



## Review

# Impact of Silymarin in individuals with nonalcoholic fatty liver disease: A systematic review and meta-analysis

Georgios Kalopitas MD, MSc<sup>a</sup>, Christina Antza MD, PhD<sup>b,c</sup>, Ioannis Doundoulakis MD, MSc<sup>b</sup>, Antonis Siargkas<sup>b</sup>, Elias Kouroumalis MD<sup>d</sup>, Georgios Germanidis MD<sup>a</sup>, Myrto Samara MD, PhD<sup>b</sup>, Michail Chourdakis MD<sup>b,\*</sup>

<sup>a</sup> Division of Gastroenterology and Hepatology, 1st Department of Internal Medicine, AHEPA University Hospital, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>b</sup> Laboratory of Hygiene, Social & Preventive Medicine and Medical Statistics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>c</sup> Third Department of Internal Medicine, G. H. "Papageorgiou", School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>d</sup> Department of Gastroenterology and Hepatology, University Hospital of Heraklion, School of Medicine, University of Crete, Greece



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## ABSTRACT

**Objectives:** Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease affecting a significant proportion of the general population. Recently, randomized clinical trials have been conducted examining the efficacy of silymarin in individuals with NAFLD, with conflicting results. The aim of this meta-analysis was to evaluate the efficacy of silymarin in the treatment of NAFLD by examining changes in liver biochemistry, body mass index, and liver histology.

**Methods:** We searched major electronic databases PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, as well as gray-literature sources, up to June 2020 for randomized clinical trials examining the efficacy of treatment with silymarin in individuals with NAFLD compared to placebo. The primary outcomes were changes in the mean values of transaminases (alanine aminotransferase and aspartate aminotransferase). Secondary outcomes included changes in body mass index and liver histology. Quality analysis was performed with the risk-of-bias tool 2.0. We synthesized results using weighted mean differences for continuous outcomes, along with 95% confidence intervals.

**Results:** In the meta-analysis, eight randomized clinical trials were included. A cutoff level of 0.05 was considered to provide statistically significant results. Silymarin treatment led to a statistically significant greater reduction in the levels of transaminases compared to placebo, irrespective of weight loss.

**Conclusions:** Silymarin seems to be effective in reducing transaminase levels in individuals with NAFLD. Despite the statistical benefits, we call attention to potential flaws related to the quality of the included studies. Further well-designed studies should be carried out to examine whether this reduction in transaminase levels corresponds to histologic improvement.

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Europe, the United States, and other regions [1], affecting almost 25% of the general population worldwide. The presence of NAFLD is strongly correlated with obesity, insulin resistance, and metabolic syndrome, and their consequences [1,2].

NAFLD is defined as the presence of steatosis in more than 5% of the liver hepatocytes in individuals who do not consume significant amounts of alcohol daily and do not have other concomitant liver

diseases [1,2]. It is a quite heterogeneous disease, with a spectrum that varies progressively from simple steatosis to steatohepatitis, liver cirrhosis, decompensated cirrhosis with its complications (rates of clinical decompensation have been reported to be 3%–4% annually), and even hepatocellular carcinoma (0.44 per 1000 person-years) [3]. NAFLD is divided into non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH), a difference observed with liver biopsy. NASH diagnosis is strictly histologic and is defined by the coexistence of steatosis, lobular inflammation, and hepatocyte ballooning [4].

Individuals with NAFLD/NASH have shortened life expectancy compared to the general population [1]. End-stage liver disease is the third most common cause of death in people with NAFLD, with cardiovascular disease the leading cause [5]. Advanced fibrosis seems to be the

\*Corresponding author. Tel.: +30 2310 999035; fax: +30 2312 205270.  
E-mail address: [mhourd@gapps.auth.gr](mailto:mhourd@gapps.auth.gr) (M. Chourdakis).

most important prognostic factor for disease progression, and is strongly associated with liver and cardiovascular morbidity and mortality. Data show that although individuals with either nonalcoholic fatty liver or NASH can be affected by liver fibrosis at any stage, the presence of NASH is associated with a twofold faster progression in liver fibrosis [6].

Although an important number of clinical studies have been conducted in order to find an effective drug therapy, there is not yet any effective drug treatment available for NAFLD/NASH. The only beneficial therapy is weight loss and lifestyle change [7]. Features of NASH are pharmacologically responsive to vitamin E or pioglitazone [2,5], but nonetheless, no more than a mere 40% of participants in trials have been benefited from a single therapy. Moreover, vitamin E and pioglitazone are not sufficiently effective to justify regulatory approval for long-term monotherapy. "Personalized" therapy for NASH remains at the moment elusive.

