Pelletier 2003). At present, S-adenosyl-L-methionine (Mato 1999), pentoxifylline (Akriviadis 2000), and potentially milk thistle may seem as promising interventions. However, more randomised clinical trials are needed before S-adenosyl-L-methionine can be recommended (Rambaldi 2001b). This also applies to pentoxifylline, which has only been evaluated in one randomised trial including patients with severe alcoholic hepatitis, and to milk thistle, for which there is insufficient evidence. However, absence of evidence is not the same as evidence of absence of effect. Future trials on milk thistle should have adequate sample size, enrol patients with well-defined liver disease, and devote adequate resources to monitor outcomes. At the present time, there is insufficient evidence to support or refute milk thistle for patients for the treatment of alcoholic liver diseases.

If milk thistle does not work for viral hepatitis B or C either, which drug therapy can we offer these patients for their liver diseases? Treatment decisions should be based on recent recommendations for treatment of acute and chronic hepatitis B (Pianko 2000; Zavaglia 2000; Liaw 2003) and of acute and chronic hepatitis C

(Pianko 2000; Zavaglia 2000; Di Bisceglie 2002; Brok 2005a; Brok 2005b).

AUTHORS' CONCLUSIONS

Implications for practice

We cannot recommend the use of milk thistle for acute or chronic alcoholic and/or hepatitis B or C virus liver diseases outside randomised clinical trials.

Implications for research

Based on this review, milk thistle could potentially affect alcoholic and/or hepatitis B or C virus liver diseases. Therefore, large-scale randomised clinical trials on milk thistle for alcoholic and/or hepatitis B or C liver diseases versus placebo are needed. Such trials ought to be performed with adequate methodologies (ie, generation of the allocation sequence; allocation concealment; blinding; intention-to-treat analyses). The randomised trials should consider including patients with alcoholic cirrhosis and should stratify patients at randomisation according to hepatitis B and hepatitis C status, the degree of liver injury, and the degree of alcoholism. Such trials should examine relevant outcomes. Based on this review such randomised clinical trials need to be large in order to be able to detect any effect. Finally, such trials ought to follow the Consolidated Standards for Reporting Trials (CONSORT) Statement (www.consort-statement.org).

ACKNOWLEDGEMENTS

We are indebted to Nader Salasshari for the expert technical computer assistance and to Dimitrinka Nikolova and Sarah Frederiksen for expert assistance with the retrieval of publications. Special thanks to Flavio Lirussi, M.I. Lucena, and A. Parés for providing us with more information on the trials they were involved in.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bunout 1992

Methods	Sample size: no justification. Generation of the allocation sequence: adequate, by random number tables. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: adequate, more than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: not used.
Participants	Seventy-one patients with alcoholic liver disease. Thirty-four patients were allocated to the silymarin while 37 to the placebo group. Chronic liver disease. Inclusion criteria: 1) alcohol intake of at least 150 gr/day; 2) at least three crisis of alcohol misuse each month; 3) advanced chronic alcoholic liver disease. Exclusion criteria: 1) HBsAg positive patients; 2) kidney failure; 3) cardiac failure; 4) end-stage liver failure.
Interventions	MT group: silymarin tablets 140 mg, two times daily (280 mg per day). Control group: placebo tablets, two times daily. Duration of treatment and of follow-up: 15 months.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.
Notes	Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Buzzelli 1993

Methods	Sample size: no justification. Generation of the allocation sequence: unclear, not described. Allocation concealment: unclear, not described. Blinding: adequate, double blind with identical placebo. Follow-up: adequate, less than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Twenty patients (6 males, 14 females, mean age 53± 3.0 years, range 31-70) with HBV and/or HCV chronic active hepatitis. Chronic liver disease. Inclusion criteria: 1) histologically chronic active hepatitis; 2) increased AST and/or ALT serum activities (twice to sixfold the upper limit of the reference range) for more than 12 months; 3) age range: 30 to 70 years. Exclusion criteria: 1) portal hypertension; 2) hepatic encephalopathy; 3) ascites; 4) hepatocellular carcinoma; 5) clinical signs and biochemical parameters of cholestasis; 6) drug addiction; 7) positive antinuclear, antimitochondrial, and antismooth muscle antibodies; 8) ethanol intake more than 30 gr per day; 9) malabsorption syndromes; 10) cardiovascular, renal or endocrine disorders; 11) pregnancy; 12) any pharmacological treatment three months before the beginning of the trial.
Interventions	MT group: IdB1016 two capsules, twice a day (equivalent to 120 mg of silybin in each capsule) (480 mg per day). IdB1016 is a lipophilic complex with phosphatidylcholine and silybin in a molar ratio of 1:1. Control group: placebo, 2 capsules twice a day. Duration of treatment and of follow-up: seven days. Eight patients were also treated for two months in total. No adverse events occurred in these patients.
Outcomes	Mortality. Liver biochemistry. Adverse events.
Notes	Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Buzzelli 1994

Methods	Sample size: no justification. Generation of the allocation sequence: unclear, not described.

Buzzelli 1994 *(Continued)*

	Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: adequate, less than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Ten patients (8 males and 2 females, mean age 59 years) with chronic hepatitis C. Chronic liver disease. Inclusion criteria: 1) chronic hepatitis C; 2) no significant variations of AST and ALT (non-responders) to a previous treatment with recombinant interferon alpha 2B (3 million units thrice weekly for 6 months) (6 months withdrawal).
Interventions	MT group: Silipide® (IdB1016) capsules 360 mg per day. Control group: placebo capsules. Duration of treatment and follow-up: two months of treatment and one month of washout.
Outcomes	Mortality. Liver biochemistry. Adverse events.
Notes	Trial characteristics: cross over design. Patients were assigned to the Silipide® group for two months treatment, and one month washout. Results were not reported separately, we give overall results. Only published as abstract. Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fehér 1989

Methods	Sample size: no justification. Generation of the allocation sequence: unclear, not described. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: adequate, less than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Thirty-six patients with compensated alcoholic liver cirrhosis. Of these 17 patients were allocated to the silymarin group (15 males and two females, mean age 48± 7 years), while 19 to the placebo group (12 males and seven females, mean age 44± 6 years).

Fehér 1989 *(Continued)*

	Chronic liver disease.
Interventions	MT group: silymarin tablets (Legalon®) 140 mg, three times tablets daily (420 mg per day). Control group: placebo, three times daily. Patients were discouraged from consuming alcoholic beverages. Duration of treatment and follow-up: six months.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.
Notes	Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ferenci 1989

Methods	Sample size: no justification. Generation of the allocation sequence: adequate, according to a random-number sequence. Allocation concealment: unclear, not described. Blinding: adequate, double blind with placebo of identical appearance. Follow-up: adequate, more than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Multicentre clinical trial including patients from four medical departments. Of these 92 patients 47 were allocated to silymarin group and 45 to the placebo group. Chronic liver disease. Inclusion criteria: liver cirrhosis diagnosed by biopsy in 70% of the patients. In the remaining patients no liver biopsy could be obtained due to coagulation disorders. The severity of the underlying liver disease was classified using Child-Turcotte criteria. Exclusion criteria: 1) end-stage liver failure; 2) known malignancies; 3) immunosuppressive treatment. The use of steroids and of D-penicillamine was not allowed. Patients were recruited from all the patients seen at one of the four participating centres.
Interventions	MT group: silymarin tablets (Legalon®) 140 mg, three times daily (420 mg per day). Control group: placebo tablets, three times per day.

Ferenci 1989 *(Continued)*

	Patients were advised not to drink alcoholic beverages. Alcohol consumption was estimated and blood levels monitored. The use of steroids and of D-penicillamine was not allowed. Mean duration of treatment and of follow-up: 41 months (range, 2 to 6 years).
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.
Notes	170 patients with cirrhosis of the liver were included in the study originally from the authors. The data on 78 patients with liver cirrhosis of unknown etiology are not extracted in our Systematic Review. Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fintelmann 1980

Methods	We exclude this randomised clinical trial because the etiology is toxic liver disease. We report this randomised clinical trial, however, only to be able to include it in a exploratory analysis as the toxic liver disease was mostly due to alcoholic liver disease. Sample size: no justification. Generation of the allocation sequence: adequate, by random table. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: adequate, less than 10% of patients dropped out or were withdrawn Intention-to-treat analysis: not used.
Participants	Clinical trial including 70 patients; 35 were treated with silymarin while 35 received placebo. Inclusion criteria: liver biopsy proven toxic liver disease of any cause, mostly alcoholic liver disease.
Interventions	MT group: silymarin tablets (Legalon®), no dosage was given. Control group: placebo. Collateral interventions: diet with 1000 kgcal/day Duration of treatment: 28 days.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.

Fintelmann 1980 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lirussi 2002

Methods	Sample size: no justification. Generation of the allocation sequence: adequate, by random table. Allocation concealment: unclear, not described. Blinding: adequate, double blind with placebo of identical appearance. Follow-up: adequate, more than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Sixty out-patients with chronic alcoholic liver disease and non-insulin dependent type 2 diabetes were enrolled in a three centre study. Forty-two out-patients (21 in the treatment group, and 21 in the placebo group) concluded the treatment period. Chronic liver disease. Inclusion criteria: 1) more than 60 to 80 grams of daily alcohol intake for at least 5 years; 2) biochemistry and ultrasound of the liver; 3) transaminase level not more twice the upper limit of normal values and body mass index less than 31 Kg/m2. Exclusion criteria: 1) decompensated liver cirrhosis; 2) presence of antibodies to hepatitis B or hepatitis C; 3) autoimmune liver diseases; 4) Wilson's disease; 5) alfa1-antitrypsin deficiency; 6) liver neoplasms; 7) porphyria cutanea tarda; 8) impaired renal function, 9) heart failure, 10) insulin treatment, 11) alcohol abuse.
Interventions	MT group: Silybin-beta-cyclodextrin (Lorenzini, Milan, Italy) sachets three times per day - 135 mg silybin per day. Control group: placebo. Duration of treatment: six months.
Outcomes	Mortality. Liver biochemistry. Adverse events.
Notes	Letter to the trialist: sent December 2003. F. Lirussi answered.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lucena 2002

Methods	Sample size: no justification. Generation of the allocation sequence: adequate, computer generated. Allocation concealment: adequate, randomisation labels were kept in sealed envelopes. Blinding: adequate, double blind with placebo of identical appearance. Follow-up: adequate, more than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: not used.
Participants	Multicentre clinical trial including 122 consecutive in-patients from five clinical departments. Chronic liver disease. Inclusion criteria: chronic alcohol abuse and hospitalisation for liver disease. Exclusion criteria: HBsAg positivity and/or patients with decompensated liver cirrhosis.
Interventions	MT group: silymarin MZ-80 tablets (Legalon®) 150 mg, three times per day (450 mg per day). Control group: placebo tablets, three times per day. Patients were advised not to drink alcoholic beverages. All patients who completed the trial reported abstinence from alcohol during the study period. Duration of treatment and of follow-up: six months.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events. Alcohol consumption was estimated and blood alcohol levels monitored.
Notes	Letter to the trialist: sent (August 2002). M.Isabel Lucena answered.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Láng 1990

Methods	Sample size: no justification. Generation of the allocation sequence: unclear, not described. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described.

Láng 1990 *(Continued)*

	Follow-up: adequate, less than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Forty patients with compensated alcoholic liver cirrhosis. Of these 40 patients, 20 (16 males and 4 females, mean age 46.8 years) were allocated to silymarin group and 20 (12 males and eight females, mean age 44.4 years) to the placebo group. Inclusion criteria: histological micronodular cirrhosis. The mean alcohol consumption exceed 60 gr in males and 30 gr in females. Duration of alcohol consumption was between 6-11 years (mean 8.6 years). Chronic liver disease. Exclusion criteria: symptoms of vascular and/or parenchymal decompensation and HBsAg positivity.
Interventions	MT group: silymarin tablets (Madaus Cerafarm, Barcelona, Spain) 140 mg, three times tablets daily (420 mg per day). The non-standardized silymarin MZ 80 is obtained by reformulation of non-active plant ingredients using new excipients that enhance humectation, dissolution and availability of the main active agent (70-80% of the silymarin complex; silibin 35.07%). Control group: placebo tablets, three times daily. Alcohol consumption was registered by careful detailed interview. Patients were discouraged from consuming alcoholic beverages. Duration of treatment and follow-up: one month.
Outcomes	Mortality. Liver biochemistry. Adverse events.
Notes	The data on the 20 patients treated with the flavonoid synthetical derivate Aica-P are excluded. Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Magliulo 1978

Methods	Sample size: no justification. Generation of the allocation sequence: unclear, not described. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: adequate, more than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.

Magliulo 1978 *(Continued)*

Participants	Two-centres clinical trial from Italy including fifty-nine patients with acute viral hepatitis A or B. Thirteen patients with acute hepatitis B were allocated to the treatment group, while the other fifteen patients were allocated to the placebo group. Acute liver disease.
Interventions	MT group: silymarin two tablets 70 mg, three times daily (420 mg per day). Control group: placebo tablets, three times daily. Duration of treatment and of follow-up: 28 days.
Outcomes	Mortality. Liver biochemistry. Adverse events.
Notes	The data on 31 patients with acute hepatitis A are excluded. Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Parés 1998

Methods	Sample size: no justification. Generation of the allocation sequence: adequate, according to a random-number sequence table. Allocation concealment: adequate, the assigned treatment was obtained from the coordinating centre by telephone (central randomisation). Blinding: adequate, double blind with placebo of identical appearance, smell and taste. Follow-up: adequate, more than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Multicentre clinical trial including 200 patients from six hospitals from Catalonia with alcoholic liver cirrhosis. 103 were allocated to silymarin and 97 to the placebo group. Chronic liver disease. Inclusion criteria: chronic alcoholism defined by a daily alcohol intake over 80 gr in men and 60 gr in women for a period longer than 5 years. Criteria for liver cirrhosis were supported by histology performed within the three months before inclusion in the trial; or by laparoscopic examination in those patients with very low prothrombin index or platelet count. Exclusion criteria: 1) previous treatment with colchicine, malotilate, penicillamine, corticosteroids; 2) life expectancy less than 6 months; 3) drug addiction; 4) pregnancy. Patients with other known etiologies for liver cirrhosis such as hepatitis B, autoimmunity, primary biliary cirrhosis or cryptogenic cirrhosis were excluded as well.

Parés 1998 *(Continued)*

	All patients were advised to abstain from alcohol. Alcohol intake was estimated by questioning the patients and their relatives about the amount of alcohol consumed and by assessing alcohol in urine before and during the study.
Interventions	MT group: silymarin tablets (Legalon®) 150 mg three times daily (450 mg per day). Control group: placebo tablets. Duration of treatment: two years. Duration of follow-up: five years.
Outcomes	Mortality. Histology. Liver biochemistry. Adverse events.
Notes	Antibodies against hepatitis C virus were assessed by third-generation ELISA test (Ortho Diagnostics, Raritan, NJ, USA) in stored sera from 75 patients after completion of the trial. Twenty-none of the 75 patients resulted positive (13 receiving silymarin and 16 receiving placebo). Letter to the trialist: sent (August 2002). A. Parés answered.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Salmi 1982

Methods	We exclude this randomised clinical trial because the etiology is mixed. We report this randomised clinical trial only to be able to include it in exploratory analysis as most of the patients had alcoholic liver disease. Sample size: no justification. Generation of the allocation sequence: unclear, not described. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: adequate, less than 10% of patients dropped out or were withdrawn. Intention-to-treat analysis: not used.
Participants	One hundred and six consecutive military personnel admitted to a military hospital in Finland after serving a United Nation peace-keeping force in Cyprus or Sinai with raised transaminases levels. The majority (81% in the experimental arm and 76% in the placebo arm admitted previous alcohol consumption). Forty-nine patients treated with silymarin and 52 with placebo. Inclusion criteria: AST, ALT and GGT raised above the upper normal limit despite one month order to abstain from alcohol.