*Silybum marianum*, or milk thistle, is a plant that has been known since ancient times to be effective in treating liver diseases [8]. Nowadays it is the most extensively studied plant for the treatment of liver diseases and the most commonly used non-prescribed therapy for liver diseases [9]. Silymarin, its active extract, is composed of four isomer flavonolignans. Its beneficial effect on the liver is attributed to possible antiinflammatory, antioxidant, and antifibrotic activity. Silymarin also decreases insulin resistance [10]. It has been tested in the treatment of different liver diseases, showing positive results with remarkable safety [11].

A few years ago, data concerning silymarin as a possible treatment for NAFLD were limited, but several clinical trials have been conducted lately. A randomized controlled trial (RCT) conducted by Hashemi et al. [12] with NAFLD patients concluded that silymarin was efficient in reducing alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in comparison to placebo treatment. In a double-blind, placebo-controlled RCT by Kheong et al. [13] with adults with biopsy-proven NASH, a 48-wk silymarin treatment did not lead to an improvement in NAFLD activity score in comparison to the placebo group, but it led to a significant improvement in fibrosis after a repeat liver biopsy. Another clinical trial with NAFLD patients, conducted by Solhi et al. [14], examined the effect of silymarin after a treatment period of 8 wk. It led to a marked improvement in transaminase levels in comparison to placebo. Besides the aforesaid RCTs that examined silymarin monotherapy in NAFLD/NASH versus placebo treatment, more studies either with methodological drawbacks or not placebo controlled have also been performed [15,16].

The results of these studies are varied and conflicting. The aim of our study was to conduct a systematic review and meta-analysis of the available literature in order to evaluate the efficacy of silymarin in the treatment of NAFLD by examining changes in liver biochemistry, body mass index (BMI), and liver histology.

## Materials and methods

The study was conducted according to a prespecified protocol (<https://osf.io/2b54z/>) and in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Table 1) [17].

### Data sources

We searched PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to January 2020 for studies evaluating the efficacy of silymarin in NAFLD treatment. Conference proceedings (United European Gastroenterology Week, the European Association for the Study of the Liver, the American Association for the Study of Liver Disease, Digestive Disease Week) and Clinicaltrials.gov were screened for possible completed unpublished trials. Finally, we searched PROSPERO in order to confirm that there was no other similar study in progress. The search was updated June 3, 2020, for possible new records. The search strategy used relevant terms in the English language for NAFLD and

silymarin. We included studies written in English (the detailed search strategy can be found in Supplementary Figs. 1–3).

### Study selection criteria

We included RCTs with a follow-up time of 8 wk or more which compared silymarin monotherapy with placebo treatment in adults with NAFLD diagnosed by liver sonography, radiography, or histology according to the international criteria for the diagnosis of NAFLD [2]. There were no limitations on the type or date of publication. Exclusion criteria were pregnancy and severe cardiac, pulmonary, or renal comorbidities.

### Data collection and extraction

All references found from our search were imported into a reference management program (Mendeley or EndNote X7). Duplicate references were identified and removed. The remaining references were screened initially at the title and abstract level and then the full-text level independently by two reviewers (G.K., A.S.). The screening procedure was conducted with online software (Covidence). Any disagreements were solved by a third reviewer (C.A.). Data extraction was also performed independently by two reviewers (G.K., A.S.). A common predecided data extraction form was used for the extraction of the baseline characteristics and the outcomes of the included studies. Disagreements were solved by a third reviewer (C.A.). In cases of limited trial data, corresponding authors were contacted.

### Quality assessment

Quality assessment was performed according to the revised Cochrane risk-of-bias (ROB) tool 2.0 [18] independently by two reviewers (G.K., A.S.). The tool consists of five different domains (randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results). Every domain consists of unique questions. Each domain was evaluated separately for each outcome. The overall risk of bias was assessed as low, some concerns, or high according to the assessment of the five domains. Any disagreements were solved by a third reviewer (C.A.).

### Outcome measurement

Primary outcomes were changes in mean ALT and AST values after treatment with silymarin (quantitative variables). Secondary outcomes were changes in BMI (quantitative variables) and liver histology where available. Changes in liver histology were defined as one-point improvement in fibrosis staging score and one-point improvement in NAFLD activity score (qualitative variables) [4].

### Data synthesis

Data from intention-to-treat analyses were used when available. A cutoff level of 0.05 was considered to provide statistically significant results. Data synthesis was performed with the help of a random-effects model. Quantitative variables were presented as means (average  $\pm$  SD), and changes in mean values after treatment as mean differences (MDs). Qualitative variables were presented as risk ratios and 95% confidence intervals (CIs). Statistical heterogeneity was assessed with the help of  $I^2$  statistics; values below 20% indicate low heterogeneity, and higher than 60%, high heterogeneity. We also performed a preplanned sensitivity analysis after excluding studies with high risk of bias and studies which contributed to high heterogeneity. Finally, a post hoc subgroup analysis was done based on the mean dose of silymarin treatment (280 mg) and mean follow-up time. All statistical analyses were performed with Review Manager 5.3 [19].