Salmi 1982 *(Continued)*

	Exclusion criteria: not mentioned.
Interventions	MT group: silymarin tablets (Legalon®), 420 mg per day. Control group: placebo. Duration of treatment and of follow-up: four weeks.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Salvagnini 1985

Methods	Sample size: no justification. Generation of the allocation sequence: unclear, not described. Allocation concealment: unclear, not described. Blinding: unclear, described as double blind but the method to achieve this not described. Follow-up: inadequate, not described. Intention-to-treat analysis: used.
Participants	Multicentre clinical trial including 122 consecutive in-patients from five clinical departments. Chronic liver disease. Inclusion criteria: chronic alcohol abuse and hospitalisation for liver disease. Exclusion criteria: HBsAg positivity and/or patients with decompensated liver cirrhosis.
Interventions	MT group: silymarin tablets 140 mg, three times daily (420 mg per day). Control group: placebo tablets, three times daily. All patients were requested to abstain from consuming alcohol. Duration of treatment and of follow-up: 45 days.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.

Salvagnini 1985 *(Continued)*

Notes	Only published as abstract. Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Trinchet 1989

Methods	Sample size: based on liver histology response. Randomisation: patients were stratified for presence or absence of liver cirrhosis in initial liver biopsy. Generation of the allocation sequence: adequate, by random tables. Allocation concealment: adequate, with sealed envelopes. Blinding: adequate, double blind with placebo of identical presentation. Follow-up: adequate, more than 10% dropped-out or were withdrawn. Intention-to-treat: used.
Participants	Multicentre clinical trial including patients from three medical departments. Chronic liver disease. Inclusion criteria: 116 patients with histologically proven alcoholic hepatitis, 58 of them with alcoholic cirrhosis. 78 were males and 38 females with a mean age of 50± 18 years in the silymarin and of 51± 11 years in the placebo group. Exclusion criteria: 1) hepatic encephalopathy; 2) resistant ascites; 3) prothrombin activity< 50%; 4) platelet count< 100 billion/L; 5) hepatocellular carcinoma; other important diseases or refusal to participate.
Interventions	MT group: silymarin tablets 140 mg, three times daily (420 mg per day). Control group: placebo tablets, three times per day. Duration of treatment and of follow-up: three months.
Outcomes	Mortality. Liver biochemistry. Histology. Adverse events.
Notes	Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement

Trinchet 1989 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Velussi 1997

Methods	Sample size: no justification. Generation of the allocation sequence: unclear. Allocation concealment: unclear, not described. Blinding: inadequate, not blinded. Follow-up: adequate, less than 10% of the patients dropped out or were withdrawn. Intention-to-treat analysis: used.
Participants	Sixty insulin treated diabetic patients with alcoholic liver cirrhosis from the 7050 diabetic outpatients registered at the author's anti-diabetes centre. Chronic liver disease. Inclusion criteria: 1) age 45 to 70 years; 2) non-insulin-dependent diabetes mellitus with alcoholic liver cirrhosis; 3) body mass index < 29 kg/m2; 4) ascertained diabetes for a period of at least 5 years and treated with insulin only; 5) undergoing stable insulin therapy for a period of at least two years; 6) presenting raised endogenous insulin secretion; 7) fasting insulin levels and basal and stimulated C-peptide levels above normal range (above 15 mU/ml for insulin; above 1 ng/ml for basal C-peptide levels); 8) negative for markers of hepatitis A, B, C; 9) not addicted to alcohol for a period of at least two years prior to the start of the study; 10) no bleeding from variceal oesophagus; 11) liver biopsy, performed no more than four years prior to enrolment, demonstrating liver cirrhosis.
Interventions	MT group: silymarin tablets (Legalon®) 200 mg tablets, three times daily (600 mg per day). Control group: standard treatment. Duration of treatment and of follow-up: 12 months.
Outcomes	Mortality. Liver biochemistry. Adverse events.
Notes	Letter to the trialist: sent (August 2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Benda 1973	An observational study (case series) of patients with liver cirrhosis treated with silymarin.
Berenguer 1977	We were not able to obtain this publication, but it is not likely that the data could have been used as the patients had differing etiologies or chronic hepatitis.
Berkson 1999	An observational study (case series). The author describes a treatment for three patients with liver cirrhosis, portal hypertension, and oesophageal varices secondary to chronic hepatitis C. The treatment combined three antioxidants (alpha-lipoic acid [thioctic acid], silymarin, and selenium).
Bode 1977	The study is quasi-randomised (birthday) clinical study evaluating silymarin (Legalon®) in 151 patients versus no intervention for acute viral hepatitis.
Canini 1985	An observational study (case series). Ten patients with histologically confirmed alcoholic liver steatosis were treated for three months with silymarin 200 mg three times per day.
Cavalieri 1974	A randomised clinical trial evaluating 20 patients treated with silymarin (Legalon®) 420 mg versus 20 patients treated with hepatoprotective drugs for acute viral hepatitis.
Conti 1989	We were not able to obtain this publication (an abstract).
De Martiis 1984	An observational study (case series). Seventy-six patients were followed for chronic liver disease of mixed etiology and macrocytic anaemia and hyperhaemolysis; 27 of them were treated with silymarin for more than one year.
Dittrich 1980	We were not able to obtain this publication (an abstract).
Fassati 1973	An observational study (case series). Twenty-four patients with chronic liver disease of mixed etiology were treated with silymarin (Legalon®) for six months.
Fehér 1988	An observational study (case series). The effects of three hepatoprotective antioxidants (silymarin (Legalon®), cyanidol-3 (Catergen®), and 4-amino-5-imidazole-carboxamide-phosphate (Aica-P®)) were compared to placebo in 40 patients.
Fintelmann 1970	This is a quasi-randomised clinical study. Fifty-seven patients with fatty liver disease were treated with silymarin (Legalon®) compared to placebo for six weeks.
Fintelmann 1980ex	This is a randomised trial on milk thistle for patients with toxic liver disease: Most of the patients had toxic liver disease due to alcoholic. This trial was excluded due to the heterogeneity of the patients included, but all data were included in an explorative sensitivity analysis.
Flisiak 1997	This is a quasi-randomised clinical study. Fifty-two male patients with acute viral hepatitis B were treated for 28 days. Of these 20 patients were allocated by alternate inclusion to the silymarin group (silymarin tablets 70 mg, three times daily (210 mg) and 12 to the control group. The remaining 20 patients were treated with misoprostol. No adverse events were reported.
Hammerl 1971	An observational study (case series). Forty-three patients with chronic liver disease were treated with silymarin (Legalon®) for more than one year. Another 90 patients were treated for six to nine months with silymarin .
Ippolito 2002	An observational study (case series). Of 284 patients with chronic hepatitis C, 112 (39.4%) were using one or more herbal remedies, 52.7% of these ingesting MT. No significant effect on response rate was observed when patients using MT were compared with patients not using MT.
Kiesewetter 1977	A randomised clinical trial, but the etiology of the liver disease was not given. Patients with chronic alcohol abuse and with clinical or histological signs of alcoholic liver disease were excluded. The author reports two clinical studies. The first randomises 45 patients with chronic persistent or

Study	Reason for exclusion
	chronic aggressive hepatitis to silymarin (Legalon®) versus placebo from six centres in Vienna. The other clinical trial used quasi-randomisation. No adverse events were reported.
Kupcová 1987	An observational study (case series). Twenty-four patients with liver cirrhosis confirmed on laparoscopy and histology were treated with silymarin for six months.
Lirussi 1995	A randomised clinical trial evaluating silymarin versus ursodeoxycholic acid in 27 patients with liver disease of mixed etiology. Patients received either ursodeoxycholic acid capsules (Deursil®, 600 mg per day) or silymarin tablets (Legalon®, 420 mg per day) for six months treatment period according to a cross-over design. No adverse events were reported.
Loginov 1988	An observational study (case series). Forty-eight patients with chronic liver disease were administered one of the following preparations: silymarin, essentiale, trophopar, or vitamins complex for 30 days.
Muscher 1972	An observational study (case series). Two-hundred-thirty-seven patients with alcoholic and non-alcoholic liver disease were treated with silymarin (Legalon®).
Peyton 1999	An observational study (case series). One hundred-seventeen patients with hepatitis C completed the survey regarding their use of MT and of other medical herbs. MT was the predominant medical herb used in 14 patients.
Pár 2000	An observational study (two case series). It is a comparison of silymarin compared to no intervention for patients with alcoholic liver disease and chronic hepatitis C.
Realini 1975	An observational study (case series). Twenty-three patients with chronic liver disease of mixed etiology were treated with silymarin for 12 months. No adverse events were reported.
Reutter 1975	An observational study (case series). Thirty-four patients with chronic liver disease of mixed etiology were treated with silymarin (Legalon®) 210 mg/day.
Saba 1979	An observational study (two case series) evaluating 38 patients with acute liver disease with silymarin compared to standard therapy.
Salmi 1982ex	This is a randomised clinical trials on milk thistle for patients with liver disease of mixed etiology, mostly due to alcohol problems (the majority 81% in the milk thistle arm and 76% in the placebo arm admitted previous alcohol consumption). This trial was excluded due to the heterogeneity of the patients included, but all data were included in an explorative sensitivity analysis.
Sawaryn 1977	An observational study (two case series). A total of 46 patients with chronic hepatitis were treated with silymarin (Legalon®).
Schopen 1970	An observational study (case series). It evaluates 72 patients with silymarin (Legalon®) for hepatitis of mixed etiology.
Schuppan 1998	An observational study (case series). The effect of treatment with silymarin (Legalon®) 280 mg three times per day over 12 weeks in 998 patients with chronic liver disease was examined in a post-marketing-surveillance study.
Tanasescu 1988	The study is a double blind randomised clinical trial, but the etiology of liver disease was not described. The Romanian product Silimarina® (synonym Legalon®) was administered to a group of 180 patients versus placebo. No adverse events were reported.
Tkacz 1983	An observational study (two case series). The study examined 26 patients with acute viral hepatitis treated with silymarol. The results were compared with a control group of 61 patients. No adverse events were reported.

Study	Reason for exclusion
Vailati 1993	A phase II randomised, open trial was performed to evaluate three doses (160 mg, 240 mg, 360 mg) of silybin and phosphatidylcholine (IdB 1016, Silipide®) in 60 patients with chronic alcoholic or viral hepatitis. A total of six adverse events was reported in the study. Three patients, treated with 160 mg, complained of nausea, heartburn and dyspepsia; one patient, treated with 240 mg, complained of dyspepsia; two patients, treated with 360 mg, complained respectively of nausea and meteorism. The treatment lasted two weeks. No placebo or no intervention group was used.

DATA AND ANALYSES

Comparison 1. Milk thistle versus placebo/no intervention - mortality

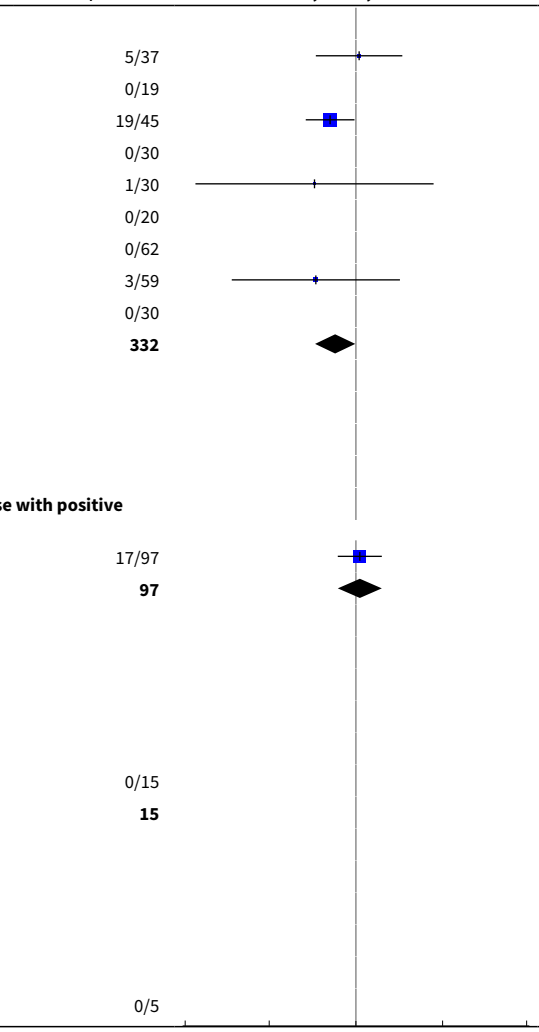
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
1.1 Alcoholic liver disease	9	657	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 0.98]
1.2 Alcoholic liver disease or alcoholic liver disease with positive HCV antibodies	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.62, 1.99]
1.3 Hepatitis B	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Hepatitis C	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Hepatitis B and/or hepatitis C	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Subgroup analysis - Generation of the allocation sequence	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
2.1 Adequate generation of the allocation sequence	6	599	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
2.2 Unclear generation of the allocation sequence	7	316	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Subgroup analysis - Allocation concealment	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
3.1 Adequate allocation concealment	3	376	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.65]
3.2 Unclear allocation concealment	10	539	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.35, 1.08]
4 Subgroup analysis - Blinding	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
4.1 Adequately blinded	6	548	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.49, 1.12]
4.2 Unclearly blinded or nonblinded	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.34, 3.43]

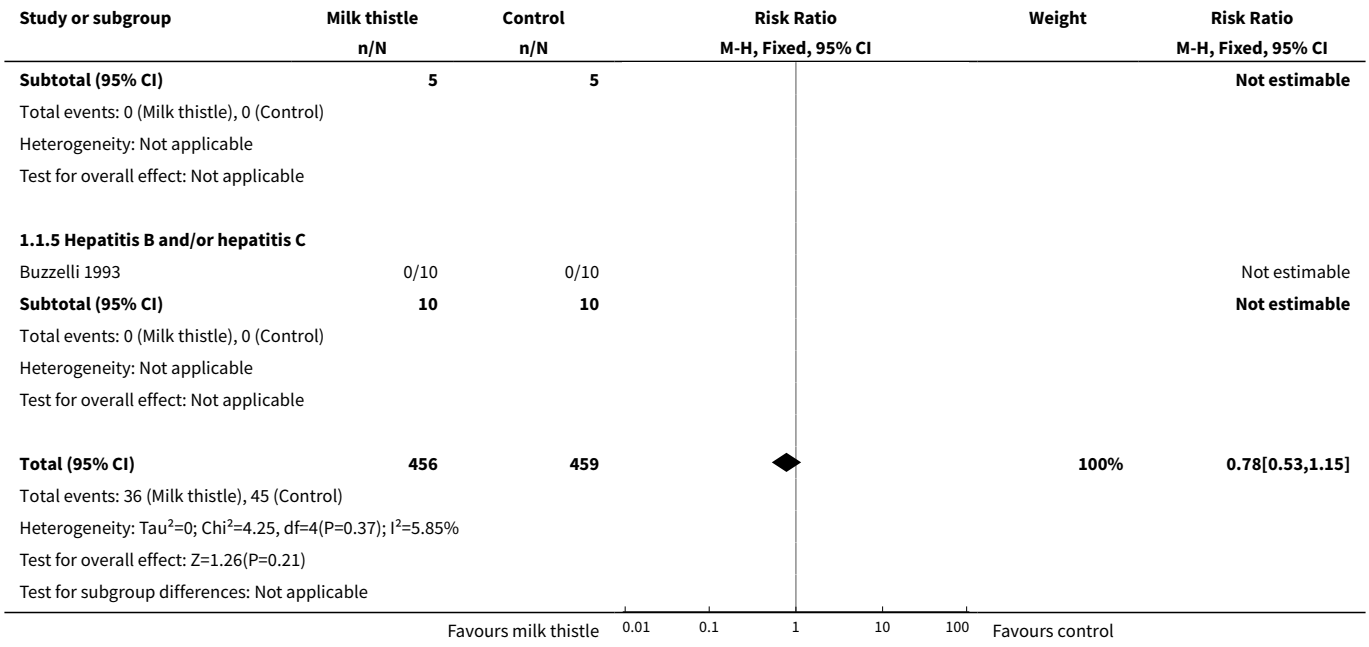
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Subgroup analysis - Follow-up	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
5.1 Adequate follow-up	12	793	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
5.2 Unclear or inadequate follow-up	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Subgroup analysis - Stratification of trials according to methodological quality	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
6.1 All four components adequate	3	376	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.65]
6.2 One or more components adequate	9	417	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.35, 1.08]
6.3 No adequate components	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Subgroup analysis - Stage	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
7.1 Chronic	12	887	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
7.2 Acute	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Subgroup analysis - Duration of treatment	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
8.1 Short-term treatment (less than six months)	6	336	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.22]
8.2 Long-term treatment (at least six months)	7	579	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.20]
9 Subgroup analysis - Different formulation	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
9.1 Silymarin (Legalon®)	10	825	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
9.2 IdB1016 (Silipide®)	2	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Silybin-beta-cyclodextrin	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Subgroup analysis - Worst-case scenario analysis	13	915	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.75, 1.58]
11 Alcoholic liver disease - high-quality trials	2	176	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.06, 2.11]
11.1 All four components adequate	2	176	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.06, 2.11]
12 Explorative sensitivity analysis - Addition of two excluded trials	15	1085	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.53, 1.15]
12.1 Alcoholic liver disease	9	657	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.62, 1.99]
12.3 Hepatitis B	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Hepatitis C	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.5 Hepatitis B and/or hepatitis C	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.6 Liver disease mostly due to alcoholic liver disease	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