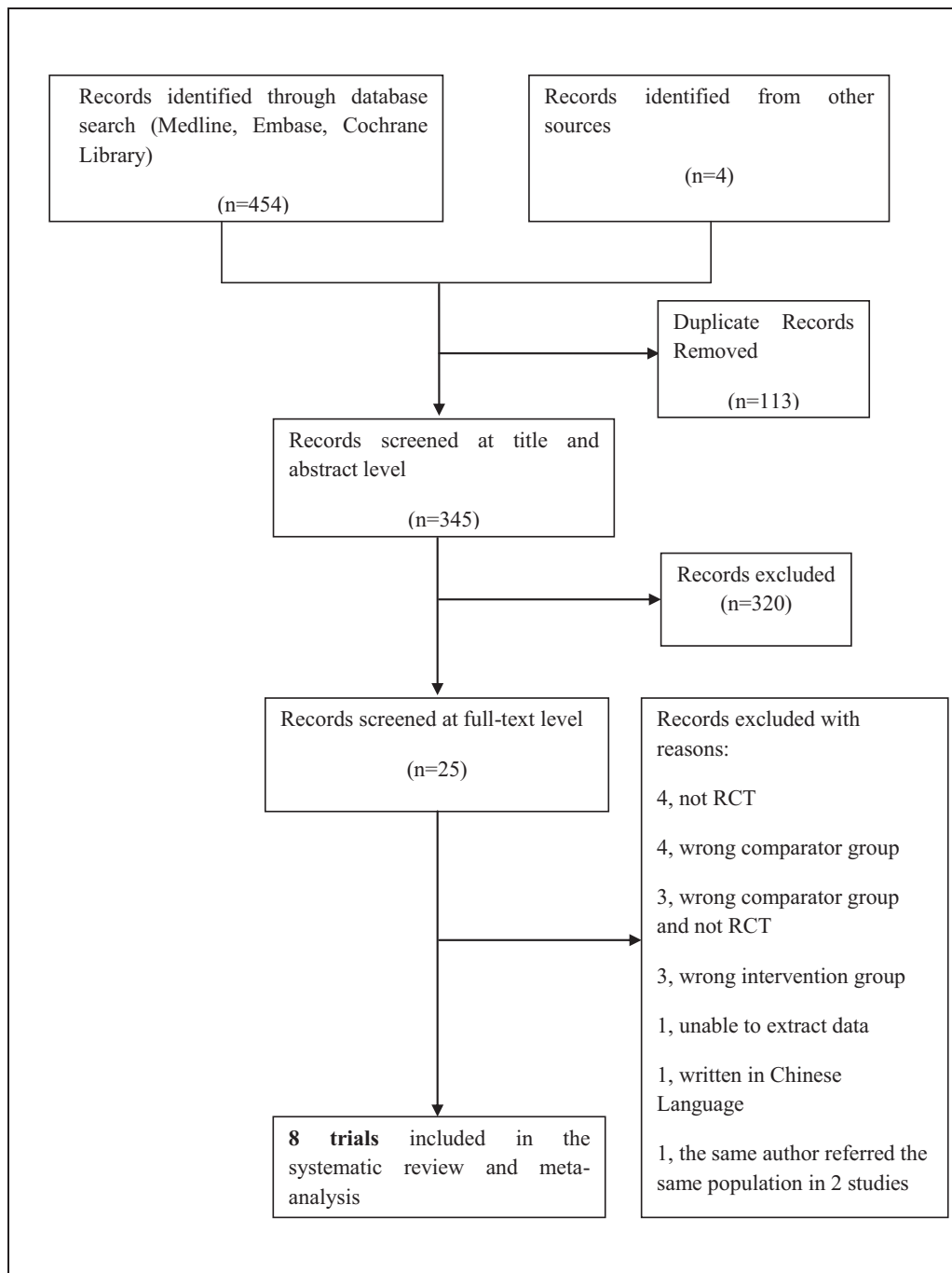
## Results

### Results of study search

From the search strategy, 454 records were identified. We also identified four records from other sources. All references (458 in total) were imported into reference management software. As can be seen in the flowchart (Fig. 1), eight studies were finally included in the systematic review and meta-analysis [12–14,20–24].

### Baseline characteristics

The total number of the participants included in our study was 622. Seven out of the eight trials examined the primary



**Fig. 1.** Flowchart and reasons for exclusion of studies.

outcomes of ALT and AST [12–14,20,22–24]. Four examined the secondary outcome of BMI [12,13,20,23], and only two trials included the secondary outcome of changes in liver histology [13,21]. All trials included were published during the past decade (2009–2019). Mean time of follow-up ranged from 8 to 48 mo. Mean daily dose of silymarin ranged from 140 to 2100 mg. The majority of the trials used 280 mg silymarin as a daily dosage. The sample size of the studies ranged from 41 to 100 patients, ages 39–50.1 y, mainly men (57%). As expected, participants were overweight or obese. A full description of the

baseline characteristics of the included trials is depicted in Table 1 and Supplementary Table 2.

#### *Risk-of-bias assessment*

The summary of the risk-of-bias assessment for the primary outcomes is presented in Table 2. Two of the eight trials in our study had high risk of bias [14,24] owing to insufficient description in most of the parameters of the ROB tool. Three trials were judged to have some concerns [12,22,23], and the remaining three were

**Table 1**  
Baseline characteristics of the participants included in the meta-analysis

Study	NCT number	Country	Intervention	Mean dose (mg/d)	Follow-up (wk)	Participants randomized into group	Mean age (y)	Male/female (%)	Mean BMI (kg/m <sup>2</sup> )	Mean ALT (IU/L)	Mean AST (IU/L)
Hashemi et al. [12]	NR	Iran	Silymarin	280	24	50	39.3	56/44	26.8	113.5	71.4
			Placebo	Placebo		50	39	58/42	27.8	104.5	73
Masoodi et al. [23]	NR	Iran	Silymarin	280	12	50	48.4	62/38	29	84.1	71.9
			Placebo	Placebo		50	48.3	62/38	29.2	74.5	62.9
Taghvaei et al. [24]	IRCT138805172308N1	Iran	Silymarin	280	24	21	42	66.3/33.7	NR	69.9	56.8
			Placebo	Placebo		20	40	65/35	NR	88.6	62.2
Solhi et al. [14]	NR	Iran	Silymarin	210	8	40	43.6	56/44	27.4	91.3	62.8
			Placebo	Placebo		40	39.6	60/40	27.5	84.6	70.4
Memon et al. [22]	NR	Pakistan	Silymarin	280	12	33	49	63.6/36.4	29.9	92.1	73.2
			Placebo	Placebo		31	48	67/33	28.7	83	69.3
Kheong et al. [13]	NCT02006498	Malaysia	Silymarin	2100	48	49	49.6	49/51	30	101	63
			Placebo	Placebo		50	50.1	44/56	31	86	51
Navarro et al. [21]	NCT00680407	United States	Silymarin	1260	48	26	47.3	50/50	35.3	80	57
			Placebo	2100		27	48.2	67/33	33.5	61	46
			Placebo	Placebo		25	49.5	56/44	33.4	65	51
Anushiravani et al. [20]	IRCT201705016312N4	Iran	Silymarin	140	12	30	47	51/49	25.7	30.7	25.1
			Placebo	Placebo		30	47	51/49	26.1	22.8	19.6

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; NR, not reported.

evaluated to have low risk of bias [13,20,21]. Supplemental figures present the ROB process (Supplementary Figs. 4 and 5).

### Analysis of primary outcomes

#### Alanine aminotransferase

Seven studies [12–14,20,22–24] examined the mean value of ALT before and after treatment with silymarin. Treatment with silymarin was more efficacious than placebo therapy in reducing ALT values (IU/L) in participants with NAFLD (MD = −14.86; 95% CI, −19.37 to −10.36;  $I^2 = 39\%$ ,  $P < 0.00001$ ; Fig. 2).

#### Aspartate aminotransferase

Seven studies [12–14,20,22–24] examined AST values (IU/L) before and after treatment with silymarin. Silymarin proved to be more efficient than placebo therapy in decreasing AST values (MD = −7.11; 95% CI, −14.16 to −0.05;  $I^2 = 88\%$ ;  $P < 0.05$ ; Fig. 3).

### Analysis of secondary outcomes

#### Body mass index

The mean difference in BMI before and after treatment was examined in four studies [12,13,20,23]. There was no statistically significant difference in mean of BMI (Kg/m<sup>2</sup>) before and after treatment with silymarin (MD = −0.00; 95% CI, −0.71 to 0.7;  $I^2 = 0\%$ ;  $P = 0.99$ ; Fig. 4).

#### Liver histology

Only two studies examined the efficacy of silymarin on liver histology [13,21]. Due to the small number of studies and the small sample size, no data synthesis was performed. In the trial conducted by Kheong et al. [13], silymarin treatment seemed to be efficacious at improving liver fibrosis but not NAFLD activity score, while in the study of Navarro et al. [21], silymarin was not superior to placebo in improving liver histology.