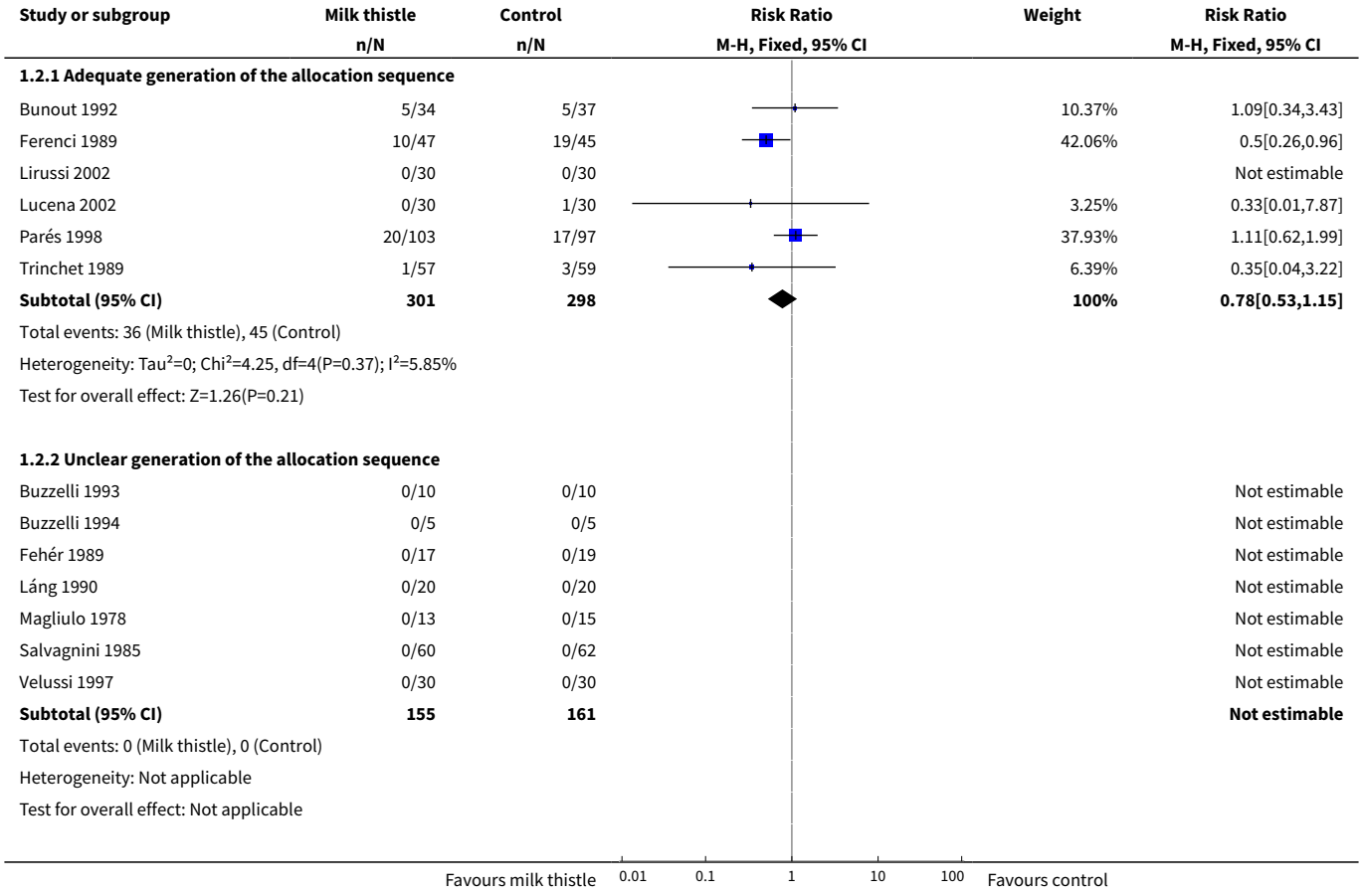
Analysis 1.1. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 1 Mortality.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Alcoholic liver disease					
Bunout 1992	5/34	5/37		10.37%	1.09[0.34,3.43]
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	10/47	19/45		42.06%	0.5[0.26,0.96]
Lirussi 2002	0/30	0/30			Not estimable
Lucena 2002	0/30	1/30		3.25%	0.33[0.01,7.87]
Láng 1990	0/20	0/20			Not estimable
Salvagnini 1985	0/60	0/62			Not estimable
Trinchet 1989	1/57	3/59		6.39%	0.35[0.04,3.22]
Velussi 1997	0/30	0/30			Not estimable
Subtotal (95% CI)	**325**	**332**		**62.07%**	**0.58[0.34,0.98]**
Total events: 16 (Milk thistle), 28 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.66, df=3(P=0.65); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					
1.1.2 Alcoholic liver disease or alcoholic liver disease with positive HCV antibodies					
Parés 1998	20/103	17/97		37.93%	1.11[0.62,1.99]
Subtotal (95% CI)	**103**	**97**		**37.93%**	**1.11[0.62,1.99]**
Total events: 20 (Milk thistle), 17 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.34(P=0.73)					
1.1.3 Hepatitis B					
Magliulo 1978	0/13	0/15			Not estimable
Subtotal (95% CI)	**13**	**15**			**Not estimable**
Total events: 0 (Milk thistle), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.4 Hepatitis C					
Buzzelli 1994	0/5	0/5			Not estimable

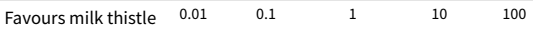




Analysis 1.2. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 2 Subgroup analysis - Generation of the allocation sequence.

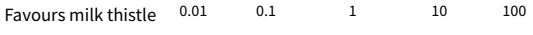


Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**456**	**459**		**100%**	**0.78[0.53,1.15]**
Total events: 36 (Milk thistle), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.25, df=4(P=0.37); I^2=5.85%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Not applicable					



Analysis 1.3. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 3 Subgroup analysis - Allocation concealment.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Adequate allocation concealment					
Lucena 2002	0/30	1/30		3.25%	0.33[0.01,7.87]
Parés 1998	20/103	17/97		37.93%	1.11[0.62,1.99]
Trinchet 1989	1/57	3/59		6.39%	0.35[0.04,3.22]
Subtotal (95% CI)	**190**	**186**		**47.57%**	**0.95[0.55,1.65]**
Total events: 21 (Milk thistle), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.47, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=0.17(P=0.86)					
1.3.2 Unclear allocation concealment					
Bunout 1992	5/34	5/37		10.37%	1.09[0.34,3.43]
Buzzelli 1993	0/10	0/10			Not estimable
Buzzelli 1994	0/5	0/5			Not estimable
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	10/47	19/45		42.06%	0.5[0.26,0.96]
Lirussi 2002	0/30	0/30			Not estimable
Láng 1990	0/20	0/20			Not estimable
Magliulo 1978	0/13	0/15			Not estimable
Salvagnini 1985	0/60	0/62			Not estimable
Velussi 1997	0/30	0/30			Not estimable
Subtotal (95% CI)	**266**	**273**		**52.43%**	**0.62[0.35,1.08]**
Total events: 15 (Milk thistle), 24 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.31, df=1(P=0.25); I^2=23.93%					
Test for overall effect: Z=1.68(P=0.09)					
Total (95% CI)	**456**	**459**		**100%**	**0.78[0.53,1.15]**
Total events: 36 (Milk thistle), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.25, df=4(P=0.37); I^2=5.85%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Not applicable					

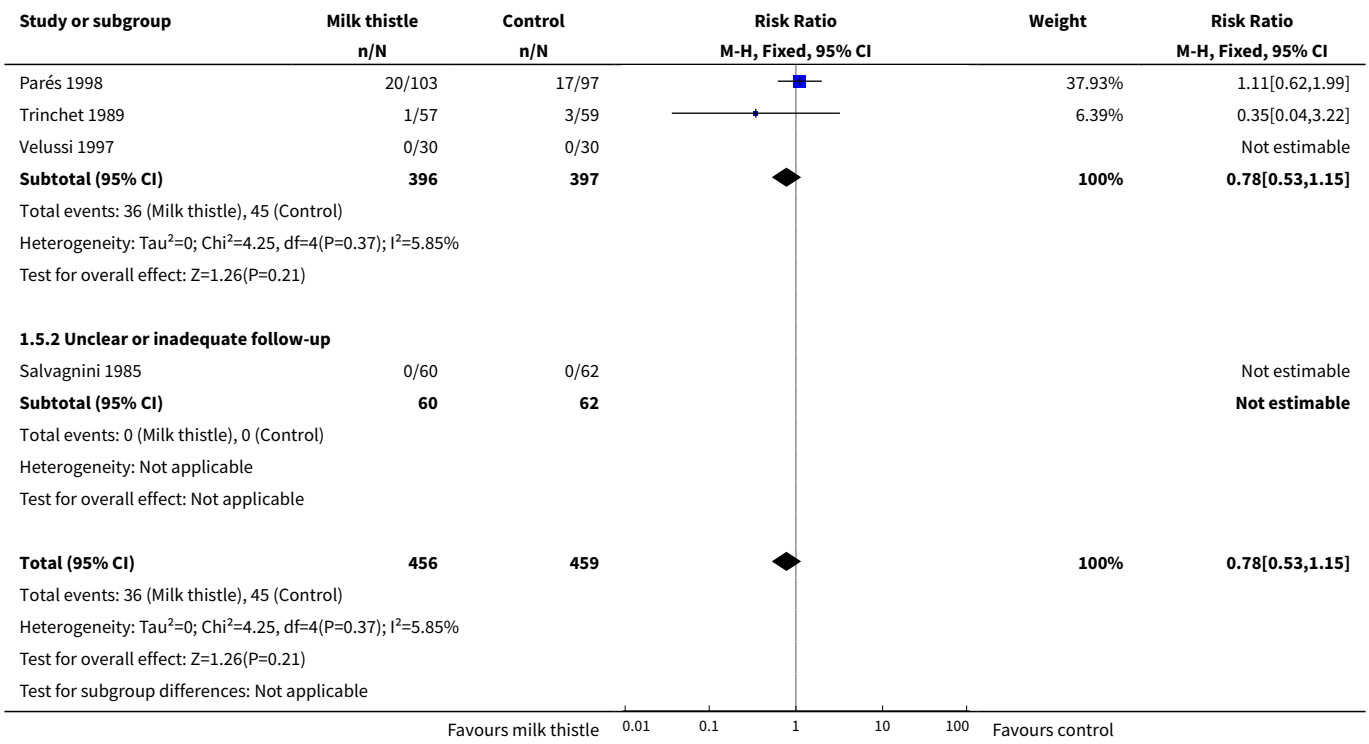


Analysis 1.4. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 4 Subgroup analysis - Blinding.

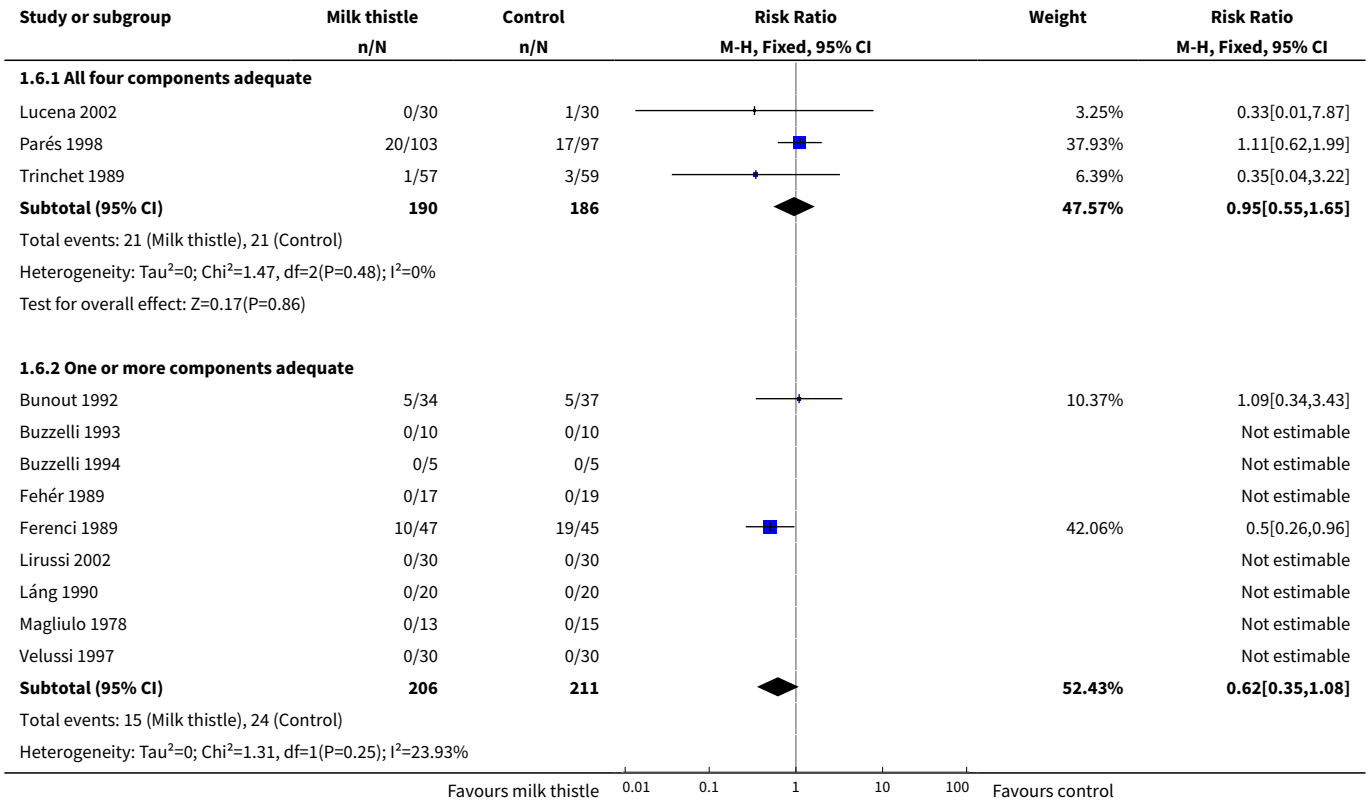
Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Adequately blinded					
Buzzelli 1993	0/10	0/10			Not estimable
Ferenci 1989	10/47	19/45		42.06%	0.5[0.26,0.96]
Lirussi 2002	0/30	0/30			Not estimable
Lucena 2002	0/30	1/30		3.25%	0.33[0.01,7.87]
Parés 1998	20/103	17/97		37.93%	1.11[0.62,1.99]
Trinchet 1989	1/57	3/59		6.39%	0.35[0.04,3.22]
Subtotal (95% CI)	**277**	**271**		**89.63%**	**0.74[0.49,1.12]**
Total events: 31 (Milk thistle), 40 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.88, df=3(P=0.27); I^2=22.67%					
Test for overall effect: Z=1.41(P=0.16)					
1.4.2 Unclearly blinded or nonblinded					
Bunout 1992	5/34	5/37		10.37%	1.09[0.34,3.43]
Buzzelli 1994	0/5	0/5			Not estimable
Fehér 1989	0/17	0/19			Not estimable
Láng 1990	0/20	0/20			Not estimable
Magliulo 1978	0/13	0/15			Not estimable
Salvagnini 1985	0/60	0/62			Not estimable
Velussi 1997	0/30	0/30			Not estimable
Subtotal (95% CI)	**179**	**188**		**10.37%**	**1.09[0.34,3.43]**
Total events: 5 (Milk thistle), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					
Total (95% CI)	**456**	**459**		**100%**	**0.78[0.53,1.15]**
Total events: 36 (Milk thistle), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.25, df=4(P=0.37); I^2=5.85%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Not applicable					