### Subgroup analysis

A subgroup analysis was done including studies with a short follow-up time ( $\leq 12$  wk) and those supplementing with the same dose of silymarin (280 mg).

Four studies [14,20,22,23] had a short follow-up time of 12 wk or less. In these studies, silymarin was more efficient at reducing ALT values than placebo therapy (MD = −15.14; 95% CI, −19.66 to −10.63;  $P < 0.00001$ ;  $I^2 = 46\%$ ; Supplementary Fig. 6). In contrast, silymarin was not efficient at significantly reducing AST values (MD = −5.83; 95% CI, −14.8 to 3.14;  $P = 0.2$ ;  $I^2 = 94\%$ ; Supplementary Fig. 7).

A subgroup analysis was also performed for trials which used the same dose of silymarin (280mg) [12,22–24]. Silymarin was more efficacious at reducing ALT values compared to placebo (MD = −15.87; 95% CI, −19.62 to −12.12;  $P < 0.00001$ ). Heterogeneity was significantly reduced to  $I^2 = 14\%$  (Supplementary Fig. 8). In contrast, silymarin could not statistically significantly reduce AST values compared to placebo (MD = −10.22; 95% CI, −21.01 to 0.56;  $P = 0.06$ ;  $I^2 = 86\%$ ; Supplementary Fig. 9).

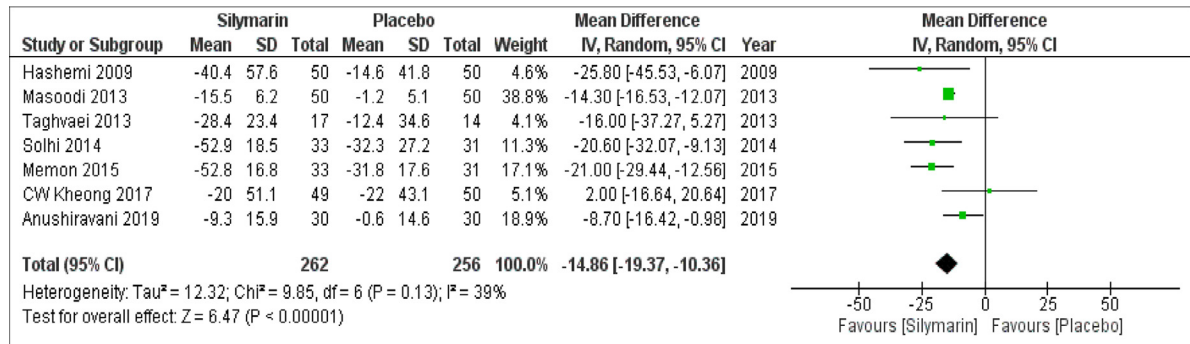
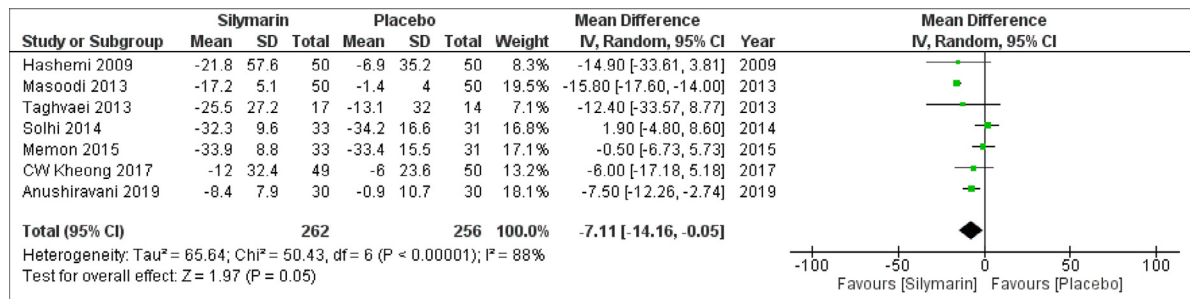
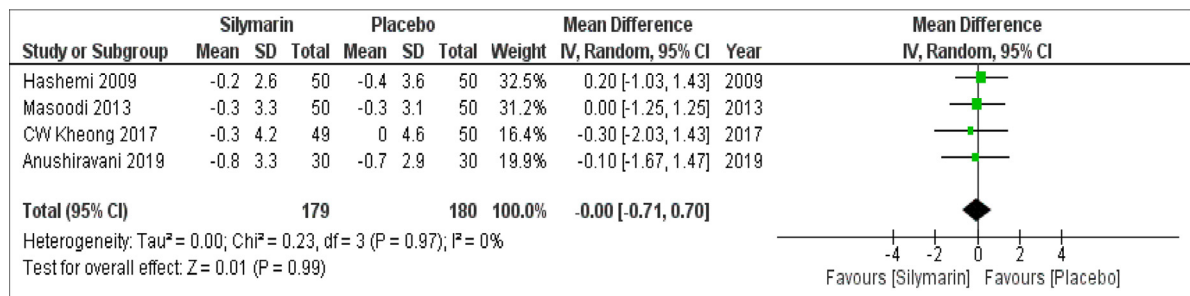
### Sensitivity analysis