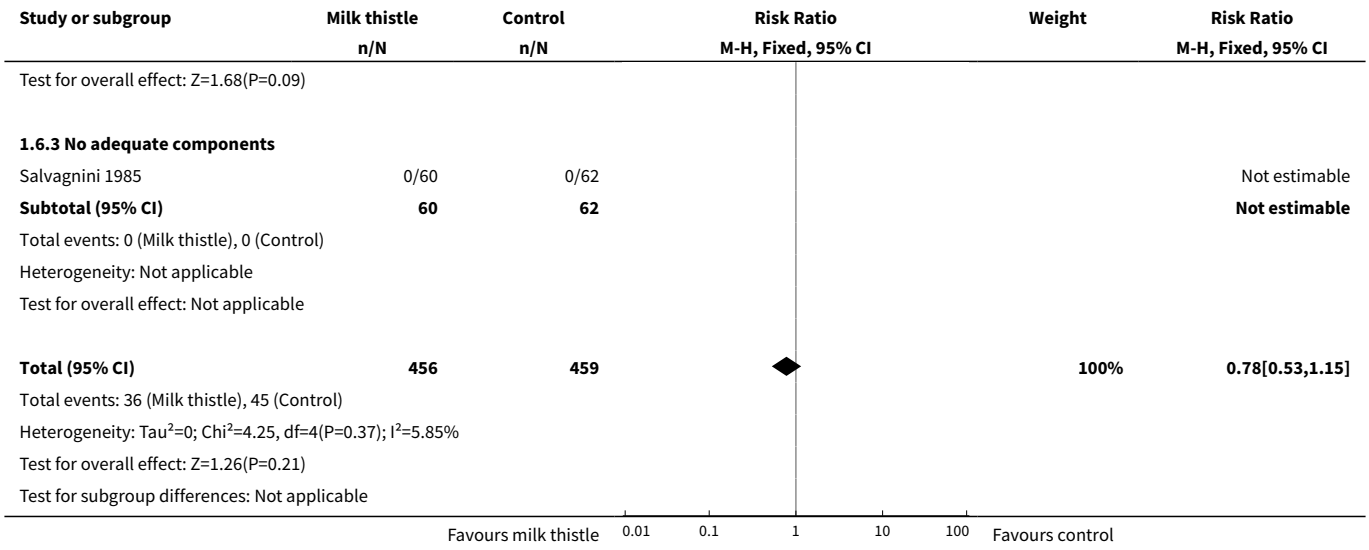
Analysis 1.5. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 5 Subgroup analysis - Follow-up.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Adequate follow-up					
Bunout 1992	5/34	5/37		10.37%	1.09[0.34,3.43]
Buzzelli 1993	0/10	0/10			Not estimable
Buzzelli 1994	0/5	0/5			Not estimable
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	10/47	19/45		42.06%	0.5[0.26,0.96]
Lirussi 2002	0/30	0/30			Not estimable
Lucena 2002	0/30	1/30		3.25%	0.33[0.01,7.87]
Láng 1990	0/20	0/20			Not estimable
Magliulo 1978	0/13	0/15			Not estimable

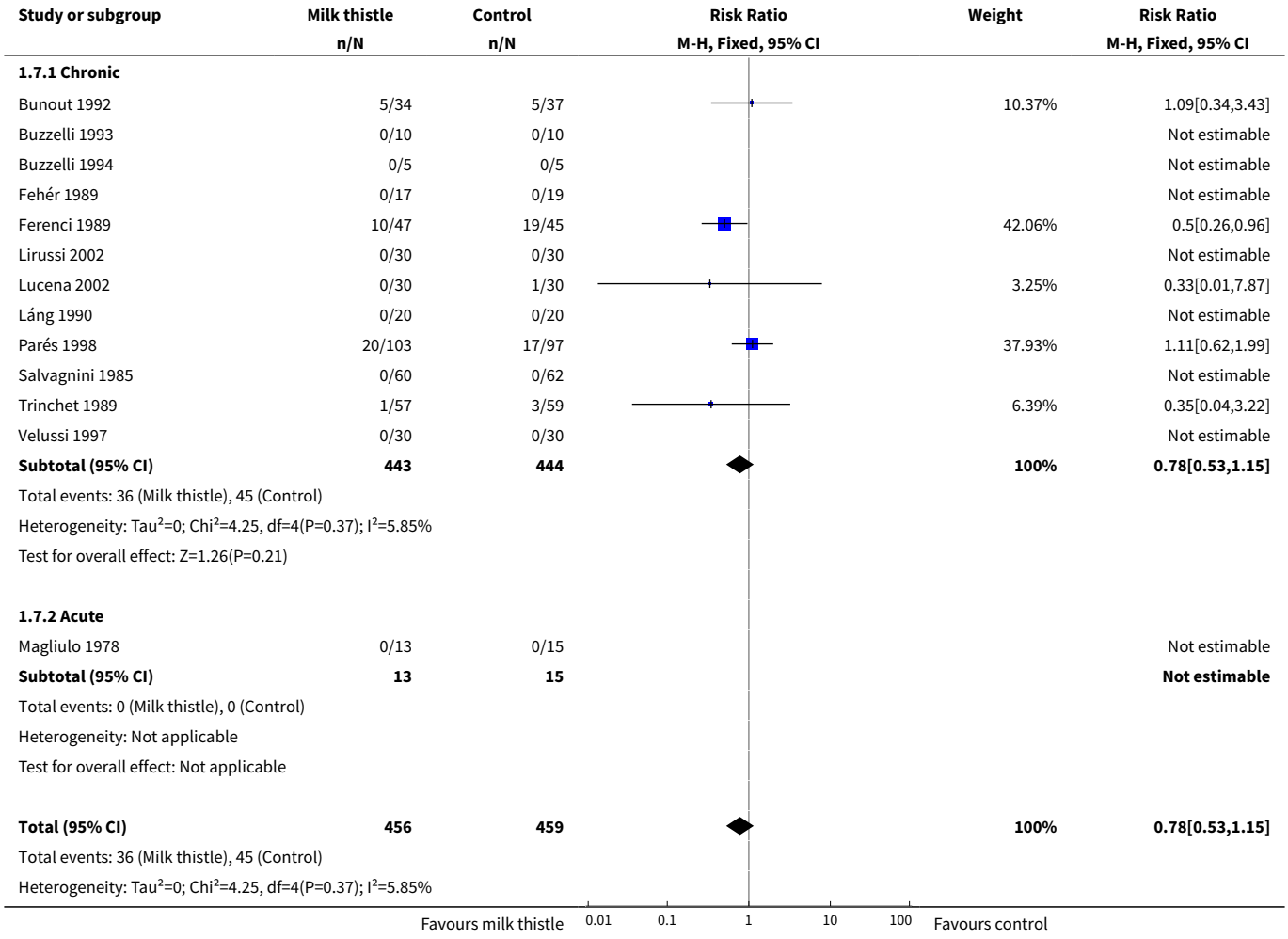


Analysis 1.6. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 6 Subgroup analysis - Stratification of trials according to methodological quality.





Analysis 1.7. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 7 Subgroup analysis - Stage.



Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Not applicable					

Favours milk thistle 0.01 0.1 1 10 100 Favours control

Analysis 1.8. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 8 Subgroup analysis - Duration of treatment.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Short-term treatment (less than six months)					
Buzzelli 1993	0/10	0/10			Not estimable
Buzzelli 1994	0/5	0/5			Not estimable
Láng 1990	0/20	0/20			Not estimable
Magliulo 1978	0/13	0/15			Not estimable
Salvagnini 1985	0/60	0/62			Not estimable
Trinchet 1989	1/57	3/59		6.39%	0.35[0.04,3.22]
Subtotal (95% CI)	**165**	**171**		**6.39%**	**0.35[0.04,3.22]**
Total events: 1 (Milk thistle), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.93(P=0.35)					
1.8.2 Long-term treatment (at least six months)					
Bunout 1992	5/34	5/37		10.37%	1.09[0.34,3.43]
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	10/47	19/45		42.06%	0.5[0.26,0.96]
Lirussi 2002	0/30	0/30			Not estimable
Lucena 2002	0/30	1/30		3.25%	0.33[0.01,7.87]
Parés 1998	20/103	17/97		37.93%	1.11[0.62,1.99]
Velussi 1997	0/30	0/30			Not estimable
Subtotal (95% CI)	**291**	**288**		**93.61%**	**0.81[0.54,1.2]**
Total events: 35 (Milk thistle), 42 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.72, df=3(P=0.29); I^2=19.44%					
Test for overall effect: Z=1.06(P=0.29)					
Total (95% CI)	**456**	**459**		**100%**	**0.78[0.53,1.15]**
Total events: 36 (Milk thistle), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.25, df=4(P=0.37); I^2=5.85%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Not applicable					

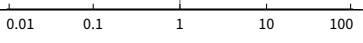
Favours milk thistle 0.01 0.1 1 10 100 Favours control

Analysis 1.9. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 9 Subgroup analysis - Different formulation.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Silymarin (Legalon®)					

Favours milk thistle 0.01 0.1 1 10 100 Favours control

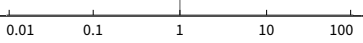
Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bunout 1992	5/34	5/37		10.37%	1.09[0.34,3.43]
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	10/47	19/45		42.06%	0.5[0.26,0.96]
Lucena 2002	0/30	1/30		3.25%	0.33[0.01,7.87]
Láng 1990	0/20	0/20			Not estimable
Magliulo 1978	0/13	0/15			Not estimable
Parés 1998	20/103	17/97		37.93%	1.11[0.62,1.99]
Salvagnini 1985	0/60	0/62			Not estimable
Trinchet 1989	1/57	3/59		6.39%	0.35[0.04,3.22]
Velussi 1997	0/30	0/30			Not estimable
Subtotal (95% CI)	**411**	**414**		**100%**	**0.78[0.53,1.15]**
Total events: 36 (Milk thistle), 45 (Control)					
Heterogeneity: Tau²=0; Chi²=4.25, df=4(P=0.37); I²=5.85%					
Test for overall effect: Z=1.26(P=0.21)					
1.9.2 IdB1016 (Silipide®)					
Buzzelli 1993	0/10	0/10			Not estimable
Buzzelli 1994	0/5	0/5			Not estimable
Subtotal (95% CI)	**15**	**15**			**Not estimable**
Total events: 0 (Milk thistle), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.9.3 Silybin-beta-cyclodextrin					
Lirussi 2002	0/30	0/30			Not estimable
Subtotal (95% CI)	**30**	**30**			**Not estimable**
Total events: 0 (Milk thistle), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**456**	**459**		**100%**	**0.78[0.53,1.15]**
Total events: 36 (Milk thistle), 45 (Control)					
Heterogeneity: Tau²=0; Chi²=4.25, df=4(P=0.37); I²=5.85%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Not applicable					



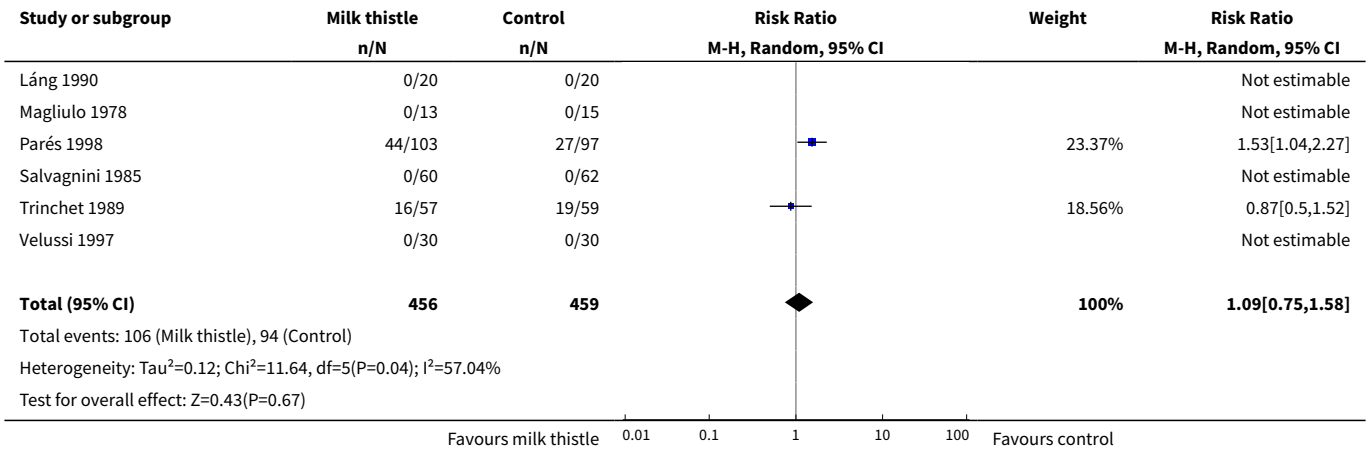
Favours milk thistle — Favours control

Analysis 1.10. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 10 Subgroup analysis - Worst-case scenario analysis.

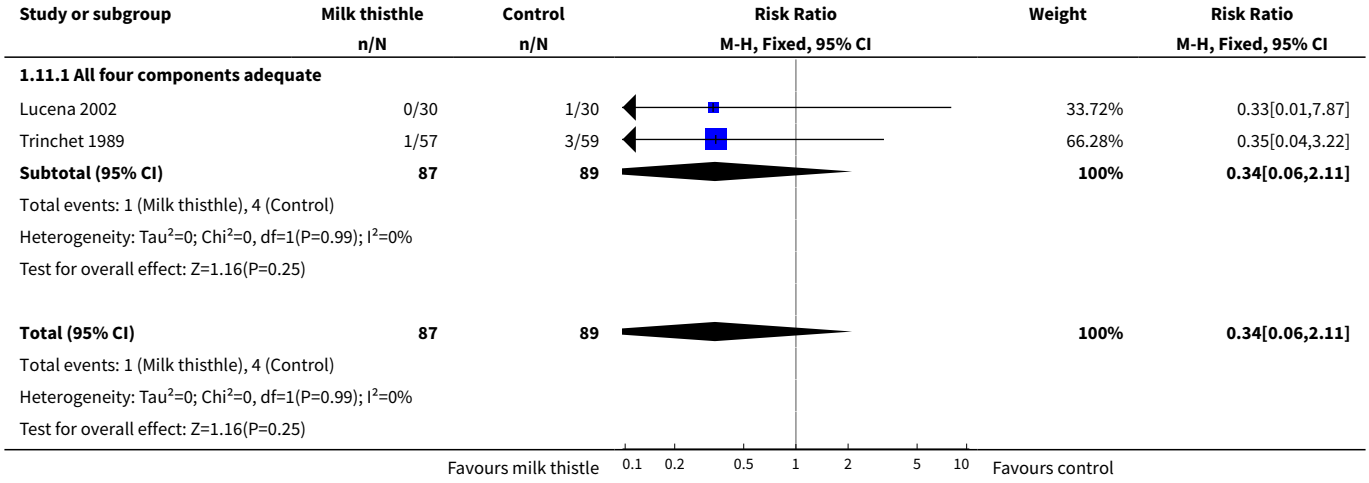
Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bunout 1992	14/34	8/37		14.3%	1.9[0.91,3.96]
Buzzelli 1993	0/10	0/10			Not estimable
Buzzelli 1994	0/5	0/5			Not estimable
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	17/47	26/45		21.46%	0.63[0.4,0.99]
Lirussi 2002	9/30	9/30		13.48%	1[0.46,2.17]
Lucena 2002	6/30	5/30		8.83%	1.2[0.41,3.51]



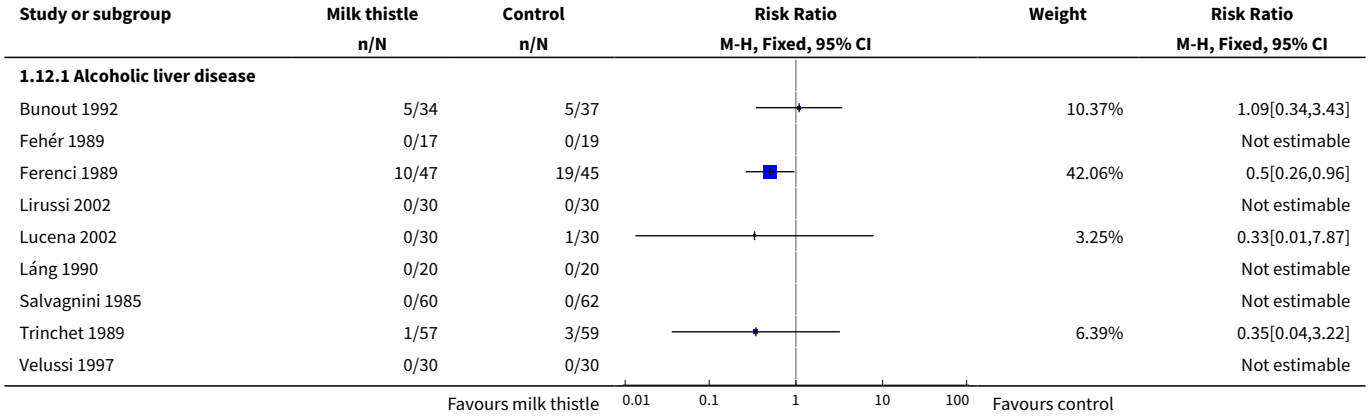
Favours milk thistle — Favours control

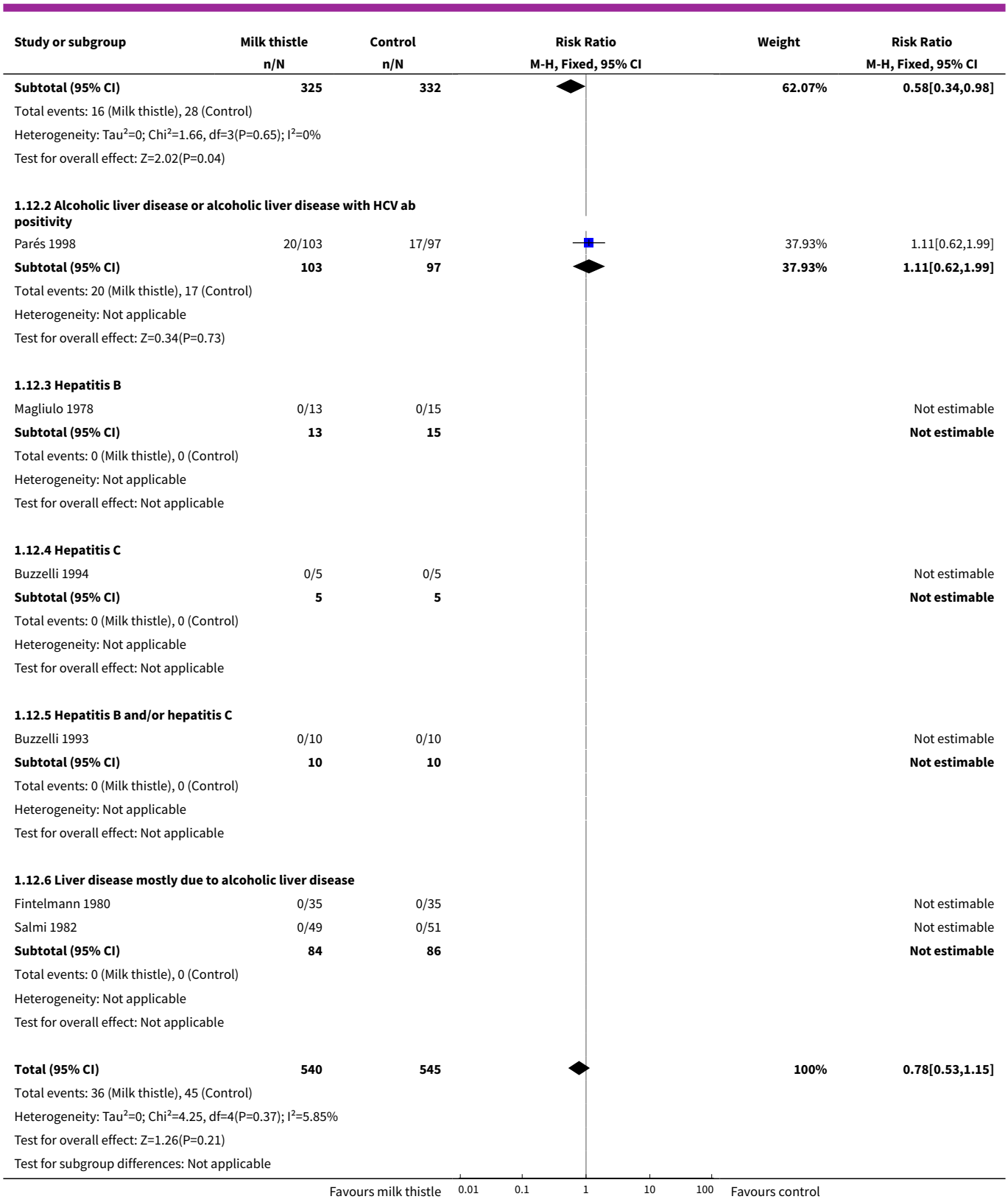


Analysis 1.11. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 11 Alcoholic liver disease - high-quality trials.



Analysis 1.12. Comparison 1 Milk thistle versus placebo/no intervention - mortality, Outcome 12 Explorative sensitivity analysis - Addition of two excluded trials.



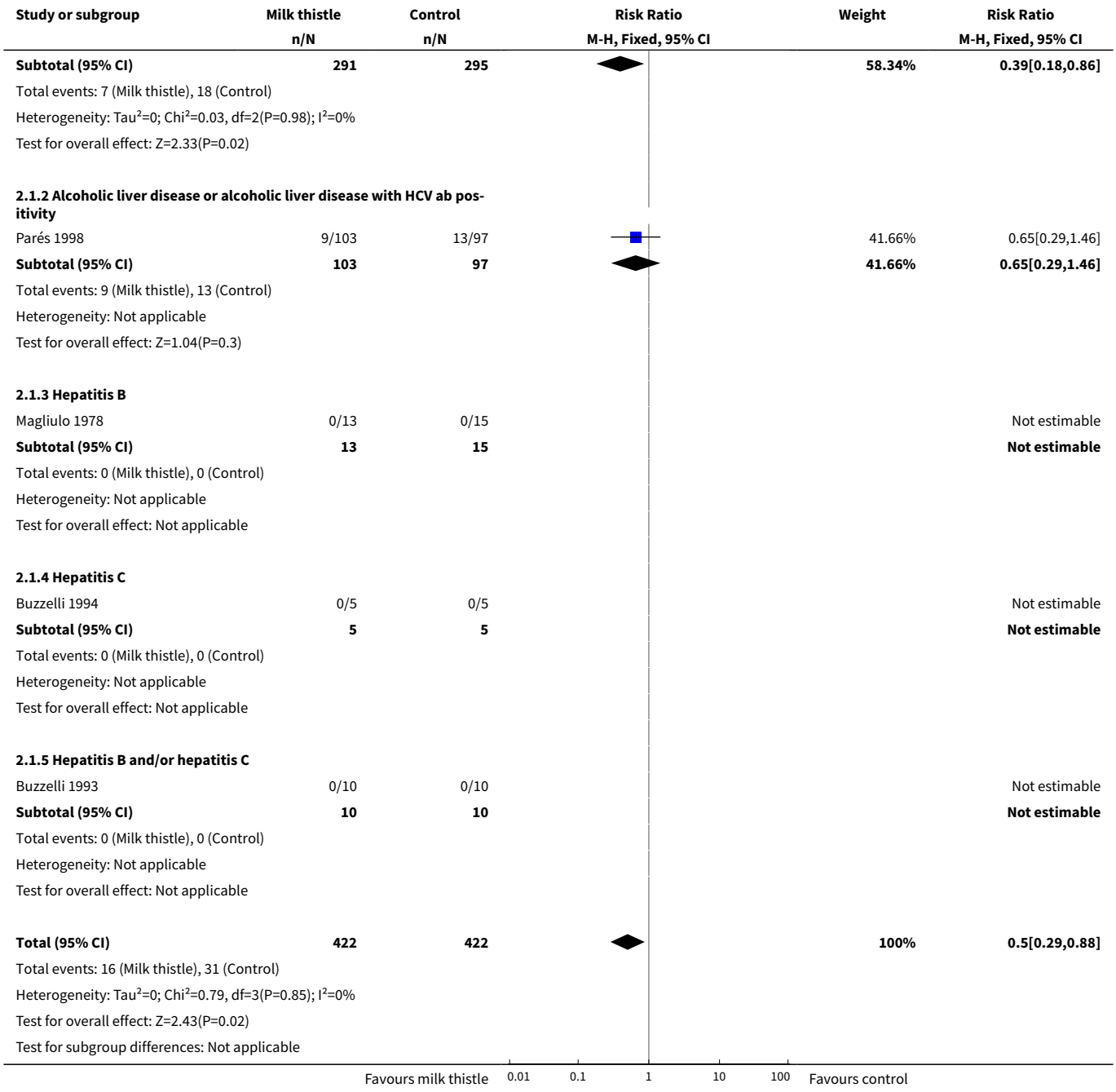


Comparison 2. Milk thistle versus placebo/no intervention - liver-related mortality

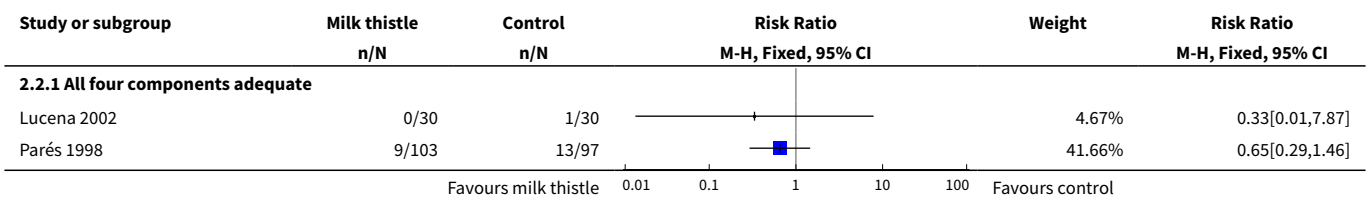
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Liver-related mortality	12	844	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.88]
1.1 Alcoholic liver disease	8	586	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.18, 0.86]
1.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.29, 1.46]
1.3 Hepatitis B	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Hepatitis C	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Hepatitis B and/or hepatitis C	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Subgroup analysis - Stratification of trials according to methodological quality	12	844	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.88]
2.1 All four components adequate	3	376	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.28, 1.19]
2.2 One or more components adequate	8	346	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.17, 0.97]
2.3 No adequate components	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Subgroup analysis - Worst-case scenario in patients with alcoholic liver disease	8	586	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.13]

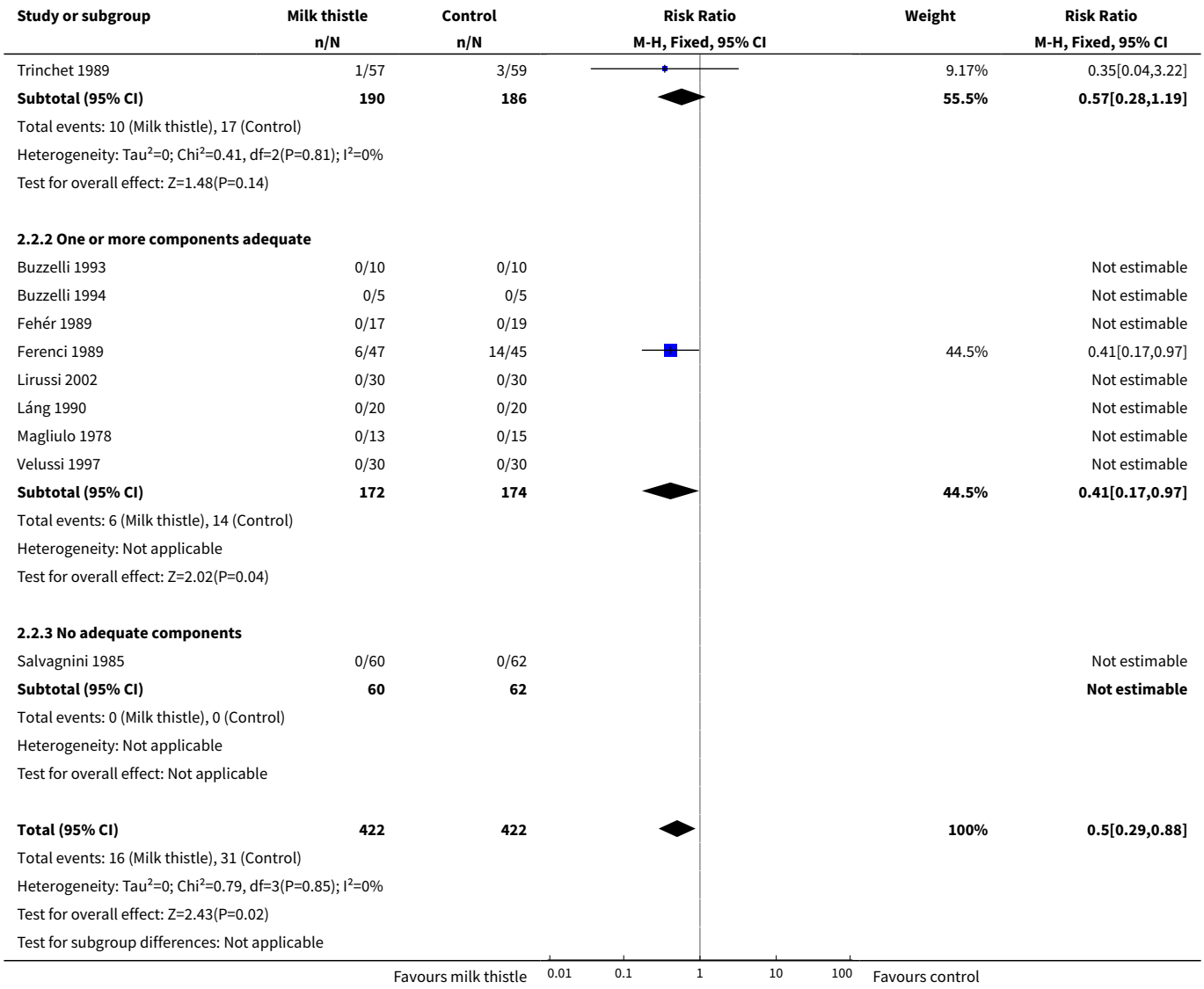
Analysis 2.1. Comparison 2 Milk thistle versus placebo/no intervention - liver-related mortality, Outcome 1 Liver-related mortality.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Alcoholic liver disease					
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	6/47	14/45		44.5%	0.41[0.17,0.97]
Lirussi 2002	0/30	0/30			Not estimable
Lucena 2002	0/30	1/30		4.67%	0.33[0.01,7.87]
Láng 1990	0/20	0/20			Not estimable
Salvagnini 1985	0/60	0/62			Not estimable
Trinchet 1989	1/57	3/59		9.17%	0.35[0.04,3.22]
Velussi 1997	0/30	0/30			Not estimable