We performed a sensitivity analysis and searched for major differences in the summary effect estimate by excluding each study separately for each outcome. No major differences were found in

**Table 2**

Risk-of-bias assessment for primary outcomes (change in alanine transaminase and aspartate transaminase) using Cochrane risk-of-bias tool 2.0

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Hashemi et al. [12]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Masoodi et al. [23]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Taghvaei et al. [24]	Low	High	High	Low	Low	High
Solhi et al. [14]	Some concerns	Some concerns	Some concerns	Low	Some concerns	High
Memon et al. [22]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Kheong et al. [13]	Low	Low	Low	Low	Low	Low
Navarro et al. [21]	Low	Low	Low	Low	Low	Low
Anushiravani et al. [20]	Low	Low	Low	Low	Low	Low

**Fig. 2.** Forest plot of the change in the value (IU/L) of alanine aminotransferase (mean difference = -14.86; 95% confidence interval, -19.37 to -10.36;  $P < 0.00001$ ;  $I^2 = 39\%$ ).**Fig. 3.** Forest plot of the change in the value (IU/L) of aspartate aminotransferase (mean difference = -7.11; 95% confidence interval, -14.16 to -0.05;  $P < 0.05$ ;  $I^2 = 88\%$ ).**Fig. 4.** Forest plot of the change in the value (kg/m<sup>2</sup>) of body mass index (mean difference = -0.00; 95% confidence interval, -0.71 to 0.7;  $P = 0.99$ ;  $I^2 = 0$ ).

ALT values. The sensitivity analysis concluded that after the studies of Solhi et al. and Masoodi et al. [14,23] were excluded, heterogeneity in AST values decreased remarkably to a low level,  $I^2 = 12\%$ . Furthermore, AST values decreased with statistical significance ( $MD = -5.56$ ; 95% CI, -9.56 to -1.56;  $P = 0.006$ ) in the silymarin treatment group compared to the placebo group (Supplementary Fig. 10).

A further sensitivity analysis was performed to examine silymarin's efficacy on the primary outcomes after studies were excluded that were assessed to have high risk of bias [12,13,20,22,23]. In this group of studies, silymarin also proved to be more efficient at reducing ALT ( $MD = -14.00$ ; 95% CI, -19.58 to -8.42;  $P < 0.00001$ ;  $I^2 = 54\%$ ) and AST ( $MD = -8.60$ ; 95% CI, -15.88 to -1.33;  $P = 0.02$ ;  $I^2 = 87\%$ ) compared to placebo (Supplementary Figs. 11 and 12).



## Discussion

This systematic review and meta-analysis examined the efficacy of silymarin in the treatment of NAFLD. Our review included eight studies with a total of 622 participants. **The results show that supplementation with silymarin led to a statistically significantly greater reduction in transaminase levels compared to treatment with placebo, irrespective of weight loss.**

Further subgroup and sensitivity analyses were carried out and showed that the reduction in ALT values after treatment with silymarin was approximately the same—statistically and clinically significant—regardless of dosage administered, short- or long-term time of follow-up, or ROB in the included studies. As only two studies included data from serial liver biopsies before and after treatment, this outcome was not further evaluated.

The efficacy of treatment with silymarin in NAFLD was also explored in another recent meta-analysis [25]. However, that meta-analysis had a different design from ours and incorporated only three studies comparing silymarin monotherapy with placebo for the treatment of NAFLD. Furthermore, the intervention group was not the same in the included studies, as silymarin was used either as monotherapy or in combination therapy, raising questions as to whether the improvement in liver function was due to silymarin or the combination therapy used. Because there was not a steady comparison group, the placebo effect was not estimated.

To our knowledge, there is no other available meta-analysis incorporating the most recent clinical trials examining the efficacy of silymarin in the treatment of NAFLD. Our study includes RCTs which examined a specific patient population (individuals with NAFLD). Moreover, it includes more studies (eight in total) and a larger total patient population than the previous meta-analysis. The basic strength of our study is that a pure comparison was made of the efficacy of silymarin treatment as monotherapy and the placebo effect in individuals with NAFLD. The results of our meta-analysis are in accordance with the results of the previous one [25], but ours gives a clearer proof that silymarin is efficient in reducing transaminase levels in individuals with NAFLD. Furthermore, a post hoc subgroup analysis was performed to examine silymarin efficacy with different mean dosages and different mean follow-up times. Another strength of our study is that the literature search was conducted not only in major electronic databases but also in gray literature, for more data. Finally, quality analysis was conducted with the most recent Cochrane ROB tool 2.0 [12].

Our study has some limitations that must be acknowledged. It included only studies written in English. Although the exclusion of trials not written in English from meta-analyses might introduce bias and decrease the accuracy of the treatment effects, this effect is in general limited [26]. With regard to the quality of the trials included in the meta-analysis, two (25%) were judged to have high risk of bias and three were judged as causing some concerns. Furthermore, very high heterogeneity was found in one of the two primary outcomes (change in mean AST value). However, sensitivity analysis showed that after the studies by Solhi et al. and Masoodi et al. [14,23] were excluded, heterogeneity declined significantly to  $I^2 = 12\%$ . This might be attributed to the facts that the study by Solhi et al. [14] was evaluated to have high ROB and that of Masoodi et al. [23] provided incomplete details on the randomization process and the selection of reported results. These critical issues of the quality of the included trials and high heterogeneity could substantially affect the validity of our findings and subsequently their applicability in clinical practice.

Another point that should be kept in mind is that only one of the eight studies included a NAFLD cohort of people from a

Western country (the United States) [21]. According to long-term observational studies [27], NAFLD is a disease which is characterized by different prevalence, severity, and progression rate based mainly on the ethnicity of the patient. Furthermore, risk factors for NAFLD/NASH such as obesity, diabetes mellitus, insulin resistance, and genetic susceptibility vary across different ethnicities. Subsequently, the treatment effect of silymarin could also differ among Western and Eastern populations. Given these data, the external validity of the results of our meta-analyses in a Western cohort of individuals with NAFLD is limited, and any generalization of these results needs to be done cautiously.

Another limitation of our study is the small number of patients with a diagnosis of NASH with or without liver fibrosis (177 total) owing to the lack of trials providing data from serial liver biopsies. The gold standard for follow-up of NAFLD/NASH is repeated liver biopsies, not transaminase levels, due to the facts that transaminase levels might be normal in up to 80% of people with NAFLD [28] and do not always reflect disease activity or severity [5,12]. However, recent studies have examined the possible role of serum biomarkers in predicting histologic changes in individuals with NAFLD, like the one conducted by Vilar-Gomez et al. [29], which showed that a scoring system with three variables including ALT normalization might be able to predict improvements in liver histology.

The decision to use AST and ALT levels as a primary outcome was made because these are general markers of hepatocellular injury. Long-term observational studies in NASH have shown that increased transaminase levels are strongly related with increased risk of developing end-stage liver disease, and are an important general prognostic factor for this patient population [30,31]. Moreover, a decrease in transaminase levels seems to correlate with improvement in steatosis and inflammation in paired liver biopsies in individuals with NAFLD [32,33]. Furthermore, in a study conducted in a pediatric population, the change in transaminase levels seemed to be a reliable marker for monitoring disease activity, and their decrease related with histologic improvement of NASH [34].

Silymarin, a phytotherapy with proven safety and without common serious adverse effects [11,13,20,21], could be a safe alternative treatment for individuals with NAFLD/NASH. Due to the relatively limited amount of available data and the low quality of the currently completed trials, further well-designed multicenter RCTs have to be conducted, focusing on the efficacy of silymarin treatment in individuals with NASH or severe liver fibrosis. The evaluation of silymarin's efficacy in NAFLD/NASH through serial liver biopsies seems to be crucial.

## Conclusions

**To conclude, silymarin seems to be efficacious in decreasing transaminase levels in individuals with NAFLD, without this decrease being a result of weight loss.** Despite the statistically demonstrated benefits in this meta-analysis, we call attention to the potential flaws related to the quality of the studies included. Therefore, we recommend that further well-designed studies be carried out. It is also crucial to examine whether this reduction in transaminase levels corresponds to histologic improvement.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.nut.2020.111092](https://doi.org/10.1016/j.nut.2020.111092).

## References

- [1] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73–84.
- [2] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–57.
- [3] Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. *N Engl J Med* 2017;377:2063–72.
- [4] Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;41:1313–21.
- [5] Marchesini G, Day CP, Dufour JF, Canbay A, Nobili V, Ratzliff V, et al. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388–402.
- [6] Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol* 2015;13:643–54.
- [7] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med* 2018;24:908–22.
- [8] Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *Phytother Res* 2010;24:1423–32.
- [9] Flora K, Hahn M, Rosen H, Benner K. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol* 1998;93:139–43.
- [10] Li HB, Yang YRY, Mo ZJ, Ding Y, Jiang WJ. Silibinin improves palmitate-induced insulin resistance in C2C12 myotubes by attenuating IRS-1/PI3K/Akt pathway inhibition. *Braz J Med Biol Res* 2015;48:440–6.
- [11] Polyak SJ, Ferenci P, Pawlotsky JM. Hepatoprotective and antiviral functions of silymarin components in hepatitis C virus infection. *Hepatology* 2013;57:1262–71.
- [12] Hashemi SJ, Hajiani E, Sardabi EH. A placebo-controlled trial of silymarin in patients with nonalcoholic fatty liver disease. *Hepat Mon* 2009;9:265–70.
- [13] Kheong CW, Nik Mustapha NR, Mahadeva S. A randomized trial of silymarin for the treatment of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2017;15:1940–9.
- [14] Solhi H, Ghahremani R, Kazemifar AM, Yazdi ZH. Silymarin in treatment of non-alcoholic steatohepatitis: a randomized clinical trial. *Caspian J Intern Med* 2014;5:9–12.
- [15] Loguercio C, Federico A, Trappoliere M, Tuccillo C, de Sio I, Di Leva A, et al. The effect of a silybin-vitamin e-phospholipid complex on nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2007;52:2387–95.
- [16] Abenavoli L, Greco M, Nazionale I, Peta V, Milic N, Accattato F, et al. Effects of Mediterranean diet supplemented with silybin–vitamin E–phospholipid complex in overweight patients with non-alcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2015;9:519–27.
- [17] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [18] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
- [19] Review Manager (RevMan) [Computer software]. Version 5.3. Copenhagen: The Nordic Cochrane Centre TCC; 2014.
- [20] Anushiravani A, Haddadi N, Pourfarmanbar M, Mohammadkarimi V. Treatment options for nonalcoholic fatty liver disease: a double-blinded randomized placebo-controlled trial. *Eur J Gastroenterol Hepatol* 2019;31:613–7.
- [21] Navarro VJ, Belle SH, D'Amato M, Adfhal N, Brunt EM, Fried MW, et al. Silymarin in non-cirrhotics with non-alcoholic steatohepatitis: a randomized, double-blind, placebo controlled trial. *PLoS One* 2019;14:e0221683.
- [22] Memon IA, Akbar M, Bhurgri AN. Effect of silymarin therapy on liver aminotransferase in non-alcoholic fatty liver disease. *Med Forum Mon* 2015;26:46–9.
- [23] Masoodi M, Rezadoost A, Panahian M, Vojdani M. Effects of silymarin on reducing liver aminotransferases in patients with nonalcoholic fatty liver diseases. *Govaresh* 2013;18:181–5.
- [24] Taghvaei T, Bahar A, Hosseini V, Maleki I, Kasrai M. Efficacy of silymarin on treatment of nonalcoholic steatohepatitis. *J Mazandaran Univ Med Sci* 2013;23:164–71.
- [25] Zhong S, Fan Y, Yan Q, Fan X, Wu B, Han Y, et al. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease: a meta-analysis (PRISMA) of randomized control trials. *Medicine (Baltimore)* 2017;96:e9061.
- [26] Jüni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *Int J Epidemiol* 2002;31:115–23.
- [27] Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol* 2013;10:686–90.
- [28] Dyson JK, Anstee QM, McPherson S. Non-alcoholic fatty liver disease: a practical approach to diagnosis and staging. *Frontline Gastroenterol* 2014;5:211–8.
- [29] Vilar-Gomez E, Calzadilla-Bertot L, Friedman SL, Gra-Oramas B, Gonzalez-Fabian L, Lazo-del Vallin S, et al. Serum biomarkers can predict a change in liver fibrosis 1 year after lifestyle intervention for biopsy-proven NASH. *Liver Int* 2017;37:1887–96.
- [30] Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006;44:865–73.
- [31] Vuppalanchi R, Jain AK, Deppe R, Yates K, Comerford M, Masuoka HC, et al. Relationship between changes in serum levels of keratin 18 and changes in liver histology in children and adults with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2014;12:2121–30.
- [32] Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005;42:132–8.
- [33] Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. *J Hepatol* 2018;68:305–15.
- [34] Arsik I, Frediani J, Frezza D, Chen W, Ayer T, Keskinocak P, et al. Alanine aminotransferase as a monitoring biomarker in children with nonalcoholic fatty liver disease: a secondary analysis using TONIC trial data. *Children* 2018;5:64.