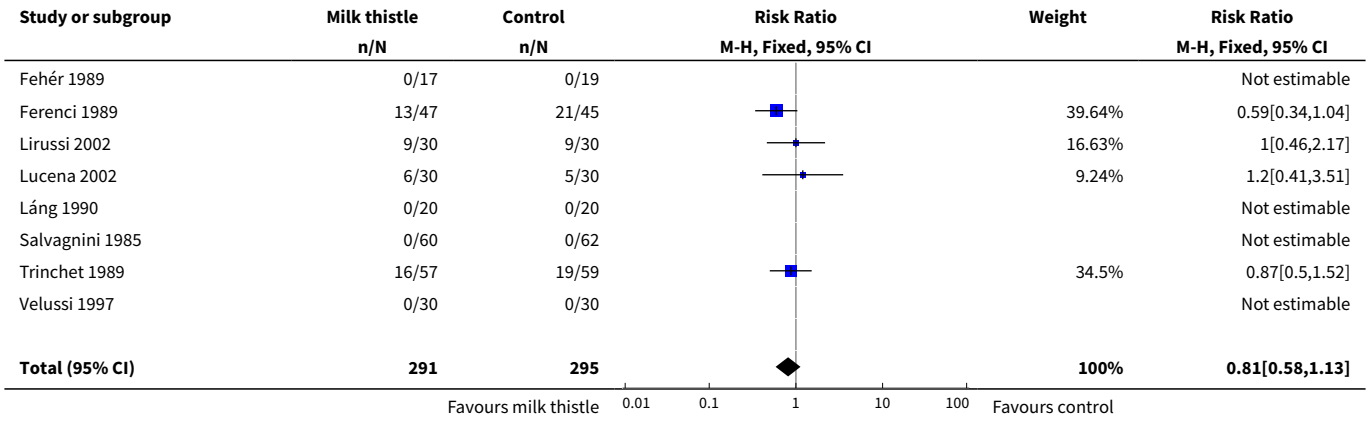


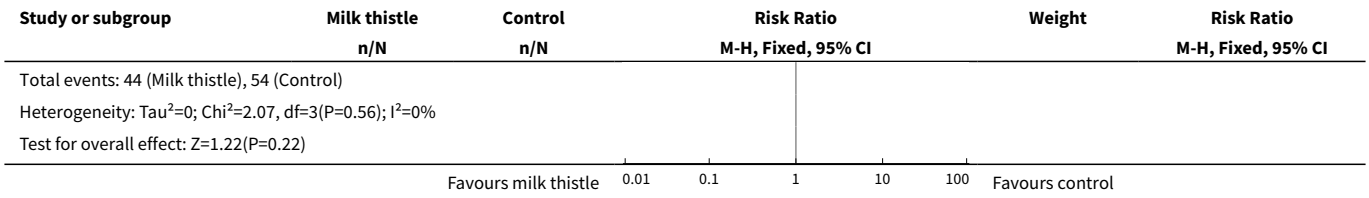
Analysis 2.2. Comparison 2 Milk thistle versus placebo/no intervention - liver-related mortality, Outcome 2 Subgroup analysis - Stratification of trials according to methodological quality.





Analysis 2.3. Comparison 2 Milk thistle versus placebo/no intervention - liver-related mortality, Outcome 3 Subgroup analysis - Worst-case scenario in patients with alcoholic liver disease.





Comparison 3. Millk thistle versus placebo/no intervention - other outcome measures

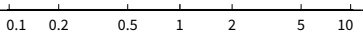
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ascites	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.20]
1.1 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.20]
2 Hepatic encephalophaty	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.16]
2.1 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.16]
3 Gastro-intestinal bleeding	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.53, 1.34]
3.1 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.53, 1.34]
4 Any complications	2	260	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.09]
4.1 Alcoholic liver disease	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.71]
4.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.10]
5 Prothrombin time (%)	4	378	Mean Difference (IV, Fixed, 95% CI)	-2.77 [-6.42, 0.88]
5.1 Alcoholic liver disease	3	178	Mean Difference (IV, Fixed, 95% CI)	-4.70 [-9.46, 0.05]
5.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	0.0 [-5.69, 5.69]
6 Serum-albumin (g/L)	5	414	Mean Difference (IV, Fixed, 95% CI)	0.15 [-1.35, 1.65]

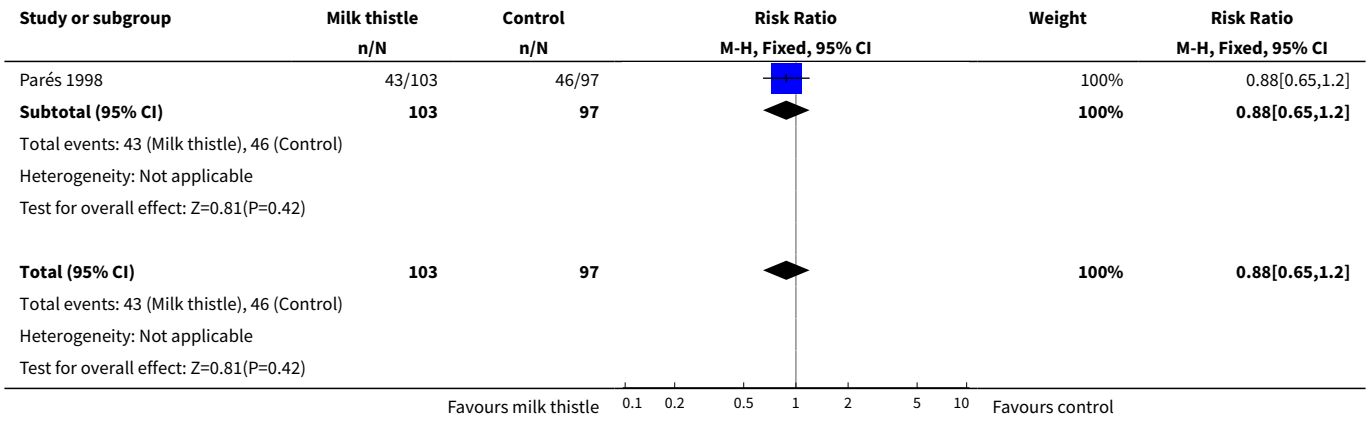
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Alcoholic liver disease	4	214	Mean Difference (IV, Fixed, 95% CI)	0.56 [-1.36, 2.48]
6.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.91, 1.91]
7 Serum-bilirubin (µmol/L)	8	494	Mean Difference (IV, Fixed, 95% CI)	-4.68 [-7.72, -1.64]
7.1 Alcoholic liver disease	5	254	Mean Difference (IV, Fixed, 95% CI)	-4.57 [-7.65, -1.50]
7.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	-10.68 [-32.44, 11.08]
7.3 Hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	1.60 [-72.85, 76.05]
7.4 Hepatitis B and/or hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	-3.92 [-49.21, 41.37]
8 Serum-aspartate aminotransferase (U/L)	8	494	Mean Difference (IV, Fixed, 95% CI)	-7.55 [-12.10, -2.99]
8.1 Alcoholic liver disease	5	254	Mean Difference (IV, Fixed, 95% CI)	-11.68 [-16.93, -6.43]
8.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	8.0 [-1.84, 17.84]
8.3 Hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	8.0 [-36.66, 52.66]
8.4 Hepatitis B and/or hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	-24.60 [-55.19, 5.99]
9 Serum-alanine aminotransferase (U/L)	6	365	Mean Difference (IV, Fixed, 95% CI)	-6.35 [-10.26, -2.44]
9.1 Alcoholic liver disease	3	125	Mean Difference (IV, Fixed, 95% CI)	-9.29 [-13.61, -4.98]
9.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	9.0 [-0.84, 18.84]
9.3 Hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-57.40, 53.40]
9.4 Hepatitis B and/or hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-38.06, 22.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Serum-gamma-glutamyl transferase (U/L)	10	658	Mean Difference (IV, Fixed, 95% CI)	-26.80 [-32.86, -20.73]
10.1 Alcoholic liver disease	7	418	Mean Difference (IV, Fixed, 95% CI)	-31.93 [-38.66, -25.21]
10.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	38.0 [2.17, 73.83]
10.3 Hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	14.00 [-20.65, 48.65]
10.4 Hepatitis B and/or hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	-18.40 [-35.41, -1.39]
11 Serum-alkaline phosphatases (U/L)	6	373	Mean Difference (IV, Fixed, 95% CI)	0.58 [-13.65, 14.80]
11.1 Alcoholic liver disease	3	133	Mean Difference (IV, Fixed, 95% CI)	6.41 [-19.60, 32.41]
11.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity	1	200	Mean Difference (IV, Fixed, 95% CI)	16.0 [-17.33, 49.33]
11.3 Hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [-41.55, 41.55]
11.4 Hepatitis B and/or hepatitis C	1	20	Mean Difference (IV, Fixed, 95% CI)	-10.60 [-33.05, 11.85]
12 Score of hepatitis	1	67	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.85, 0.65]
12.1 Alcoholic liver disease	1	67	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.85, 0.65]
13 Score of fibrosis	1	67	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.55, 0.55]
13.1 Alcoholic liver disease	1	67	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.55, 0.55]

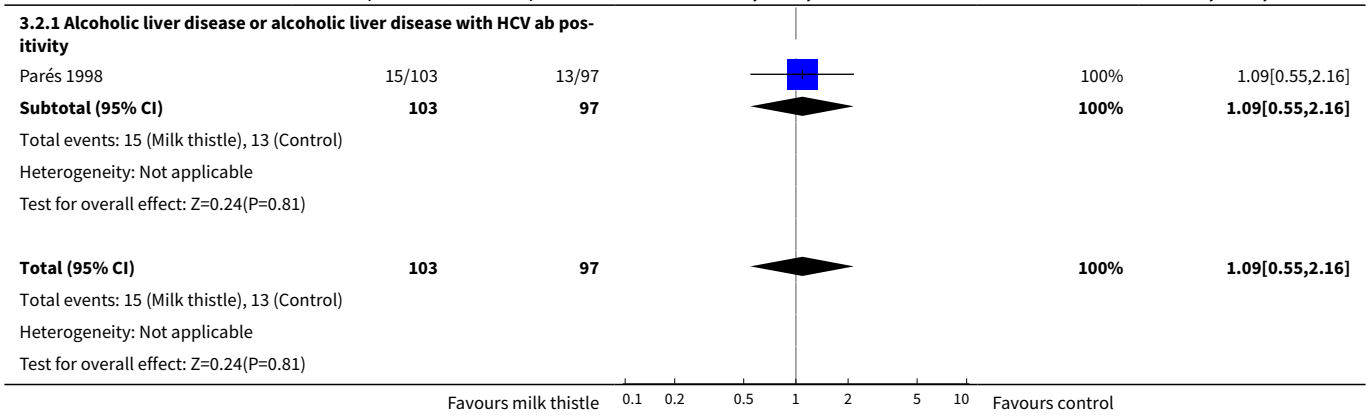
Analysis 3.1. Comparison 3 Millk thistle versus placebo/ no intervention - other outcome measures, Outcome 1 Ascites.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity					

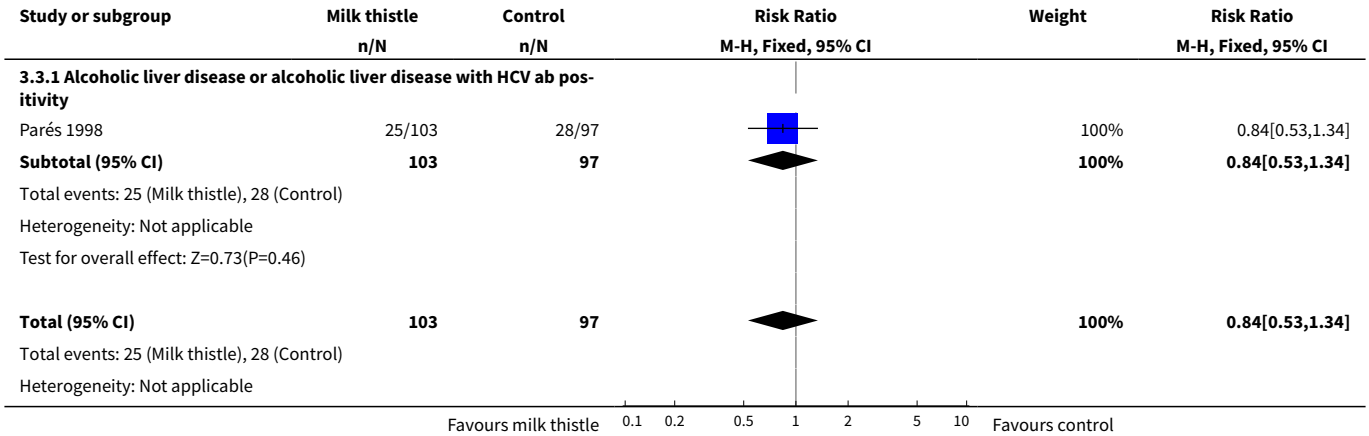




Analysis 3.2. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 2 Hepatic encephalophaty.



Analysis 3.3. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 3 Gastro-intestinal bleeding.



Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.73(P=0.46)					

Favours milk thistle 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 3.4. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 4 Any complications.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Alcoholic liver disease					
Lucena 2002	2/30	3/30		3.47%	0.67[0.12,3.71]
Subtotal (95% CI)	**30**	**30**		**3.47%**	**0.67[0.12,3.71]**
Total events: 2 (Milk thistle), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.64)					
3.4.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity					
Parés 1998	83/103	81/97		96.53%	0.97[0.85,1.1]
Subtotal (95% CI)	**103**	**97**		**96.53%**	**0.97[0.85,1.1]**
Total events: 83 (Milk thistle), 81 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	**133**	**127**		**100%**	**0.95[0.83,1.09]**
Total events: 85 (Milk thistle), 84 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					

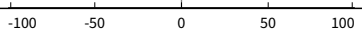
Favours milk thistle 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 3.5. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 5 Prothrombin time (%).

Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.5.1 Alcoholic liver disease							
Bunout 1992	19	79.5 (16.1)	29	77.1 (17.3)		14.47%	2.4[-7.19,11.99]
Lucena 2002	24	71.5 (18.8)	25	82.1 (22.7)		9.81%	-10.6[-22.25,1.05]
Trinchet 1989	41	73 (15.8)	40	79 (12.5)		34.6%	-6[-12.2,0.2]
Subtotal ***	**84**		**94**			**58.88%**	**-4.7[-9.46,0.05]**
Heterogeneity: Tau^2=0; Chi^2=3.26, df=2(P=0.2); I^2=38.62%							
Test for overall effect: Z=1.94(P=0.05)							
3.5.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity							
Parés 1998	103	73 (20)	97	73 (21)		41.12%	0[-5.69,5.69]
Subtotal ***	**103**		**97**			**41.12%**	**0[-5.69,5.69]**
Heterogeneity: Not applicable							

Favours control -100 -50 0 50 100 Favours milk thistle

Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Not applicable							
Total ***	**187**		**191**			**100%**	**-2.77[-6.42,0.88]**
Heterogeneity: Tau²=0; Chi²=4.8, df=3(P=0.19); I²=37.53%							
Test for overall effect: Z=1.49(P=0.14)							
Test for subgroup differences: Chi²=1.54, df=1 (P=0.21), I²=35.24%							

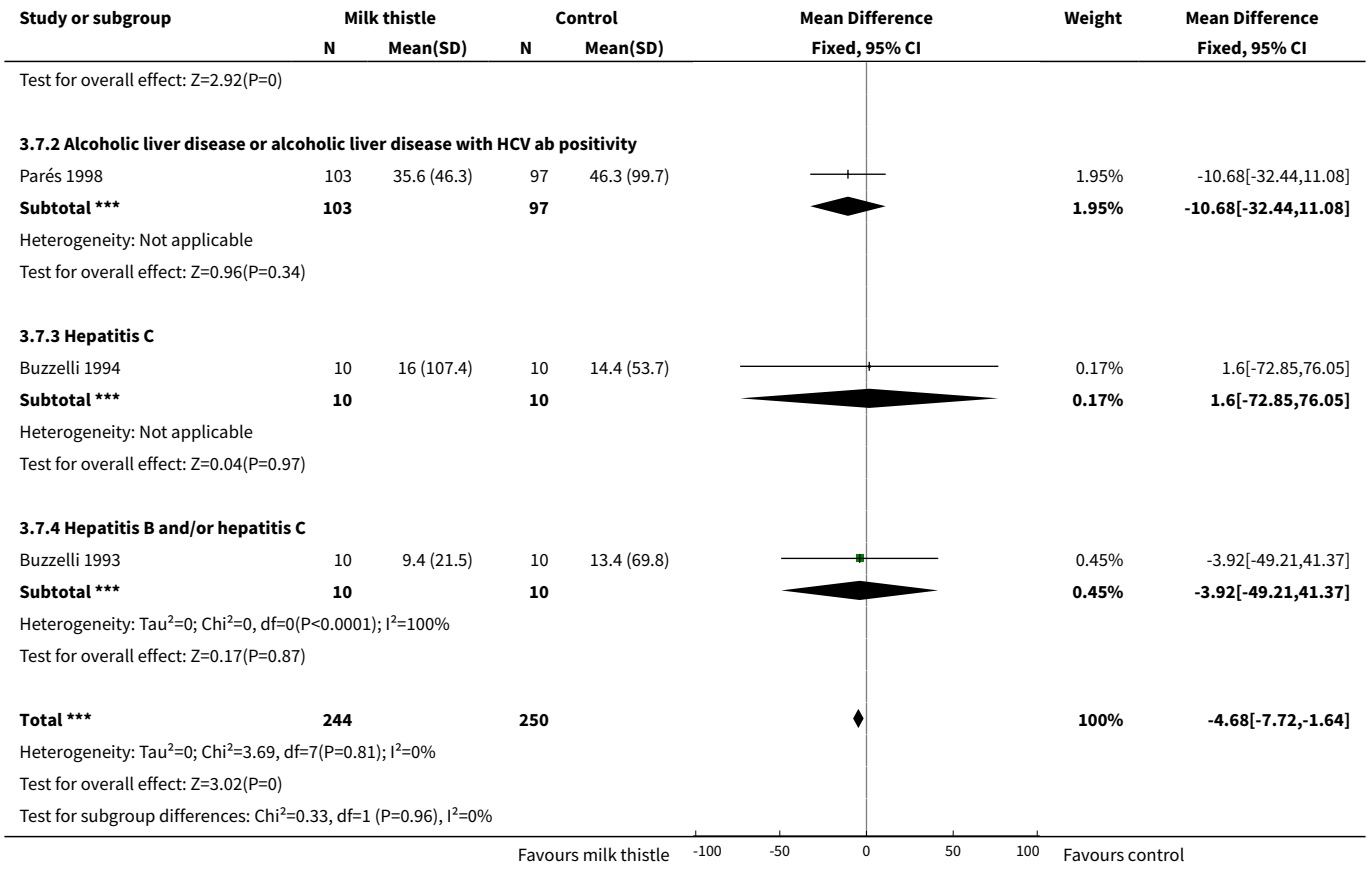


Analysis 3.6. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 6 Serum-albumin (g/L).

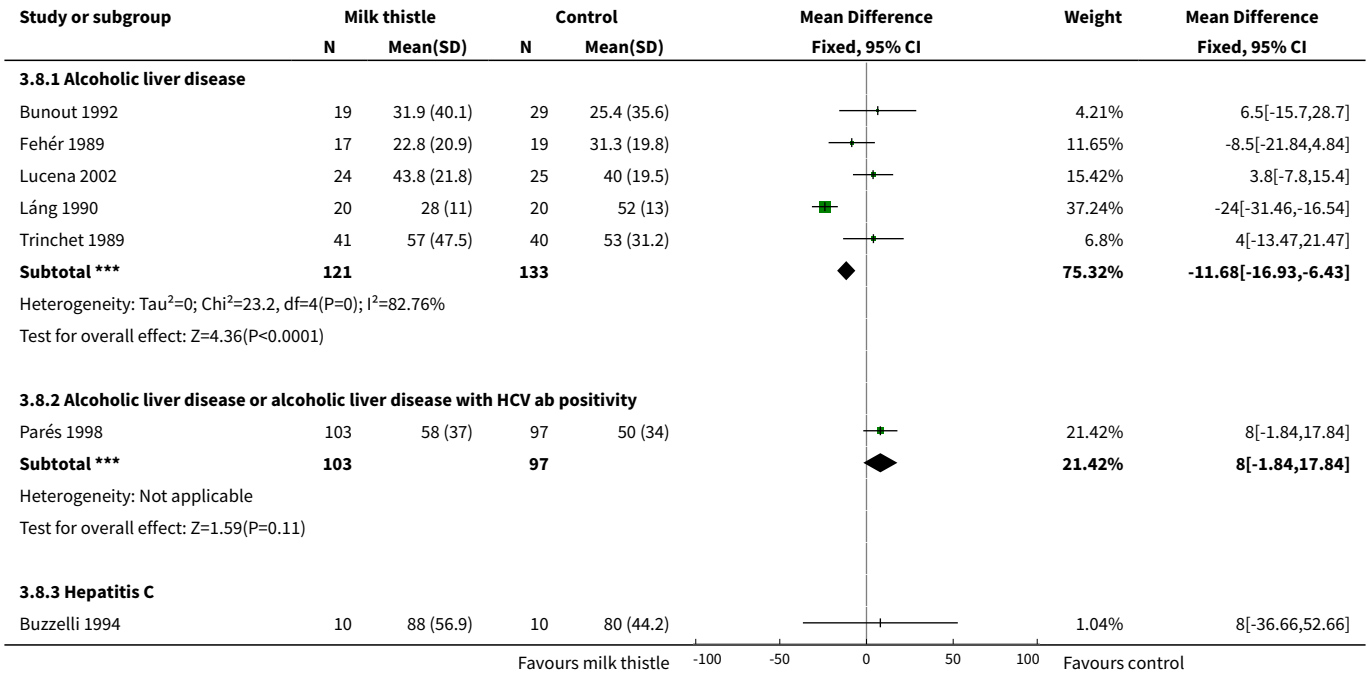
Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.6.1 Alcoholic liver disease							
Bunout 1992	19	44 (4.4)	29	40 (5.4)		29.29%	4[1.23,6.77]
Fehér 1989	17	45.1 (23.4)	19	43.5 (18)		1.19%	1.6[-12.16,15.36]
Lucena 2002	24	39.7 (9.5)	25	42.1 (5.1)		12.19%	-2.4[-6.7,1.9]
Trinchet 1989	41	37 (6.3)	40	40 (9.4)		18.49%	-3[-6.49,0.49]
Subtotal ***	**101**		**113**			**61.16%**	**0.56[-1.36,2.48]**
Heterogeneity: Tau²=0; Chi²=11.75, df=3(P=0.01); I²=74.47%							
Test for overall effect: Z=0.57(P=0.57)							
3.6.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity							
Parés 1998	103	39.1 (8.1)	97	39.6 (9.2)		38.84%	-0.5[-2.91,1.91]
Subtotal ***	**103**		**97**			**38.84%**	**-0.5[-2.91,1.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
Total ***	**204**		**210**			**100%**	**0.15[-1.35,1.65]**
Heterogeneity: Tau²=0; Chi²=12.21, df=4(P=0.02); I²=67.23%							
Test for overall effect: Z=0.19(P=0.85)							
Test for subgroup differences: Chi²=0.46, df=1 (P=0.5), I²=0%							

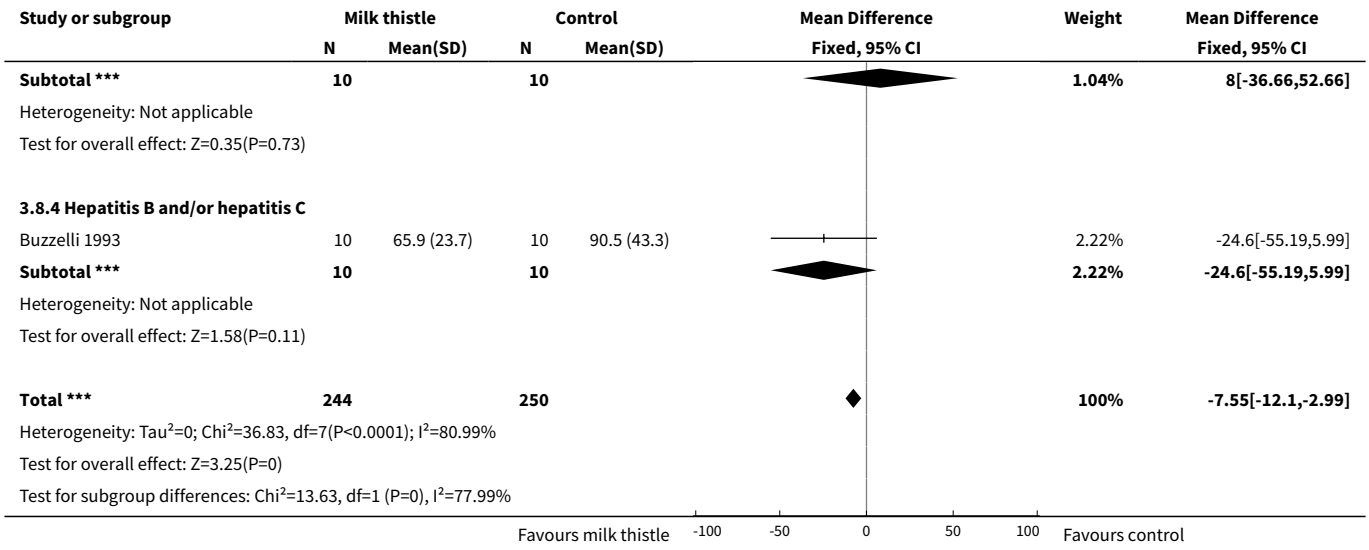
Analysis 3.7. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 7 Serum-bilirubin (µmol/L).

Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.7.1 Alcoholic liver disease							
Bunout 1992	19	21.4 (4.4)	29	26.7 (10.8)		47.91%	-5.34[-9.73,-0.95]
Fehér 1989	17	19.4 (16)	19	32.5 (33.4)		3.25%	-13.1[-29.95,3.75]
Lucena 2002	24	39.2 (30.3)	25	37.4 (39.2)		2.41%	1.78[-17.77,21.33]
Láng 1990	20	18 (7)	20	22 (8)		42.47%	-4[-8.66,0.66]
Trinchet 1989	41	32 (82.3)	40	19 (15.6)		1.4%	13[-12.66,38.66]
Subtotal ***	**121**		**133**			**97.44%**	**-4.57[-7.65,-1.5]**
Heterogeneity: Tau²=0; Chi²=3.37, df=4(P=0.5); I²=0%							

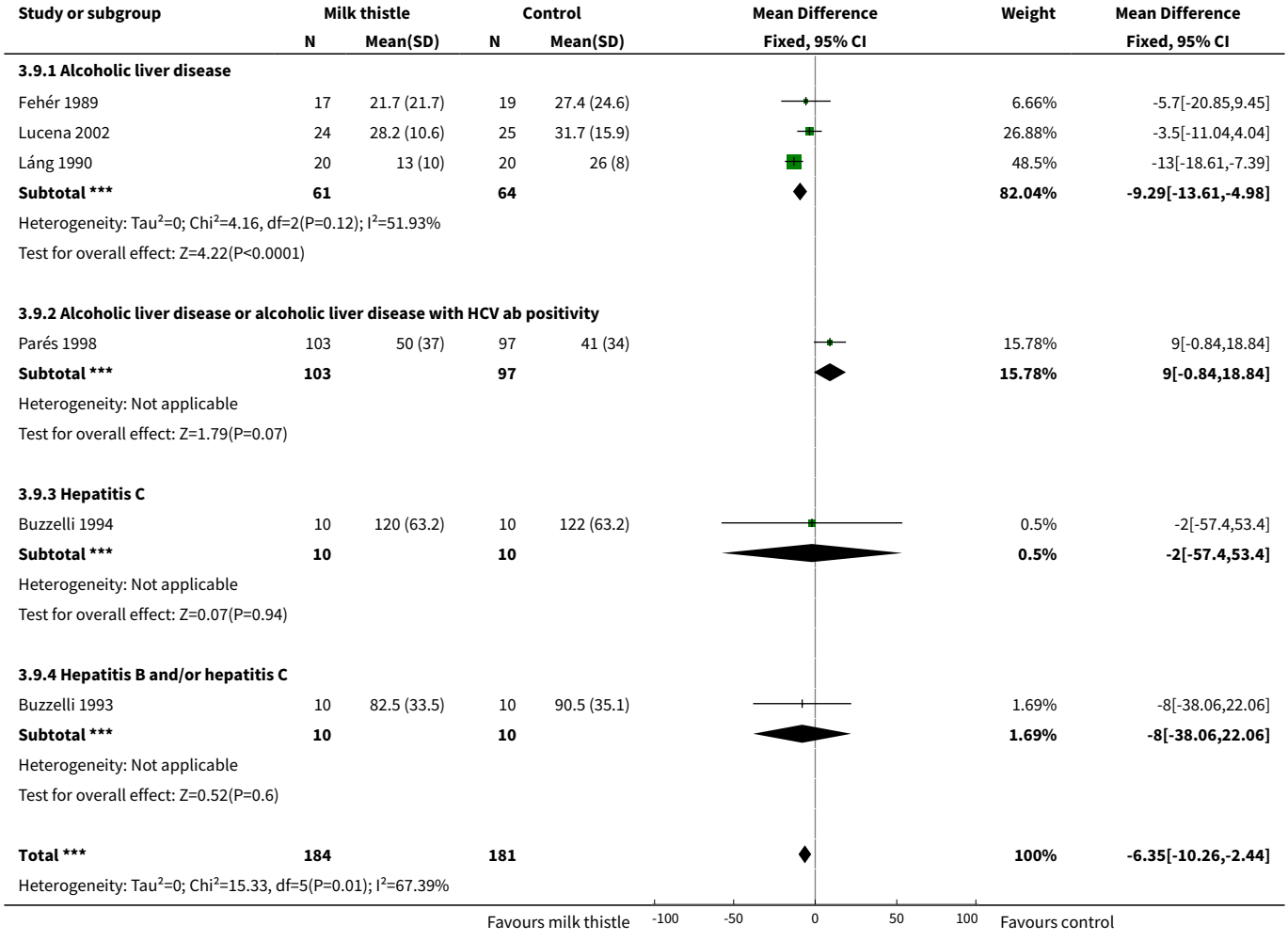


Analysis 3.8. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 8 Serum-aspartate aminotransferase (U/L).

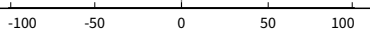




Analysis 3.9. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 9 Serum-alanine aminotransferase (U/L).



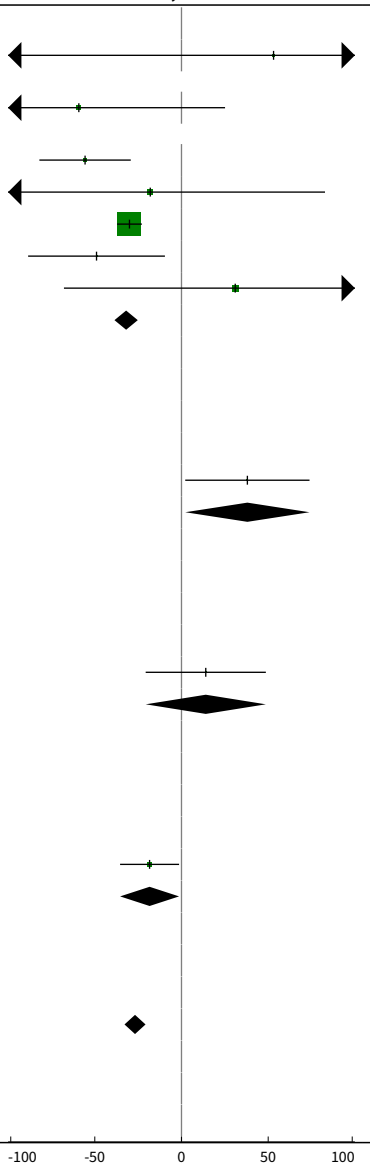
Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=3.18(P=0)							
Test for subgroup differences: Chi²=11.17, df=1 (P=0.01), I²=73.14%							



Favours milk thistle — Favours control

Analysis 3.10. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 10 Serum-gamma-glutamyl transferase (U/L).

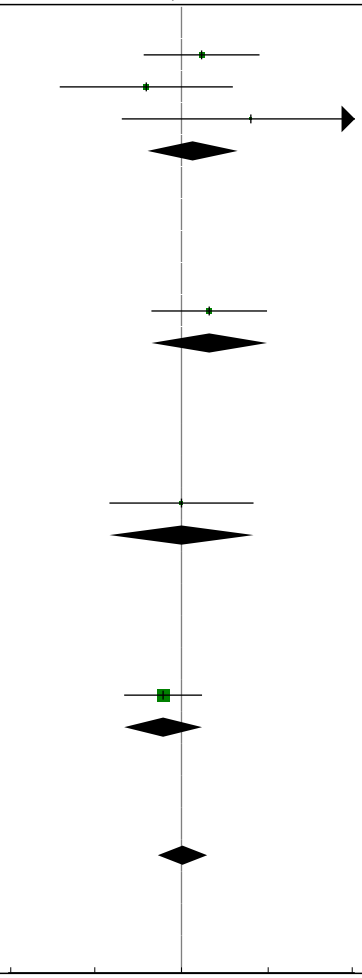
Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.10.1 Alcoholic liver disease							
Bunout 1992	19	153.8 (278.6)	29	100.7 (292.7)		0.14%	53.1[-111.34,217.54]
Fehér 1989	17	111.2 (87.3)	19	170.4 (163.2)		0.52%	-59.2[-143.53,25.13]
Lirussi 2002	21	60.4 (39.6)	21	116 (47.2)		5.3%	-55.6[-81.95,-29.25]
Lucena 2002	24	142 (141)	25	160 (213)		0.36%	-18[-118.76,82.76]
Láng 1990	20	42 (11)	20	72 (12)		72.29%	-30[-37.13,-22.87]
Salvagnini 1985	60	59 (69.7)	62	108 (141.7)		2.37%	-49[-88.44,-9.56]
Trinchet 1989	41	197 (215.3)	40	166 (237.4)		0.38%	31[-67.79,129.79]
Subtotal ***	**202**		**216**			**81.35%**	**-31.93[-38.66,-25.21]**
Heterogeneity: Tau²=0; Chi²=7.16, df=6(P=0.31); I²=16.22%							
Test for overall effect: Z=9.31(P<0.0001)							
3.10.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity							
Parés 1998	103	137 (150)	97	99 (106)		2.87%	38[2.17,73.83]
Subtotal ***	**103**		**97**			**2.87%**	**38[2.17,73.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.08(P=0.04)							
3.10.3 Hepatitis C							
Buzzelli 1994	10	71 (41.1)	10	57 (37.9)		3.06%	14[-20.65,48.65]
Subtotal ***	**10**		**10**			**3.06%**	**14[-20.65,48.65]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.79(P=0.43)							
3.10.4 Hepatitis B and/or hepatitis C							
Buzzelli 1993	10	41.3 (13.3)	10	59.7 (24)		12.72%	-18.4[-35.41,-1.39]
Subtotal ***	**10**		**10**			**12.72%**	**-18.4[-35.41,-1.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.12(P=0.03)							
Total ***	**325**		**333**			**100%**	**-26.8[-32.86,-20.73]**
Heterogeneity: Tau²=0; Chi²=28.22, df=9(P=0); I²=68.11%							
Test for overall effect: Z=8.66(P<0.0001)							
Test for subgroup differences: Chi²=21.06, df=1 (P=0), I²=85.75%							



Favours milk thistle — Favours control

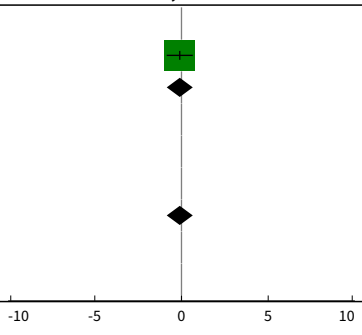
Analysis 3.11. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 11 Serum-alkaline phosphatases (U/L).

Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.11.1 Alcoholic liver disease							
Bunout 1992	19	207.2 (61.9)	29	195.6 (50.7)		18.15%	11.6[-21.79,44.99]
Fehér 1989	17	143.6 (70.9)	19	163.9 (81.8)		8.12%	-20.3[-70.21,29.61]
Lucena 2002	24	278 (140)	25	238 (125)		3.65%	40[-34.42,114.42]
Subtotal ***	**60**		**73**			**29.92%**	**6.41[-19.6,32.41]**
Heterogeneity: Tau²=0; Chi²=1.98, df=2(P=0.37); I²=0%							
Test for overall effect: Z=0.48(P=0.63)							
3.11.2 Alcoholic liver disease or alcoholic liver disease with HCV ab positivity							
Parés 1998	103	205 (116)	97	189 (124)		18.21%	16[-17.33,49.33]
Subtotal ***	**103**		**97**			**18.21%**	**16[-17.33,49.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.94(P=0.35)							
3.11.3 Hepatitis C							
Buzzelli 1994	10	214 (47.4)	10	214 (47.4)		11.72%	0[-41.55,41.55]
Subtotal ***	**10**		**10**			**11.72%**	**0[-41.55,41.55]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.11.4 Hepatitis B and/or hepatitis C							
Buzzelli 1993	10	137.5 (24.7)	10	148.1 (26.5)		40.14%	-10.6[-33.05,11.85]
Subtotal ***	**10**		**10**			**40.14%**	**-10.6[-33.05,11.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.93(P=0.35)							
Total ***	**183**		**190**			**100%**	**0.58[-13.65,14.8]**
Heterogeneity: Tau²=0; Chi²=3.94, df=5(P=0.56); I²=0%							
Test for overall effect: Z=0.08(P=0.94)							
Test for subgroup differences: Chi²=1.97, df=1 (P=0.58), I²=0%							



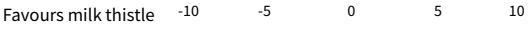
Analysis 3.12. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 12 Score of hepatitis.

Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.12.1 Alcoholic liver disease							
Trinchet 1989	32	2 (1.7)	35	2.1 (1.5)		100%	-0.1[-0.85,0.65]
Subtotal ***	**32**		**35**			**100%**	**-0.1[-0.85,0.65]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.26(P=0.79)							
Total ***	**32**		**35**			**100%**	**-0.1[-0.85,0.65]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.26(P=0.79)							



Analysis 3.13. Comparison 3 Millk thistle versus placebo/no intervention - other outcome measures, Outcome 13 Score of fibrosis.

Study or subgroup	Milk thistle N	Milk thistle Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.13.1 Alcoholic liver disease							
Trinchet 1989	32	3.1 (1.1)	35	3.1 (1.2)		100%	0[-0.55,0.55]
Subtotal ***	**32**		**35**			**100%**	**0[-0.55,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**32**		**35**			**100%**	**0[-0.55,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

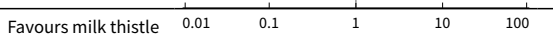


Comparison 4. Adverse events

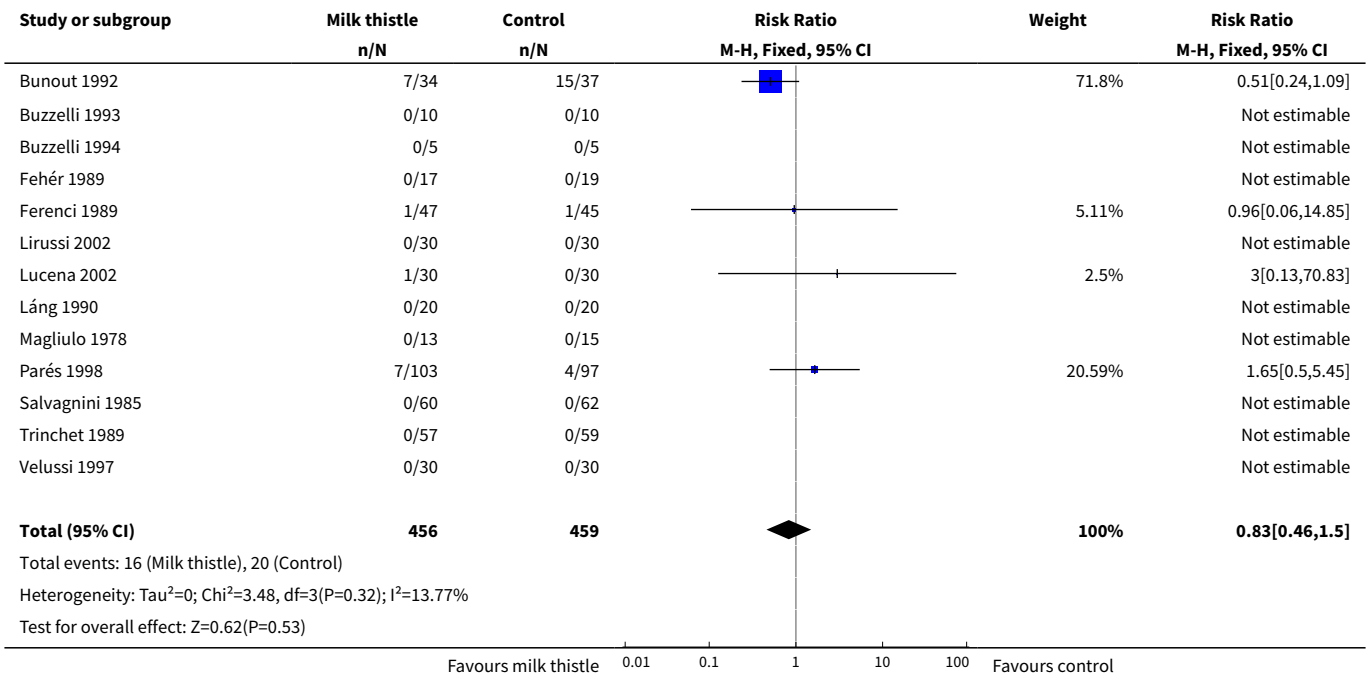
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Non-serious adverse events	13	915	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.50]

Analysis 4.1. Comparison 4 Adverse events, Outcome 1 Serious adverse events.

Study or subgroup	Milk thistle n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bunout 1992	0/34	0/37			Not estimable
Buzzelli 1993	0/10	0/10			Not estimable
Buzzelli 1994	0/5	0/5			Not estimable
Fehér 1989	0/17	0/19			Not estimable
Ferenci 1989	0/47	0/45			Not estimable
Lirussi 2002	0/30	0/30			Not estimable
Lucena 2002	0/30	0/30			Not estimable
Láng 1990	0/20	0/20			Not estimable
Magliulo 1978	0/13	0/15			Not estimable
Parés 1998	0/103	0/97			Not estimable
Salvagnini 1985	0/60	0/62			Not estimable
Trinchet 1989	0/57	0/59			Not estimable
Velussi 1997	0/30	0/30			Not estimable
Total (95% CI)	**456**	**459**			**Not estimable**
Total events: 0 (Milk thistle), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 4.2. Comparison 4 Adverse events, Outcome 2 Non-serious adverse events.



ADDITIONAL TABLES

Table 1. Database searches

Database	Date of search	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	December 2003	('milk thistle' OR silymarin OR silybin OR silibinin OR silydianin OR silychristin OR Legalon OR Silipide OR Realsil OR Carcil OR Siliphos) AND ('liver disease' OR 'hepatitis B' OR 'hepatitis C')
The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 4, 2003	#1 MILK THISTLE explode all trees (MeSH) #2 SILYMARIN explode all trees (MeSH) #3 ((milk next thistle) or silymarin or silimarin or silybin or silibin or silybinin or silibinin or silydianin or silidianin or silychristin or silichristin or legalon or silipide or realsil or carsil or siliphos) #4 (#1 or #2 or #3) #5 LIVER DISEASES explode all trees (MeSH) #6 LIVER DISEASES ALCOHOLIC explode all trees (MeSH) #7 HEPATITIS B explode all trees (MeSH) #8 HEPATITIS C explode all trees (MeSH) #9 ((liver next disease) or (alcoholic next liver next disease) or (viral next liver next disease) or (hepatitis next b) or (hepatitis next c)) #10 (#5 or #6 or #7 or #8 or #9) #11 (#4 and #10)
MEDLINE	1966 to December 2003	#1 explode "Milk-Thistle"/ all subheadings #2 explode "Silymarin"/ all subheadings #3 milk thistle or sil*marin or sil*bin* or sil*dianin or sil*christin or legalon or silipide or realsil or Carsil or siliphos

Table 1. Database searches *(Continued)*

		#4 #1 or #2 or #3 #5 explode "Liver-Diseases"/ all subheadings #6 explode "Liver-Diseases-Alcoholic"/ all subheadings #7 explode "Hepatitis-B"/ all subheadings #8 explode "Hepatitis-C"/ all subheadings #9 liver disease or alcoholic liver disease or viral liver disease or hepatitis B or hepatitis C #10 #5 or #6 or #7 or #8 or #9 #11 #4 and #10 #12 random* or blind* or placebo or meta-analysis #13 #11 and #12
EMBASE	1974 to December 2003	#1 explode "Silybum-marianum"/ all subheadings #2 explode "silymarin"/ all subheadings #3 explode "silibinin"/ all subheadings #4 explode "silidianin"/ all subheadings #5 explode "silicristin"/ all subheadings #6 explode "silibinin-phosphatidylcholine-complex"/ all subheadings #7 milk thistle or sil*marin or silbi* or sil*dianin or sil*christin or legalon or silipide or realsil or carsil or siliphos #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 explode "liver-disease"/ all subheadings #10 explode "alcohol-liver-disease"/ all subheadings #11 explode "virus-hepatitis"/ all subheadings #12 explode "hepatitis-B"/ all subheadings #13 explode "hepatitis-C"/ all subheadings #14 liver disease or alcoholic liver disease or viral liver disease or hepatitis B or hepatitis C #15 #9 or #10 or #11 or #12 or #13 or #14 #16 #8 and #15 #17 random* or blind* or placebo or meta-analysis #18 #16 and #17

WHAT'S NEW

Date	Event	Description
12 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

AR drafted and revised the protocol and the review; AR coordinated the identification of trials. BPJ and GI revised the data extraction as well as the protocol and the review. CG revised the selection of trials and revised the protocol and the review.

DECLARATIONS OF INTEREST

BPJ is author of a report (Lawrence VA, Jacobs BP, Dennehy C. Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects. Evidence Report/Technology Assessment No. 21 (Contract 290-97-0012 to the San Antonio Evidence-based Practice Centre, based at the University of Texas Health Science Centre at San Antonio, and the Veterans Evidence-based Research, Dissemination, and Implementation Centre, a Veterans Affairs Services Research and Development Centre of Excellence), AHRQ Publication No. 01-E025, Agency for Healthcare Research and Quality, Rockville, MD, October 2000) and of a meta-analysis based on this report (Jacobs BP, Dennehy C, Ramirez G, Sapp J, Lawrence VA. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. American Journal of Medicine: 2002: 113(6); 506-15) on milk thistle for liver diseases. Apart from this, no conflicts of interest are known.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Denmark.

External sources

- The 1991 Pharmacy Foundation, Denmark.
- The Copenhagen Hospital Corporation's Research Grant on Getting Research into Practice (GRIP), Denmark.
- The Danish Medical Research Council's Grant on Getting Research into Practice (GRIP), Denmark.

NOTES

We have contacted the following companies in order to obtain additional data, published or unpublished:

Istituto Biochimico Italiano
Giovanni Lorenzini Spa
Via Tucidide 56
Torre 6 Milano
Italy

Madaus
Via Galvani 33
39100
Bolzano Italy

INDEX TERMS

Medical Subject Headings (MeSH)

Hepatitis B [*drug therapy] [mortality]; Hepatitis C [*drug therapy] [mortality]; Liver Cirrhosis [drug therapy] [mortality]; Liver Cirrhosis, Alcoholic [*drug therapy] [mortality]; Phytotherapy [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans