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SYSTEMATIC REVIEW

The effect of silymarin (milk thistle) on cirrhosis: A systematic review and meta-analysis of clinical trials

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Points to Note

- **Synthesis of Current Evidence:** Silymarin may improve AST, ALT, and albumin levels in cirrhosis, with no serious adverse effects reported.
- **Major Controversies:** Evidence remains limited by few studies, small samples, heterogeneity, and lack of control groups in some trials.
- **Future Directions:** Larger, well-designed randomized controlled trials are needed to confirm efficacy, optimal dose, and clinical relevance.

ABSTRACT

Background and Aim: Cirrhosis is a fatal liver disease. Silymarin, by improving inflammation, oxidative stress, and the regeneration of liver cells, can improve cirrhosis. Therefore, this study aimed to conduct a systematic review and meta-analysis of silymarin in cirrhosis.

Materials and Methods: PubMed, Scopus, and Web of Science were systematically searched up to 16 May 2025 to find clinical trials that investigated the effect of silymarin on cirrhosis. No time or language limitations were considered.

Results: Eight clinical trials with nine intervention arms were included. The results of this study showed that silymarin significantly reduced aspartate aminotransferase (AST) (weighted mean difference [WMD]: −5.41 IU/L, 95% confidence interval [CI]: −8.92, −1.91; I^2=89.4%, P for heterogeneity<0.001) and alanine aminotransferase (ALT) (WMD: −6.07 IU/L, 95% CI: −11.31, −0.84; I^2=96.1%, P for heterogeneity<0.001), and increased albumin (WMD: 0.08 g/dL, 95% CI: 0.03, 0.14; I^2=0.0%, P for heterogeneity=0.691) in cirrhosis, but had no significant effect on ALP (WMD: −14.45 IU/L, 95% CI: −30.45, 1.55; I^2=0.0%, P for heterogeneity=0.610) and bilirubin (WMD: −0.03 mg/dL, 95% CI: −0.18, 0.12; I^2=78.6%, P for heterogeneity=0.001). No significant side effects were reported in any of the studies. Only some studies reported very limited and negligible complications in a very limited number of patients.

Conclusion: The results of the present study showed the favorable effects of silymarin on reducing AST and ALT and increasing albumin levels in cirrhosis. Although due to the small number of included studies, findings should be interpreted with caution, based on the results of this meta-analysis, silymarin might be considered a safe, inexpensive, and available agent for the treatment of cirrhosis.

Keywords: Cirrhosis, meta-analysis, milk thistle, silymarin, systematic review.

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Introduction

Cirrhosis is one of the most important causes of death worldwide.[1] Alcohol abuse, metabolic disorders, viral hepatitis, and non-alcoholic fatty liver disease (NAFLD) are among the most important factors leading to cirrhosis.[2,3] Cirrhosis causes the imbalance of many inflammatory factors, especially C-reactive-protein (CRP), and tumor necrosis factor-α (TNF-α). Also, glutathione (GSH), one of the most important antioxidants, decreases significantly in cirrhosis.[4–7] In many liver problems, including cirrhosis, reactive oxygen species increase excessively, which can cause DNA damage and imbalance in the regulation of genes of inflammatory factors and disturbance in the transmission of cell signals. Also, free radicals may cause lipid peroxidation and damage to proteins inside liver cells, resulting in liver dysfunction.[8–10]

Cirrhotic patients are at high risk of hepatocellular carcinoma.[11,12] In addition, if the disease progresses, the need for a liver transplant is very likely.[13,14] Therefore, it is very important to help these patients to prevent the need for a liver transplant. This can be done by preventing the development of the disease and also by intervening in the affected people.[1] Some of the strategies available to help patients with cirrhosis include the administration of branched-chain amino acids to improve hypoalbuminemia, antiviral treatments in case of cirrhosis caused by viral hepatitis, diuretics to reduce ascites, steroids, and beta blockers, but none of these cases are not a definitive solution. Furthermore, many of these treatments have contraindications in some conditions and may cause hepatotoxicity.[13,15–18] Therefore, the high prevalence of liver diseases, especially liver cirrhosis, and the lack of a definite treatment solution for it, indicates the need to provide new cost-effective and useful treatment solutions.[19]

Silymarin is an extract from milk thistle (Silybum marianum), which contains flavonolignan and flavonoid polyphenolic.[20,21] This herbal extract helps establish oxidative balance by inhibiting free radicals and increasing intracellular glutathione. This action reduces lipid peroxidation and also protects other compounds in the cell, including DNA and proteins, from oxidative damage.[22–25] Oxidative stress causes excessive stimulation of inflammatory factors genes and aggravates liver damage, therefore silymarin reduces inflammatory responses and stabilizes the liver condition by improving oxidative stress.[22,26]

Silymarin by regulating the permeability of the liver cell membrane reduces the entry of hepatotoxic agents into the liver cells. It is also effective in stimulating the regeneration of liver cells, so it improves liver damage.[27,28] Several studies have suggested the safety of silymarin supplementation in many liver problems, including cirrhosis.[22,27,29,30] Hence, a decrease in cytotoxicity, especially in the liver, can be expected after consuming silymarin. Also, this plant extract can reverse the destruction of liver cells and prevent its progression, so it can be useful and effective in modulating the damage caused by liver fibrosis and cirrhosis.[22]

With regard to the importance of the issue, and considering the lack of a definite treatment solution for cirrhotic patients and the potential therapeutic effects of silymarin on liver diseases, so far, several trials have been conducted to investigate the effect of silymarin on cirrhosis. However, the results of these studies are somewhat contradictory and there is no systematic review and meta-analysis to fill this gap. Therefore, this study aims to systematically review and meta-analyze clinical trials that investigated the effect of silymarin supplementation on cirrhosis.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki.

Search Strategy

The present systematic review was conducted based on the preferred reporting items for systematic reviews and meta- analyses (PRISMA) guidelines.[31] A detailed and comprehensive systematic search was conducted in PubMed, ISI Web of Science, and Scopus databases to find trial studies investigating the effect of silymarin on cirrhosis up to 16 May 2025. Google Scholar was also searched to find the relevant articles. There were no restrictions on language, time of publication, and place of study. The keywords used in the search are as follows: ((“Silymarin” OR “Silybin” OR “milk thistle” OR “milk-thistle” OR “thistle plant” OR “thistle-plant” OR “Silybum marianum” OR “Silybum-marianum” OR “Silybum” OR “silibinin” OR “silydianin” OR “silychristin” OR “cardus marianus” OR “cardus-marianus” OR “isosilibinin” OR “silichristin”) AND (“cirrhotic ascites” OR “cirrhosis” OR “hepatic cirrhosis” OR “liver cirrhosis” OR “decompensated liver cirrhosis” OR “cirrhotic-ascites” OR “hepatic-cirrhosis” OR “liver-cirrhosis” OR “decompensated liver-cirrhosis” OR “decompensated-liver cirrhosis”)). In addition, Medical Subject Headings terms were used for PubMed.

Databases were reviewed by two independent authors (S.A. and M.B.). If there was a difference of opinion between the researchers, a common opinion was obtained by face-to-face discussion. Population, intervention, comparator, and outcome were as shown in Table 1.

Inclusion and Exclusion Criteria

Clinical trials in all languages that investigated the effect of silymarin on cirrhosis patients were included. We excluded the following

Table 1. Detailed information about population, intervention, comparator, and outcome (PICO)

PICO Items	Definition
Population	Cirrhotic patients
Intervention	Silymarin
Comparison	Placebo or standard therapy (do not take silymarin) or no control group
Outcome	AST, ALT, ALP, bilirubin, and albumin

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

Table 2. The main characteristics of included clinical trials

ID	First author (publication year), Country	Sample size included in analyses		Gender		Mean Age (or range of age)	Subjects	Study design	Intervention of experimental group	Intervention of control group	Duration	Side effects
		Intervention	Control	Male	Female							
1	Ferenci (1989), Austria[36]	87	83	123	47	57.4±11.9	Liver cirrhosis	Prospective, randomized trial	420 mg/day of silymarin (140 mg three times/day)	Placebo	24 months	Nausea and epigastric discomfort (2 in the silymarin and 2 in the placebo group).
2	M Velussi (1993), Italy[37]	30	30	42	18	62.5±3.5	Diabetic patients with cirrhosis	Clinical trial (parallel)	600 mg /day of silymarin+ standard therapy	Standard therapy (Do not take silymarin)	6 months	No side effects
3	Mario Velussi (1997), Italy[38]	30	30	Not mentioned		62.5±3.5 (45–70)	Diabetic patients with cirrhosis	Clinical trial (parallel)	600 mg /day of silymarin+ standard therapy	Standard therapy (Do not take silymarin)	12 months	No side effects
4	Parés (1998), Spain[39]	58	67	Not mentioned		50.4±10.7	Alcoholics with liver cirrhosis	Clinical trial (parallel)	450 mg/day of silymarin (150 mg/3 times daily)	Placebo	24 months	Eleven patients had side effects (7 in the treatment group and 4 in the placebo group). Complications included arthralgias and pruritus, headache and urticaria, and unspecified complications.
5	Angulo (2000), USA[40]	27	0	Not mentioned		51.6 ±1.4 (38–71 years)	Primary Biliary Cirrhosis With a Suboptimal Response to UDCA	Clinical trial	420 mg/day of silymarin (140 mg 3 times daily)+UDCA (13-15 mg/kg/day)	No control group	12 months	Transitory GI adverse events occurred in 2 patients
6	Lucena (2002), Spain[41]	24	25	48	1	49±13 (20–70)	Alcoholic liver cirrhosis	Clinical trial (parallel)	450 mg/day of silymarin (150 mg t.i.d./day)	Placebo	6 months	One patient in the treatment group reported impotence.
7	Fallah Huseini (2005), Iran[42]	30	30	40	20	48.6±2.4	Liver cirrhosis caused by chronic hepatitis B.	Clinical trial (parallel)	435 mg/day of silymarin (145 mg t.i.d./day)	Placebo	12 months	No side effects
8a	Fathalah (2017), Egypt[43]	31		NM (The gender in each group is not mentioned, but in 62 patients there were 38 male and 24 female)		48.9±7.7 (20–75)	Chronic HCV-decompensated cirrhotic patients	Clinical trial	1,050 mg/day of silymarin	No control group	3 months	Among 62 patients: 10 patients: Diarrhea 7 patients: GI discomfort 7 patients: Attack of hematemesis
8b	Fathalah (2017), Egypt[43]	31		NM (The gender in each group is not mentioned, but in 62 patients there were 38 male and 24 female)		48.9±7.7 (20–75)	Chronic HCV-decompensated cirrhotic patients	Clinical trial	420 mg/day of silymarin	No control group	3 months	Among 62 patients: 10 patients: Diarrhea 7 patients: GI discomfort 7 patients: Attack of hematemesis

GI: Gastrointestinal; UDCA: Ursodeoxycholic acid.

Table 3. Main results of the included studies

ID	First author (publication year), Country	Child-Pugh score	Survival rate	Ascites	MDA	TC	HDL	Fasting insuline-mia	Glycosuria	C peptide	FBS	HbA1C	Creatinine	Albumin	Bilirubin	ALP	AST	ALT	Other outcomes
1	Ferenci (1989), Austria[36]		↑												↔	↔		↔	
2	M Velussi (1993), Italy[37]				↓	↔		↓	↓	↓	↓	↓					↔	↔	
3	Mario Velussi (1997), Italy[38]				↓	↔	↑	↓	↓	↓	↓	↓	↔		↔	↔	↓*	↓*	
4	Parés (1998), Spain[39]		↔											↔	↔	↔	↔	↑	↔ Encephalopathy
5**	Angulo (2000), USA[40]													↔	↔	↔	↔		
6	Lucena et al.(2002), Spain[41]	↔			↓								↔	↔	↔	↔	↔	↔	↑ GSH
7	Fallah Huseini et al. (2005), Iran[42]	Improve		↓										↔	↔		↓	↓	
8***	Fathalah (2017), Egypt[43]	Improve		↔										↑	↓		↓	↓	Both groups showed a significant decline in ALT and AST. Moreover, group A showed a significant decline than group B. INR showed a significant decline in both groups with a significantly different pattern in favor of group A

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; HbA1C: Hemoglobin A1C; FBS: Fasting blood sugar; HDL: High-density lipoprotein; TC: Total cholesterol; INR: International normalized ratio; MDA: Malondialdehyde; GSH: Glutathione; ↓: Decreasing effect; ↑: Increasing effect; ↔: No significant effect. All the changes mentioned are compared to the control group, except *, **, and ***. *: There was a slow and continuous decrease in ALT and AST values in the silymarin-treated group compared to baseline ($p<0.01$). **: All results for this study are reported in comparison to the baseline, as there was no control group. ***: The results are related to the comparison of the group receiving a higher dose of silymarin (1,050 mg/day) (group A) compared to the group receiving a lower dose of silymarin (450 mg/day) (group B).

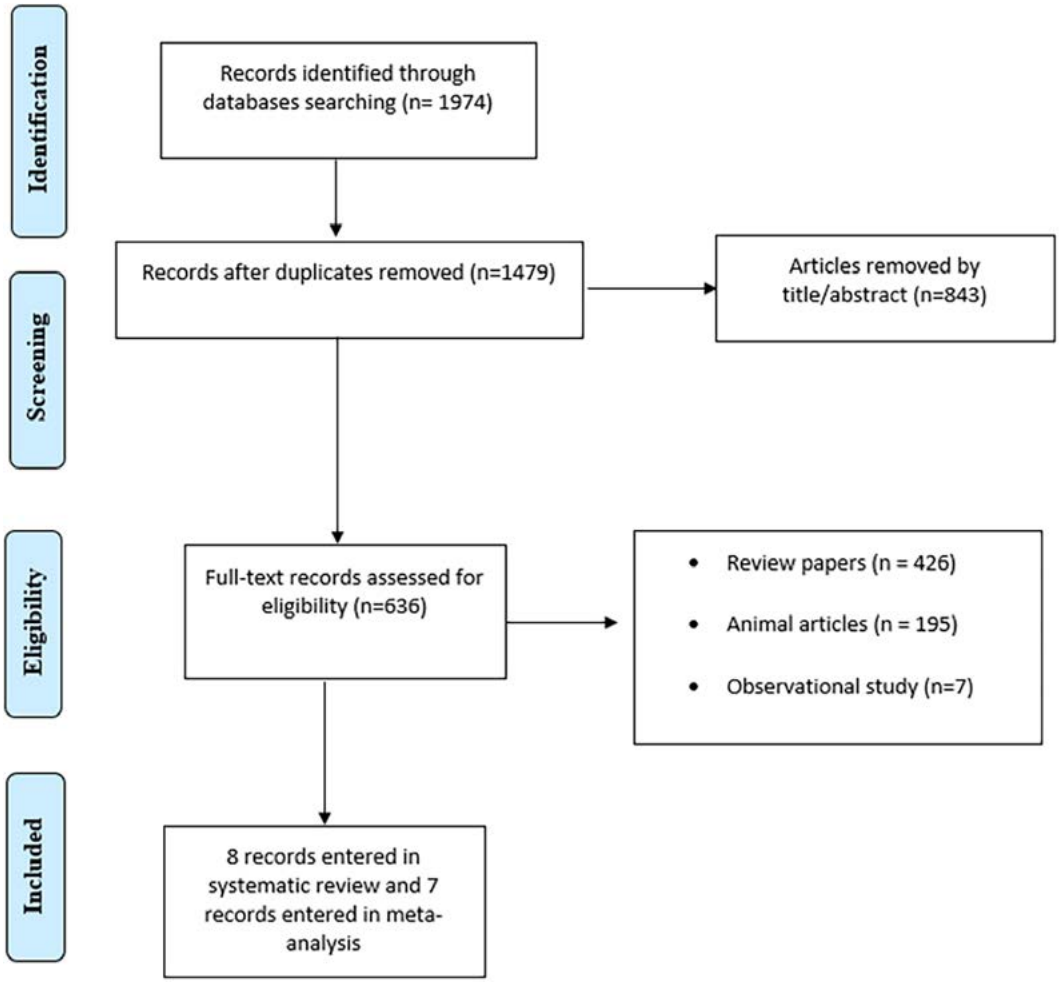


Figure 1. Flow diagram of the literature selection process.

studies: (1) Animal studies, (2) Studies that did not report sufficient data, (3) Observational studies, (4) Reviews, letters, study protocol, editorial articles, or case reports, and (5) Studies that had less than one week of intervention.

Data Extraction

The information extracted from the articles was as follows: the name of the first author, publication year, country, sample size, sex, and mean age of participants, subjects, design of the study, intervention of experimental and control groups, and duration of intervention and side effects (Table 2). Furthermore, the changes in AST, ALT, alkaline phosphatase, bilirubin, albumin, and other factors related to cirrhosis were extracted (Table 3). Data extraction was done by two independent researchers (S.A. and M.B.).

Quality Assessment of Studies

The Cochrane Collaboration tool was used to assess the risk of bias in clinical trials. According to this tool, studies in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, Selective reporting, and other sources of bias were assessed. The overall assessment result was as follows: good (low risk for more than 2 items), fairly good (low risk for 2 items), or poor (low risk for less than 2 items).[32]

Statistical Analysis

STATA statistical software version 13 (Stata Corporation, College Station, TX, USA) was used to perform the meta-analysis. Whole effects with the $p<0.05$ were considered statistically significant. The mean and standard deviation (SD) of AST, ALT, alkaline phosphatase, bilirubin, and albumin were used to calculate the effect size between intervention and control groups. In studies that reported standard errors (SE), SD was obtained by the formula $SD = SE \times \sqrt{N}$. None of the studies reported the data with a 95% confidence interval (CI). The overall effect size was reported by a random effects model as a weighted mean difference (WMD) in all results. To investigate the influence of each study or a specific group of studies on the total effect, sensitivity analysis was used, and Begg's[33] and Egger's[34] tests and funnel plots were used to check publication bias. We used the I2 statistic to assess heterogeneity between studies.[35]

Table 4. Risk of bias assessment for included randomized controlled clinical trials

ID	The first author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other risks of bias	Overall quality
1	Ferenci (1989)[36]	L	L	U	U	L	L	U	Good
2	M Velussi (1993)[37]	U	U	H	H	H	L	L	Relatively good
3	Mario Velussi (1997)[38]	U	U	H	H	L	L	L	Good
4	Parés (1998)[39]	L	L	U	U	L	L	U	Good
5	Angulo (2000)[40]	H	H	H	H	L	L	U	Relatively good
6	Lucena (2002)[41]	U	U	H	H	L	L	U	Relatively good
7	Fallah Huseini (2005)[42]	U	U	U	U	L	L	U	Relatively good
8	Fathalah (2017)[43]	L	L	U	U	L	L	U	Good

L: Low risk of bias; H: High risk of bias; U: Unclear risk of bias. Good quality; Relatively good quality.

In cases where heterogeneity was observed between the studies, the data were included in subgroup analysis based on the dose of silymarin supplementation (<600 mg/day or ≥600 mg/day), having or not having a control group, and based on the fact that only silymarin was used as an intervention or silymarin was used in combination with other compounds. The fixed-effects model was used to investigate between-subgroup heterogeneity.

Results

Search Results and Study Selection

As shown in Figure 1, 1974 studies were found in the initial search (PubMed: 416, ISI Web of Science: 395, and Scopus: 1163). Duplicates were removed, so 1479 studies remained. The first 100 records in Google Scholar were also searched and screened. After reviewing the title and abstract of the remaining studies, 843 unrelated studies were excluded. The remaining studies were reviewed for full text; Review papers (n=426), animal articles (n=195), and observational studies (n=7) were excluded. Finally, 8 clinical trials that investigated the effect of silymarin on cirrhosis were included in the current study.[36–43]

Characteristics of the Included Studies

Eight trials[36–43] with 9 intervention arms conducted between 1989 and 2017 were included. One study had two intervention arms[43] and the other studies had one intervention arm.[36–42] The characteristics of the studies are detailed in Table 2. The minimum period of study intervention was 3 months[43] and the maximum period was 24 months.[36,39] The amount of silymarin received varied between 420mg/day and 1050mg/day. All studies were conducted on adult patients with cirrhosis. The average age of the patients was between 48 and 62 years. Seven studies were in English[36–41,43] and one was in Persian.[42] The total sample size included 613 patients. Two studies were conducted without a control group,[40,43] and 4 studies had a control group that received a placebo,[36,39,41,42] and in 2 studies, the control group did not take any placebo.[37,38] Three studies[38,39,43] had control groups but did not report quantitative data for them. Thus, we referred to them as without control groups in the text, but included them as having control groups in Table 2 and reported their qualitative comparisons in Table 3. Three studies did not report gender[38–40] and the rest included both genders.[36,37,41–43] In 7 studies, only silymarin was used as an intervention,[36–39,41–43] and in one, silymarin plus Ursodeoxycholic Acid (UDCA)[40] was used as an intervention.

Side Effects

According to Table 2, none of the studies reported significant side effects of silymarin consumption. Three studies did not observe any side effects,[37,38,42] and other studies reported very mild and minor complications[36,39–41,43] including gastrointestinal complications, arthralgias and pruritus, headache and urticaria and unspecified complications in a limited number of patients.

Study Quality

The results of the quality assessment based on the Cochrane Collaboration tool determined that 4 studies are of good quality[36,38,39,43] and 4 studies are relatively good[37,40–42] (Table 4).

Main Results

Effect of silymarin on AST

So far, seven studies including 8 arms have investigated the effect of silymarin on AST among cirrhosis patients.[37–43] Pooled analysis of these studies showed that supplementation with silymarin significantly reduces AST (WMD:-5.41 IU/L, 95% CI:-8.92, -1.91;

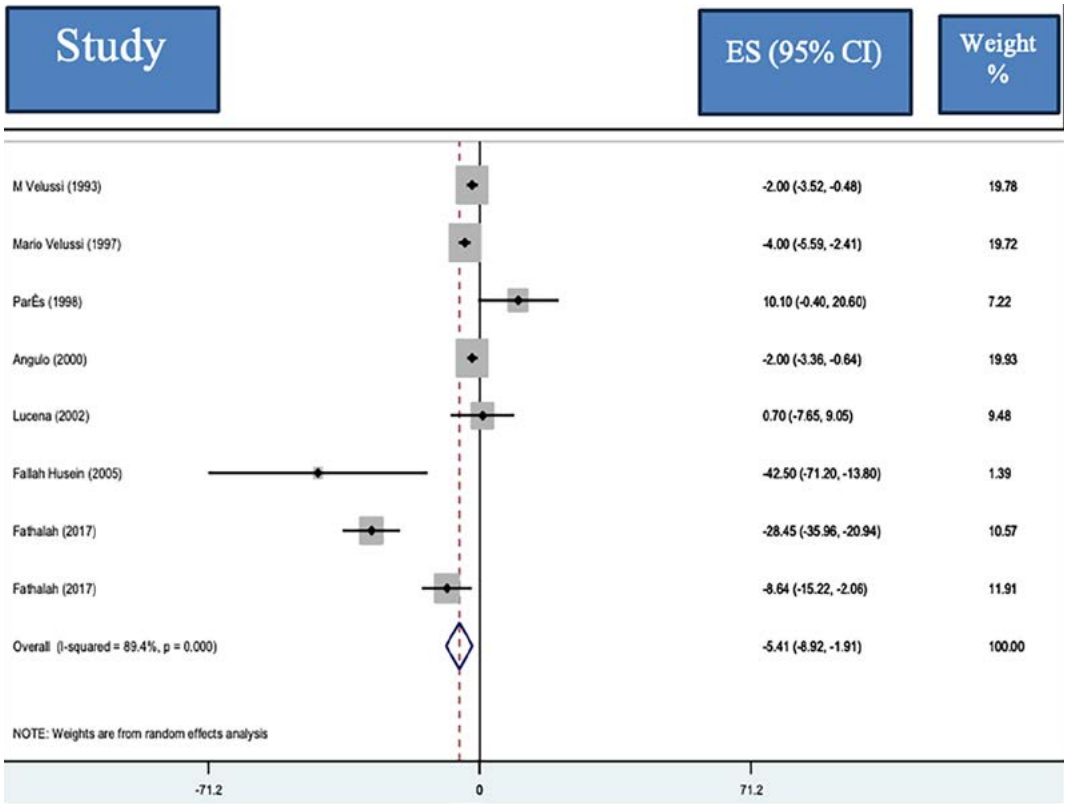


Figure 2. The effect of silymarin on aspartate aminotransferase in cirrhotic patients.

I^2=89.4%, p<0.001) (Fig. 2). Due to the existence of heterogeneity between studies, we performed several subgroup analyses to find the source of heterogeneity, which are as follows (Table 5).

Subgroup analyzes were performed based on the presence or absence of a control group, dose, and intervention with silymarin or silymarin plus other compounds.

In the subgroup analysis based on having or not having a control group, a significant decrease in AST was observed in studies without control (WMD:-7.36 IU/L, 95% CI:-11.12, -3.61; I^2=91.6%, P for heterogeneity<0.001), but the result of the analysis of studies with control did not show a significant change (WMD: 4.84 IU/L, 95% CI: -4.31, 13.98; I^2=47.0%, P for heterogeneity=0.170). According to Figure 3, subgroup analysis based on having or not having a control group detects the heterogeneity sources.

Subgroup analysis based on the dose of silymarin was also performed, which showed that receiving a dose ≥ 600 mg/day causes a significant decrease in AST in cirrhosis (WMD: -9.29 IU/L, 95% CI:-15.54, -3.05; I^2=95.7%, P for heterogeneity<0.001). However, silymarin supplementation of less than 600 mg/day did not show a significant effect on AST (WMD: -2.79 IU/L, 95% CI: -9.56, 3.99; I^2=76.5%, P for heterogeneity=0.002) (Fig. 4).

Subgroup analysis based on intervention with silymarin (WMD:-6.68 IU/L, 95% CI:-11.63, -1.72; I^2=90.5%, P for heterogeneity<0.001) or silymarin plus other compounds (WMD:-2 IU/L, 95% CI:-3.36, -0.64; I^2=0.0%, P for heterogeneity<0.001) showed that in both cases, AST significantly decreases (Fig. 5).

No publication bias was observed in these studies through the Egger (p=0.277) and Begg (p=0.322) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, the exclusion of any study had no significant effect on the overall effect size of the findings.

Effect of Silymarin on ALT

Six trials with 7 arms have reported the effect of silymarin on ALT in patients with cirrhosis. Pooled analysis of these studies showed that silymarin significantly reduces ALT in these patients (WMD: -6.07 IU/L, 95% CI: -11.31, -0.84; I^2=96.1%, P for heterogeneity <0.001) (Fig. 6). Due to the high heterogeneity, we performed several subgroup analyses to find the source of heterogeneity (Table 5).

Subgroup analysis based on having or not having a control group detects the heterogeneity source. This subgroup analysis showed that silymarin causes a significant decrease in ALT in uncontrolled studies (WMD:-11.14 IU/L, 95% CI:-16.71, -5.58; I^2=96.4%, P for heterogeneity<0.001), but no reduction effect was observed in the analysis of controlled studies (WMD:6.66 IU/L, 95% CI:1.12, 12.19; I^2=25.7%, P for heterogeneity=0.246) (Fig. 7).

Subgroup analysis based on the dose of silymarin showed that receiving ≥600 mg/day caused a significant decrease in ALT (WMD: -10.91 IU/L, 95% CI: -17.45, -4.37; I^2=98.1%, P for

Table 5. Results of subgroup analysis

Subgroup	Effect size (n)	Pooled effect	I^2	p heterogeneity	p between subgroup heterogeneity
AST (IU/L)					
Control group					
Have a control group	2	4.84 (-4.31, 13.98)	47.0	0.170	0.028
Don't have a control group	6	-7.36 (-11.12, -3.61)	91.6	<0.001	
Dose					
<600 mg/day	5	-2.79 (-9.56, 3.99)	76.5	0.002	0.106
≥600 mg/day	3	-9.29 (-15.54, -3.05)	95.7	<0.001	
Intervention					
Only silymarin	7	-6.68 (-11.63, -1.72)	90.5	<0.001	0.094
Silymarin+other compounds	1	-2.00 (-3.36, -0.64)	0.0	<0.001	
ALT (IU/L)					
Control group					
Have a control group	2	6.66 (1.12, 12.19)	25.7	0.246	<0.001
Don't have a control group	5	-11.14 (-16.71, -5.58)	96.4	<0.001	
Dose					
<600 mg/day	4	-1.96 (-13.02, 9.09)	86.2	<0.001	<0.001
≥600 mg/day	3	-10.91 (-17.45, -4.37)	98.1	<0.001	
Bilirubin (mg/dL)					
Intervention					
Only silymarin	4	-0.09 (-0.18, -0.00)	0.0	0.465	<0.001
Silymarin+other compounds	1	0.1 (0.08, 0.12)	0.0	<0.001	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

heterogeneity<0.001), but less than 600 mg/day did not show a significant effect (WMD: -1.96 IU/L, 95% CI: -13.02, 9.09; I^2=86.2%, P for heterogeneity<0.001) (Fig. 8).

No publication bias was observed in these studies through the Egger (p: 0.606) and Begg (p=0.652) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, the exclusion of Parés et al.[39]'s study had a significant effect on the overall effect size of the findings. By excluding this study, the overall effect size was "95% CI: -0.16, 9.77."

Effect of Silymarin on Alkaline Phosphatase

Three studies have investigated the effect of silymarin on alkaline phosphatase in patients with cirrhosis.[39–41] Pooled analysis of these studies did not show significant changes in ALP (WMD:-14.45 IU/L, 95% CI:-30.45, 1.55; I^2=0.0%, P for heterogeneity=0.610) (Fig. 9). No heterogeneity was observed between the studies, so subgroup analysis was not performed. According to the Egger (p=0.206) and Begg (p=0.117) tests and the appearance of the funnel diagram, no publication bias was observed in these studies. In the sensitivity analysis, no significant effect on the overall effect size of the findings was observed during the exclusion of any study.

Effect of Silymarin on Bilirubin

So far, 4 studies[39–41,43] including 5 arms have investigated the effect of silymarin on bilirubin in patients with cirrhosis. Pooled analysis of these studies did not show a significant change in bilirubin (WMD: -0.03 mg/dL, 95% CI:-0.18, 0.12; I^2=78.6%, P for heterogeneity=0.001) (Fig. 10). Due to the heterogeneity of the studies, subgroup analysis was performed based on whether the intervention was done with silymarin or silymarin plus other compounds. With this subgroup analysis, the source of heterogeneity was found (Table 5).

This subgroup analysis showed that silymarin alone can significantly reduce bilirubin in cirrhosis (WMD:-0.09 mg/dL, 95% CI:-0.18, –0.00; I^2=0.0%, P for heterogeneity=0.465), but silymarin plus other compounds did not cause significant changes (WMD:0.1 mg/dL, 95% CI:0.08, 0.12; I^2=0.0%, P for heterogeneity<0.001) (Fig. 11).

Subgroup analyses based on the dose of silymarin showed that receiving more equal to 600 mg/day caused a significant decrease in bilirubin (WMD:-0.12 mg/dL, 95% CI:-0.24, –0.00; I^2=0.0%, P for heterogeneity<0.001), but <600 mg/day did not show a significant effect (WMD: 0.02 mg/dL, 95% CI:-0.12, 0.16; I^2=54.6%, P for heterogeneity=0.086) (Fig. 12).

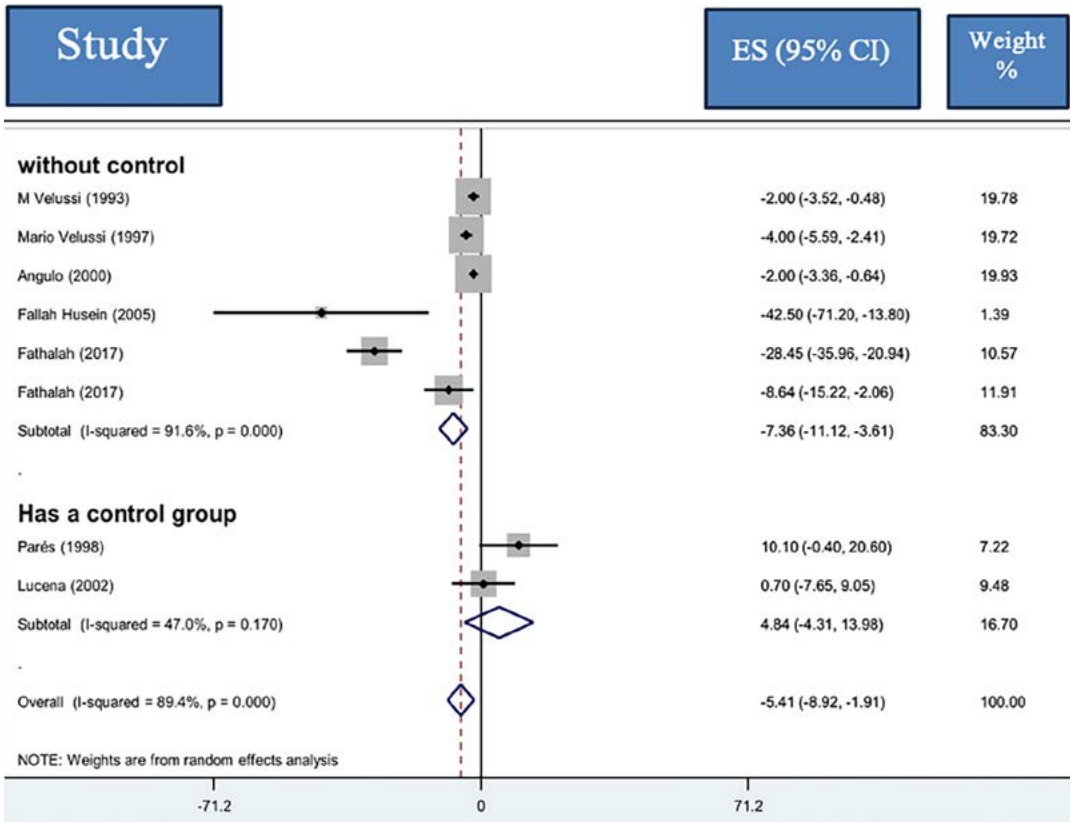


Figure 3. The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on having or not having a control group.

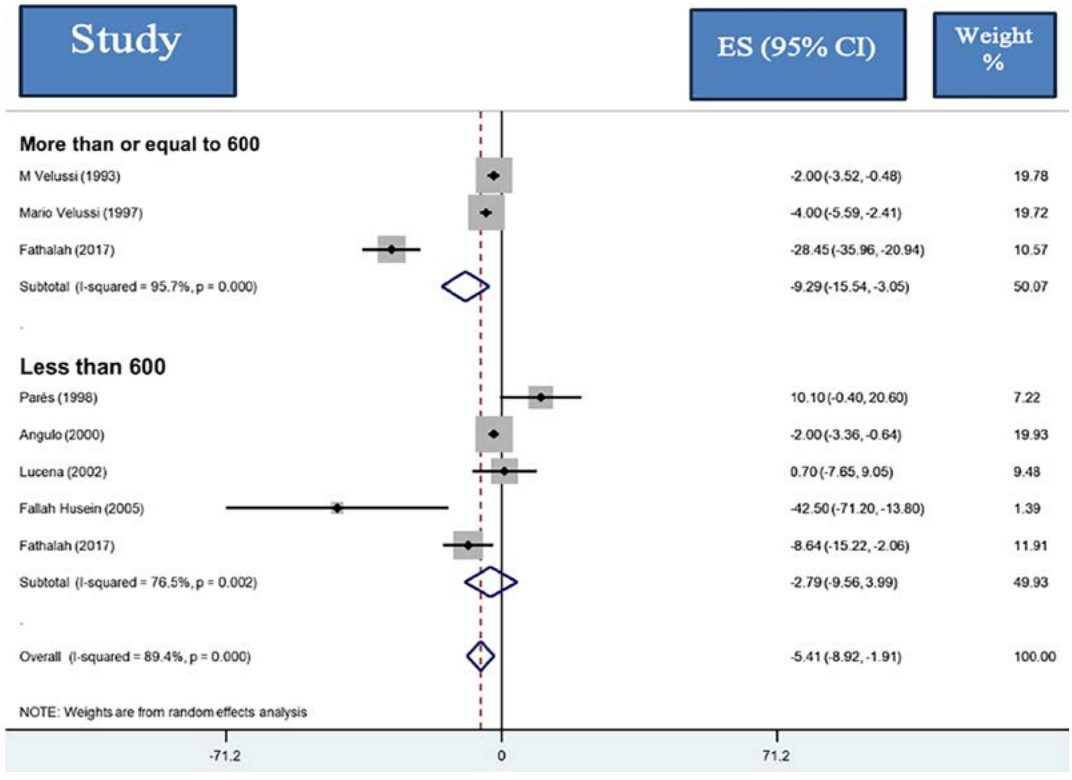


Figure 4. The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

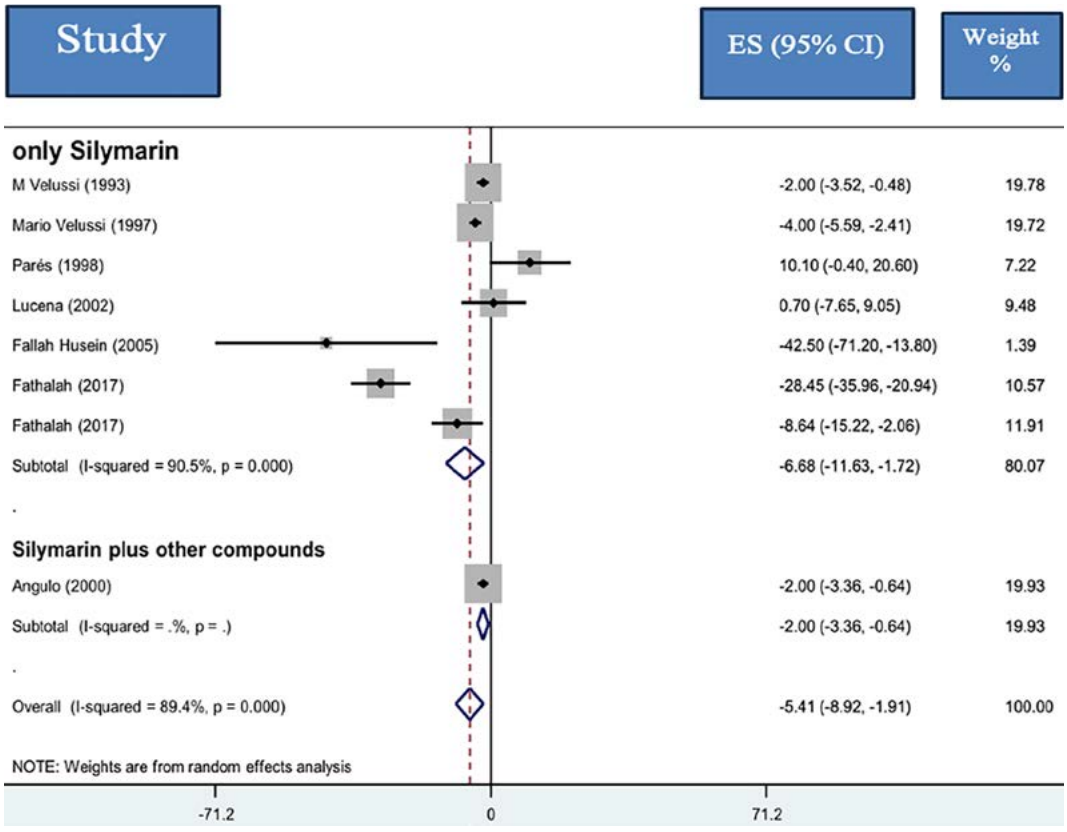


Figure 5. The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on intervention with silymarin or silymarin plus other compounds.

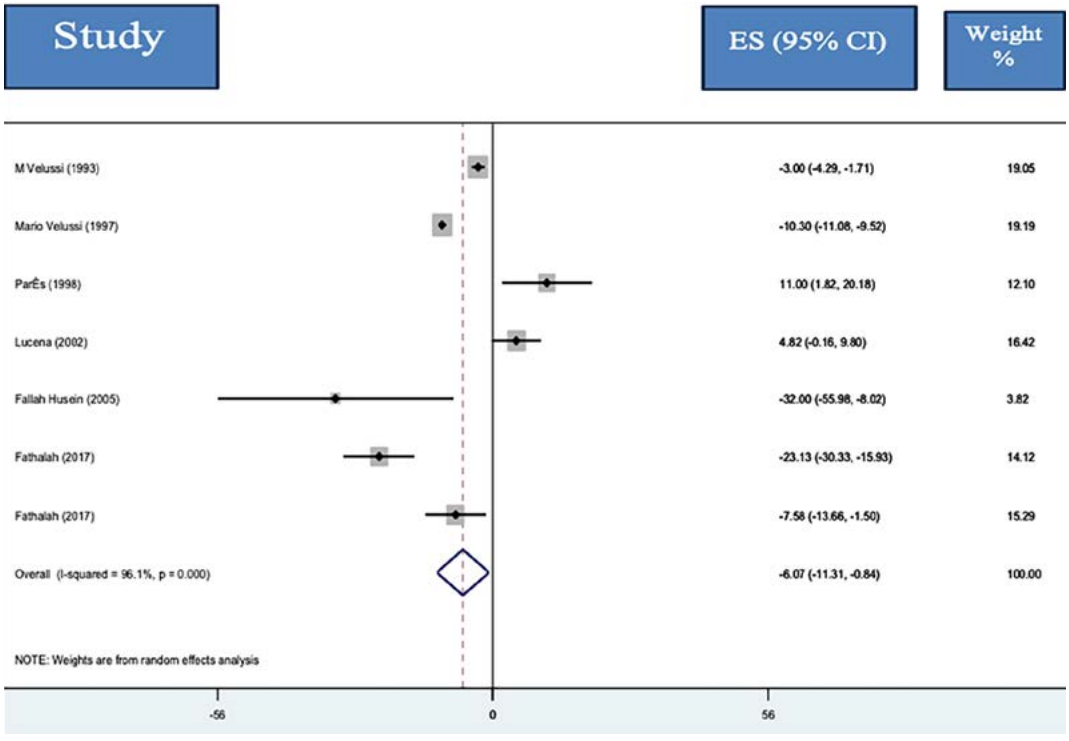


Figure 6. The effect of silymarin on alanine aminotransferase in cirrhotic patients.

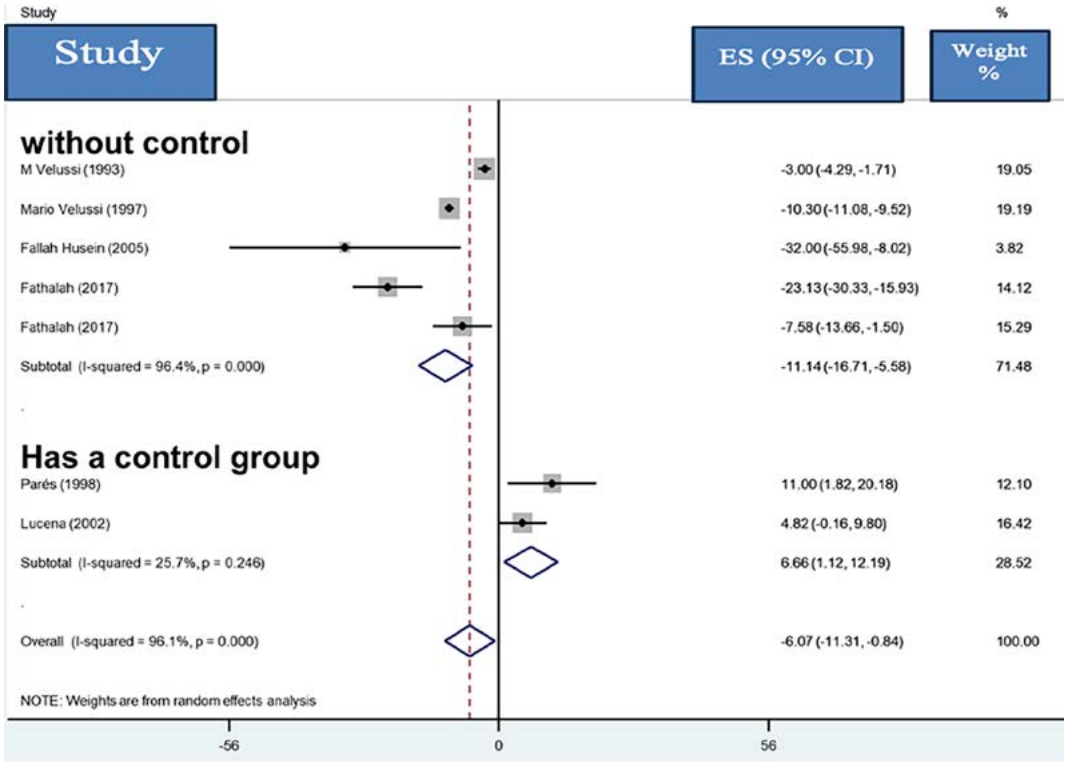


Figure 7. The effect of silymarin on alanine aminotransferase in cirrhotic patients. Subgroup analysis based on having or not having a control group.

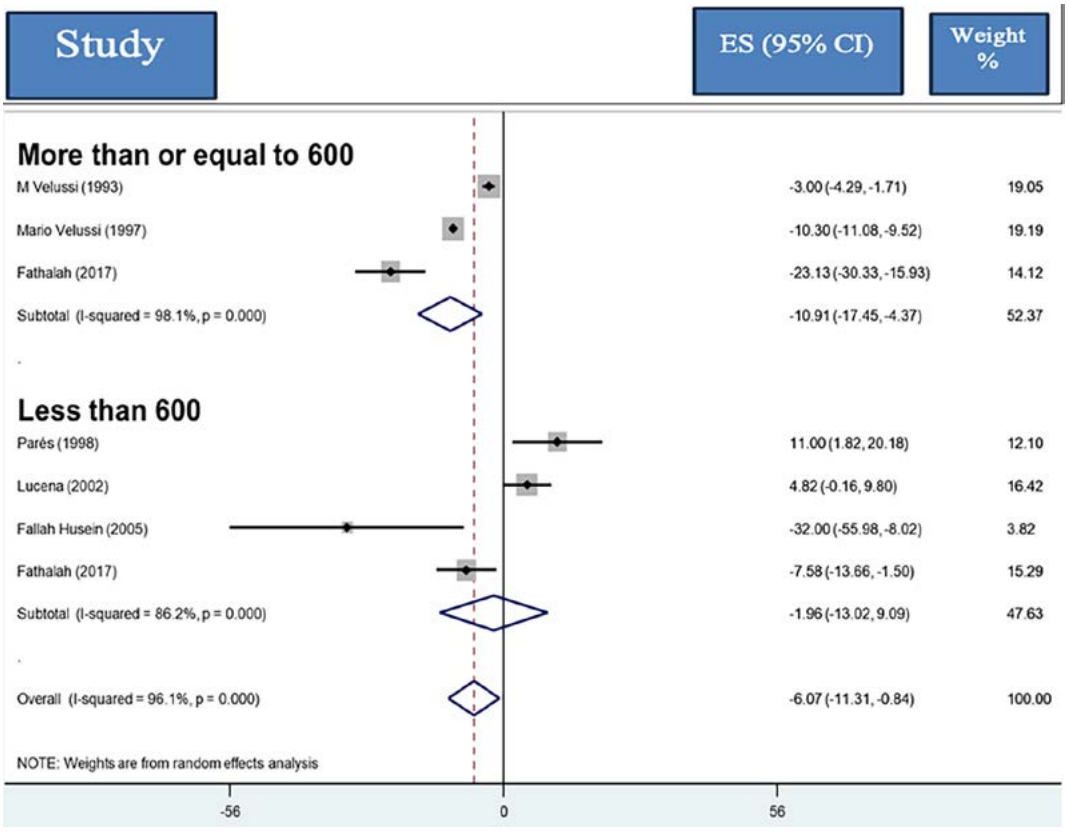


Figure 8. The effect of silymarin on alanine aminotransferase in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

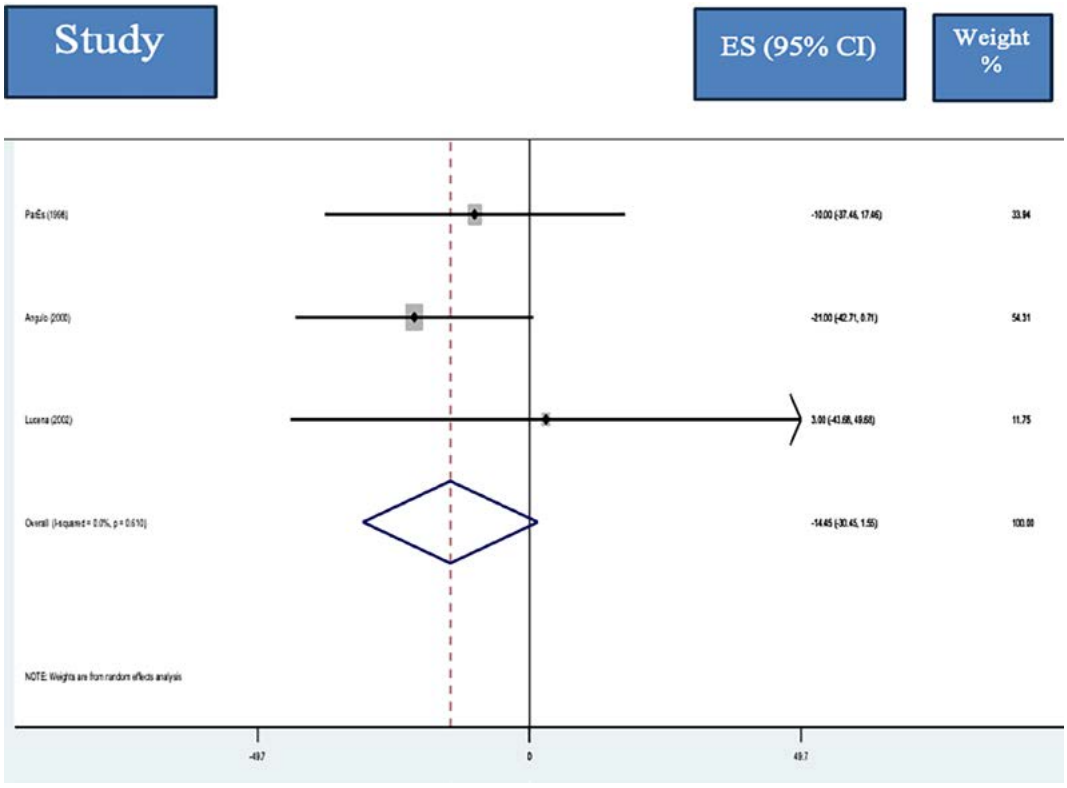


Figure 9. The effect of silymarin on alkaline phosphatase in cirrhotic patients.

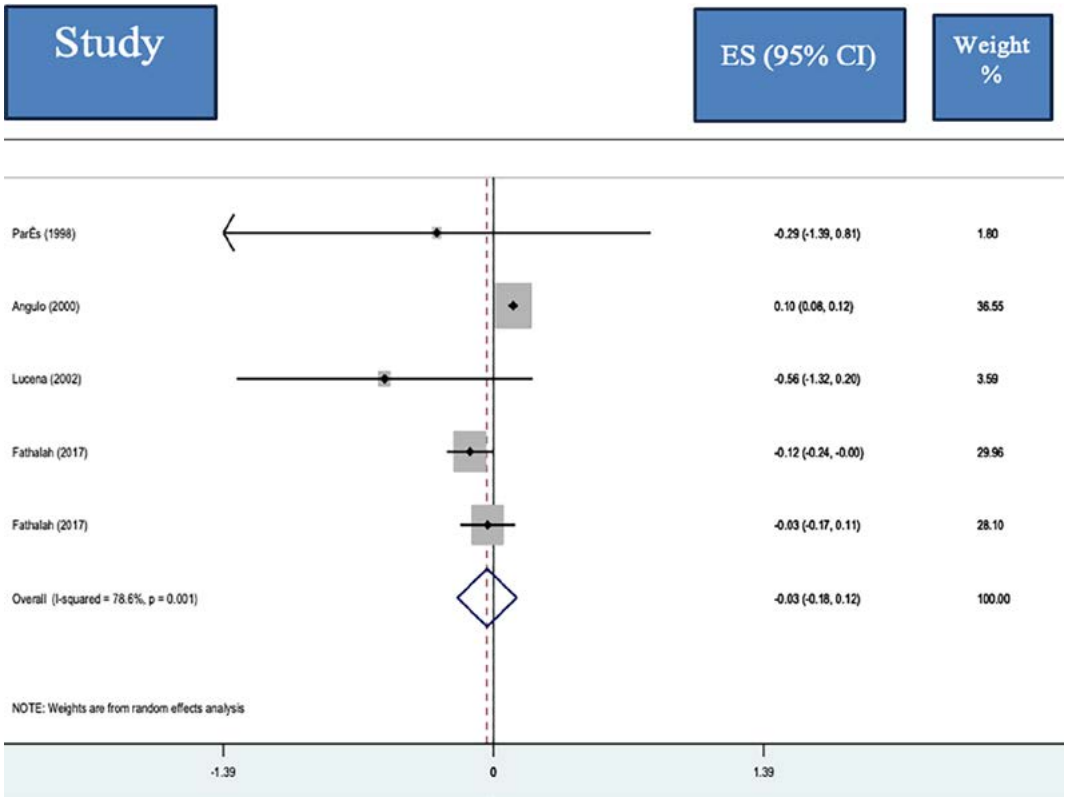


Figure 10. The effect of silymarin on bilirubin in cirrhotic patients.

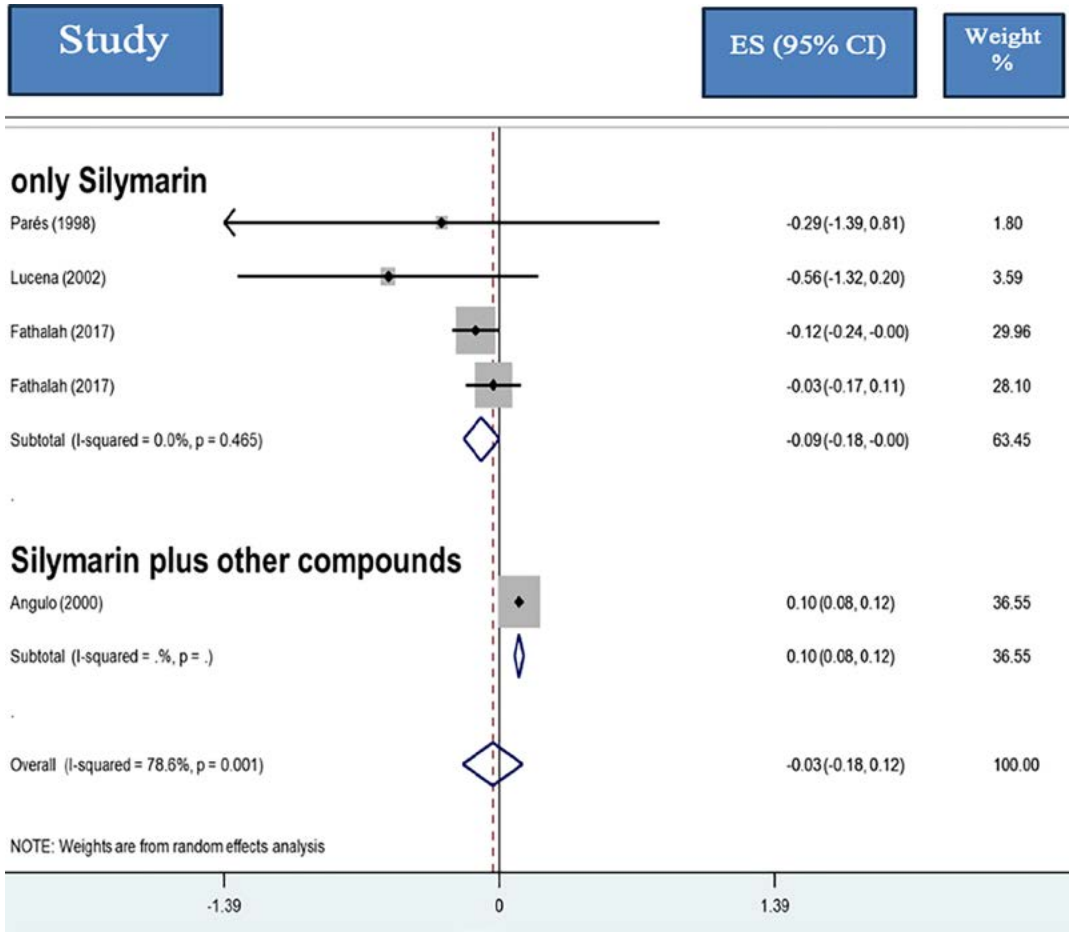


Figure 11. The effect of silymarin on bilirubin in cirrhotic patients. Subgroup analysis based on intervention with silymarin or silymarin plus other compounds.

In the subgroup analyses based on having or not having a control group, no significant results were reported in bilirubin changes; with control: (WMD: -0.47 mg/dL, 95% CI: -1.1, 0.15; I^2=0.0%, P for heterogeneity=0.692); without control: (WMD: -0.01 mg/dL, 95% CI: -0.16, 0.14; I^2=87%, P for heterogeneity<0.001) (Fig. 13).

No publication bias was observed in these studies through the Egger (p=0.076) and Begg (p=0.624) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, the exclusion of Angulo et al[40]'s study had a significant effect on the overall effect size of the findings. By excluding this study, the overall effect size was "95% CI: -0.18, -0.01".

Effect of Silymarin on Albumin

In general, 4 studies with 5 arms investigated the effect of silymarin on albumin in cirrhotic patients[39–41,43] The meta-analysis of these studies showed that albumin increased significantly in response to the silymarin supplementation (WMD: 0.08 g/dL, 95% CI:0.03, 0.14; I^2=0.0%, P for heterogeneity=0.691) (Fig. 14). Due to the lack of heterogeneity between studies, no subgroup analysis was performed. No publication bias was observed in these studies after performing the Egger (p=0.891) and Begg (p=0.624) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, no significant effect on the overall effect size of the findings was observed during the exclusion of any studies.

Discussion

The present systematic review and meta-analysis were conducted to investigate the effect of silymarin supplementation on cirrhosis. In general, eight trial studies with nine arms were included in this review. The results showed a significant decrease in AST and ALT and a significant increase in albumin. However, silymarin did not have a significant impact on alkaline phosphatase or bilirubin levels. Importantly, no serious adverse effects were reported, indicating a favorable safety profile. So far, many studies have suggested the safety of silymarin in many liver diseases, including cirrhosis.[22,27,29,30]

The observed reductions in AST and ALT levels after silymarin supplementation are of considerable clinical significance, as these enzymes serve as well-known biochemical markers of liver cell injury. In the context of cirrhosis, persistent elevations in AST and ALT levels indicate ongoing liver cell injury and inflammatory necrotic activity in the liver parenchyma.[44] Therefore, the reductions in these

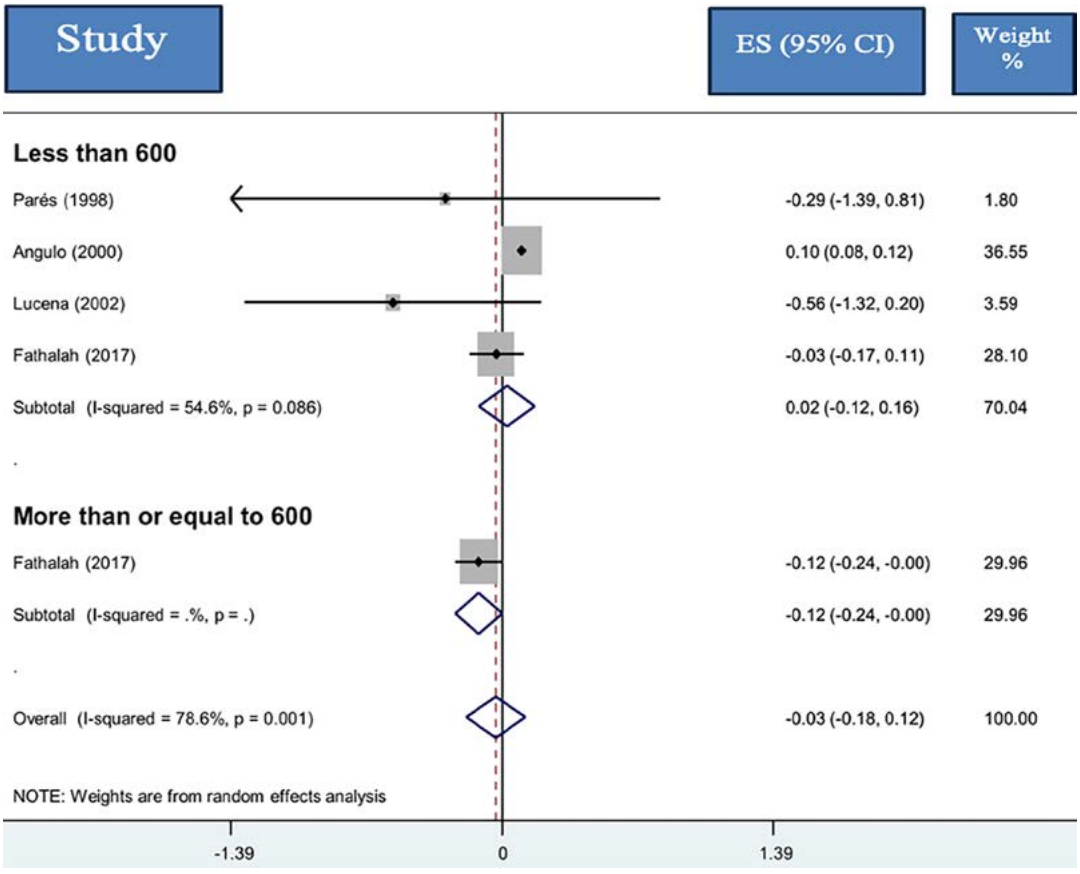


Figure 12. The effect of silymarin on Bilirubin in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

enzymes, as demonstrated in our analysis, may indicate a reduction in the extent of liver cell injury. These reductions could also indicate an improvement in the regenerative capacity of liver cells, as lower levels of transaminases may indicate stabilization or even reversal of some aspects of liver injury.[45]

Silymarin scavenges harmful free radicals produced during the liver's detoxification processes, increases levels of glutathione (a major intracellular antioxidant), and stimulates enzymes such as superoxide dismutase (SOD) that neutralize oxidative stress. This reduces oxidative damage to liver cells, which is the main cause of elevated transaminases.[46] Silymarin also inhibits the activation of NF-kB, a transcription factor that increases the expression of pro-inflammatory cytokines such as TNF-alpha and IL-6. By suppressing these inflammatory pathways and leukotriene formation, silymarin reduces liver inflammation, which helps to reduce AST and ALT levels.[23,47] In addition, silymarin inhibits the activation of hepatic stellate cells, which are responsible for the development of fibrosis, and modulates matrix metalloproteinases involved in tissue remodeling. It also enhances liver cell regeneration by stimulating protein synthesis and cell proliferation. These effects help stabilize or even reverse liver damage, as reflected by normalization or reduction of transaminase levels.[48,49]

In addition, the observed increase in serum albumin levels is particularly noteworthy. Hypoalbuminemia is a frequent and serious complication in patients with cirrhosis, resulting from a decrease in the liver's capacity to synthesize proteins as the disease progresses. Low albumin levels not only indicate impaired hepatic synthetic function, but are also strongly associated with adverse clinical outcomes, including an increased risk of ascites, edema, and a worse overall prognosis.[50] Therefore, improved albumin synthesis, as indicated by higher serum albumin concentrations, may indicate a significant increase in hepatic synthetic function. This could potentially lead to better clinical outcomes for patients, such as improved nutritional status, reduced complications related to fluid retention, and possibly even improved survival.[50] Taken together, these findings highlight the potential of silymarin as a supportive therapy in the management of cirrhosis, by helping to reduce liver cell damage and restore essential liver functions.

The lack of significant changes in alkaline phosphatase (ALP) and bilirubin levels after silymarin treatment suggests that its effects are more focused on protecting hepatocytes rather than improving cholestatic or excretory liver functions. ALP and bilirubin are markers typically elevated when bile flow is obstructed or impaired, indicating cholestasis.[51,52] Since these parameters did not improve significantly, it implies that silymarin primarily acts on liver cells themselves by reducing oxidative stress, inflammation, and stabilizing cell membranes, rather than directly affecting bile

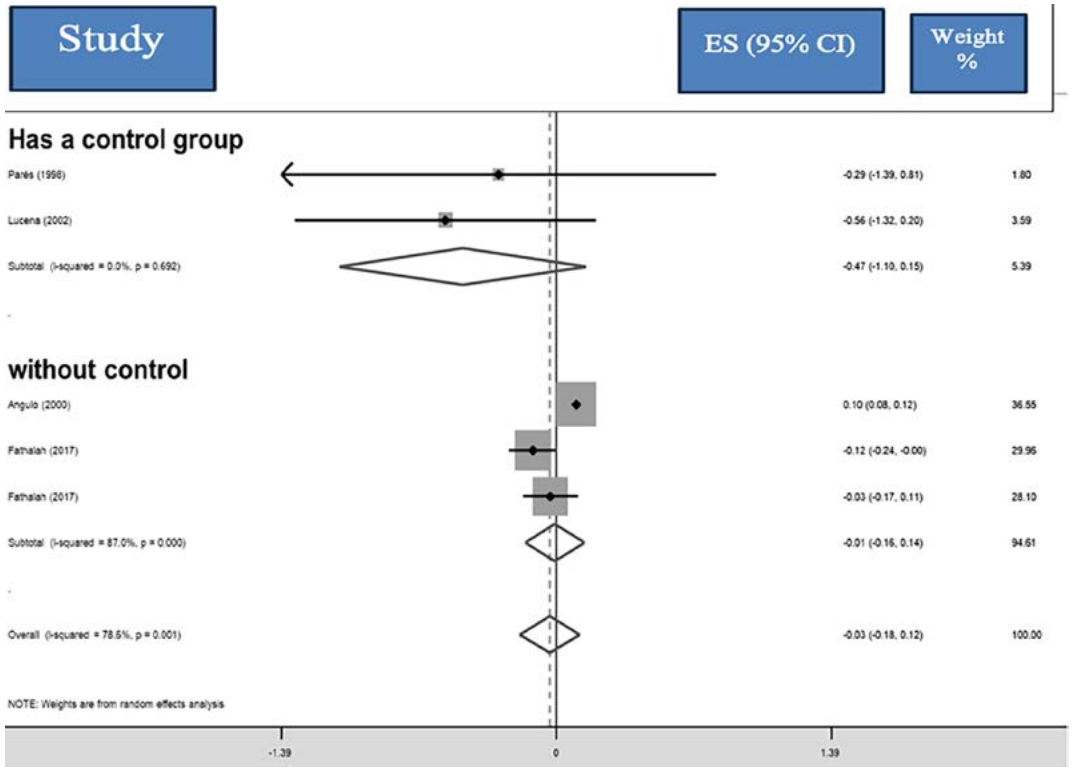


Figure 13. The effect of silymarin on Bilirubin in cirrhotic patients. Subgroup analysis based on having or not having a control group.

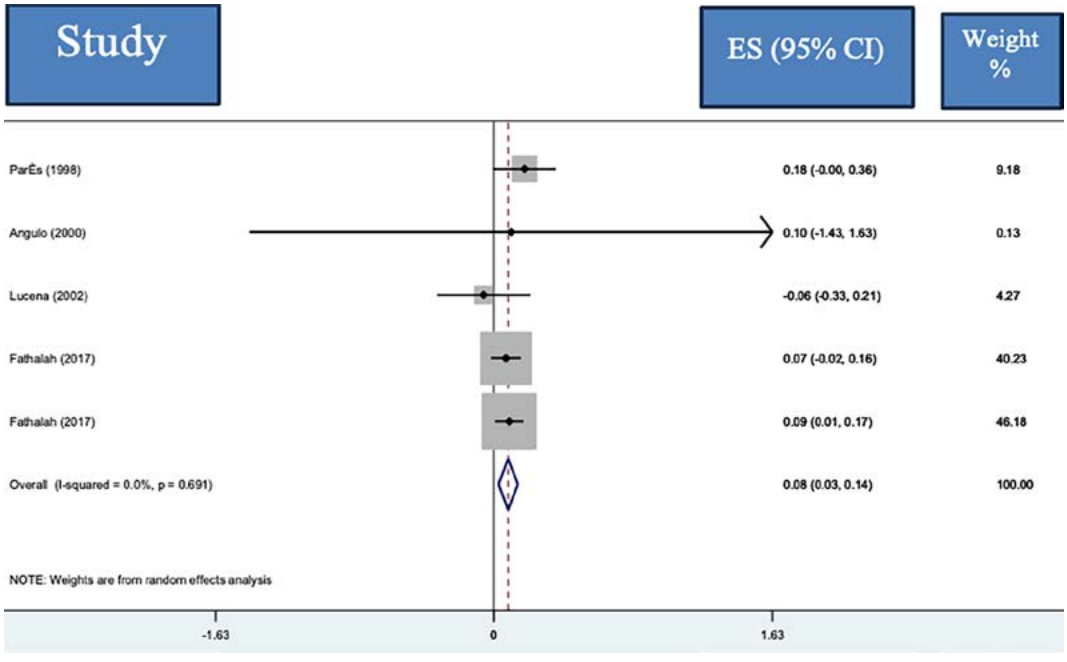


Figure 14. The effect of silymarin on the albumin in cirrhotic patients.

ducts or bile secretion pathways. This aligns with silymarin's well-documented antioxidative, anti-inflammatory, and membrane-stabilizing properties, which mainly target hepatocyte health and function rather than biliary processes.[53]

Inflammation can increase liver enzymes.[54] Two pro-inflammatory lipids, Platelet-activating factor (PAF) and lysophosphatidylcholine-PAF (lyso-PAF), are increased in liver cirrhosis and accelerate the disease process.[55] Lysophosphatidylcholine acyltransferases 1-4

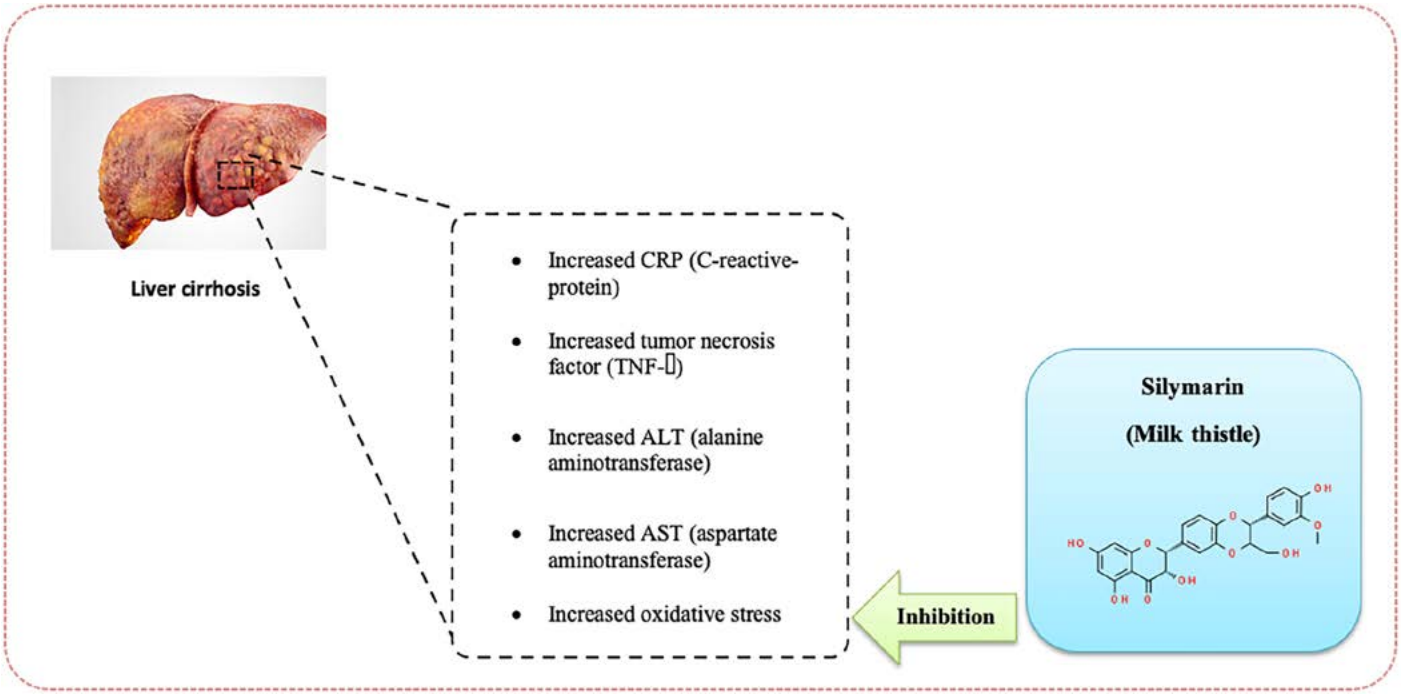


Figure 15. Possible mechanism of silymarin (milk thistle) on liver cirrhosis.

(LPCAT) are involved in PAF regeneration during inflammation.[56,57] silybin can decrease PAF and lyso-PAF in cirrhotic liver rats. This effect was attributed to the role of silybin in reducing the activity and expression of LPCAT1 and LPCAT2.[58] Therefore, silymarin is effective in improving liver enzymes by controlling inflammation, so it has hepatoprotective effects.[59,60] Also oxidative stress increases in cirrhosis.[61] Harmful oxidative factors caused by oxidative stress can increases bilirubin by destabilizing the red blood cell membrane.[62] A study reported that receiving oral silymarin at a dose of 200 mg/kg body weight, twice a week, for 8 weeks in rats with liver cirrhosis, improves cirrhosis and reduces its progression. This effect was attributed to a significant decrease in total bilirubin and ALT and an increase in antioxidant factors including SOD, MDA, and GSH.[24] In general, patients with cirrhosis have high inflammation (including increased CRP and TNF-α),[63,64] oxidative stress,[10,65] and an imbalance of liver enzymes.[66–68] Therefore, the improvement of each of the mentioned factors can slow down the course of the disease and even improve these patients.[16,69] Silymarin, a plant extract in milk thistle, with its antioxidant and anti-inflammatory effects, reduces harmful oxidative and inflammatory factors[70–73] and can regulate liver enzymes such as AST and ALT.[74–77] Therefore, this herbal extract will be useful in liver diseases, including cirrhosis[78,79] (Fig. 15).

In the sensitivity analysis of the studies that investigated ALT changes, there was a significant change in the overall effect size with the exclusion of Parés et al.'s study.[39] In this study, there is a longer period of supplementation (24 months)[39] compared to other studies in this field (3 to 12 months).[37,38,41–43] In the results of the sensitivity analysis of the studies that examined bilirubin, the exclusion of Angulo et al.'s study[40] had a significant effect on the overall effect size of the findings. In this study, silymarin along with UDCA was used as an intervention and there was no control group.

In our results, it was mentioned that the intervention with silymarin can cause a significant decrease in bilirubin, but silymarin plus other compounds did not have a significant effect. Importantly, only one study had an intervention with silymarin plus other compounds.[40] In this study, the intervention included silymarin plus UDCA and the patients in this study were primary biliary cirrhosis with a suboptimal response to UDCA. Considering the existence of only one study in this field, which has limitations such as the absence of a control group and a small sample size (n=27), it cannot be concluded that the combination of silymarin with other compounds cannot improve bilirubin in cirrhosis.

Subgroup analysis based on the dose of silymarin supplement showed that silymarin, only in ≥600 mg/day, caused a significant decrease in AST and ALT.

A recent meta-analysis examined the effect of silymarin in patients with liver diseases. The dose of silymarin received in the studies included in this meta-analysis was 210 to 700 mg/day. The results of this study showed the reducing effect of silymarin on transaminases (AST and ALT).[76] Another meta-analysis reported the effect of silymarin on the reduction of AST and ALT levels in NAFLD. The amount of silymarin received in the studies included in this meta-analysis was 140 to 2100 mg/day.[80]

A detailed and comprehensive search to find trials investigating the effect of silymarin on cirrhosis and performing subgroup analyses to find the sources of heterogeneity of studies are among the strengths of the present study. Limitations of our study include the lack of a control

group in some studies or the failure to report changes in the control group. Also, the small sample size of the studies, the small number of studies, and the lack of studies conducted within the last 8 years are limitations of this study. Therefore, according to the mentioned limitations, it is better to interpret the results of this study with caution.

Conclusion

The results of the present study showed that supplementation with silymarin in cirrhosis can cause a significant decrease in AST and ALT and a significant increase in albumin, but no significant changes in alkaline phosphatase and bilirubin in cirrhotic patients. In general, silymarin with a dose equal to or more than 600 mg/day has a better impact on ALT and AST. Although due to the small number of included studies, findings should be interpreted with caution, based on the results of this meta-analysis, silymarin might be considered as a potentially safe, inexpensive, and available agent for the treatment of cirrhosis, particularly with the dose ≥ 600 mg/day. The small number of studies, the small sample size, and the absence of a control group in many studies make it difficult to make a conclusive conclusion. Therefore, more well-designed randomized controlled trials with a higher sample size are needed to clarify the findings of this study.

Ethics Committee Approval: Ethics committee approval was not required because this study was a systematic review based solely on previously published data.

Conflict of Interest: The authors declare no conflicts of interest.

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References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383(9930):1749-1761. [CrossRef]
2. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. J Clin Gastroenterol 2015;49(8):690-696. [CrossRef]
3. Wiegand J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis: part 1 of a series on liver cirrhosis. Dtsch Arztebl Int 2013;110(6):85-91. [CrossRef]
4. Tang K-T, Dufour J-F, Chen P-H, Hernaez R, Hutfless S. Antitumour necrosis factor-α agents and development of new-onset cirrhosis or non-alcoholic fatty liver disease: a retrospective cohort. BMJ Open Gastroenterol 2020;7(1):e000349. [CrossRef]
5. Lu SC. Dysregulation of glutathione synthesis in liver disease. Liver Res 2020;4(2):64-73. [CrossRef]
6. Lai CY, Cheng SB, Lee TY, Liu HT, Huang SC, Huang YC. Possible synergistic effects of glutathione and c-reactive protein in the progression of liver cirrhosis. Nutrients. 2018 27;10(6):678. [CrossRef]
7. Czeczot H, Scibior D, Skrzycki M, Podsiad M. Glutathione and GSH-dependent enzymes in patients with liver cirrhosis and hepatocellular carcinoma. Acta Biochim Pol 2006;53(1):237-242. [CrossRef]
8. Vairappan B. Endothelial dysfunction in cirrhosis: Role of inflammation and oxidative stress. World J Hepatol 2015;7(3):443-459. [CrossRef]
9. Görg B, Qvartskhava N, Bidmon HJ, Palomero-Gallagher N, Kircheis G, Zilles K, Häussinger D. Oxidative stress markers in the brain of patients with cirrhosis and hepatic encephalopathy. Hepatology 2010;52(1):256-265. [CrossRef]
10. Natarajan SK, Thomas S, Ramamoorthy P, Basivireddy J, Pulimood AB, Ramachandran A, et al. Oxidative stress in the development of liver cirrhosis: a comparison of two different experimental models. J Gastroenterol Hepatol 2006;21(6):947-957. [CrossRef]
11. Zhou L, Wang S-B, Chen S-G, Qu Q, Rui J-A. Prognostic Value of ALT, AST, and AAR in Hepatocellular Carcinoma with B-Type Hepatitis-Associated Cirrhosis after Radical Hepatectomy. Clin Lab 2018;64(10):1739-1747. [CrossRef]
12. Ioannou GN, Green P, Lowy E, Mun EJ, Berry K. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. PLoS One 2018;13(9):e0204412. [CrossRef]
13. Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, et al. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. J Gastroenterol 2021;56(7):593-619. [CrossRef]
14. Smith A, Baumgartner K, Bositis C. Cirrhosis: Diagnosis and Management. Am Fam Physician 2019;100(12):759-770.
15. Chinese Society of Hepatology, Chinese Medical Association; Xu X, Duan Z, Ding H, Li W, Jia J, Wei L, et al. Chinese guidelines on the management of ascites and its related complications in cirrhosis. Hepatol Int 2019;13(1):1-21. [CrossRef]
16. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406-460. [CrossRef]
17. Ivashkin VT, Mayevskaya MV, Pavlov CS, Fedosyina YA, Bessonova YN, Pirogova IY, Garbuzenko DV. Treatment of liver cirrhosis complications: Clinical guidelines of the Russian Scientific Liver Society and Russian gastroenterological association. Russian J Gastroenterol Hepatol Coloproctol 2016;26(4):71-102. [CrossRef]
18. Ge PS, Runyon BA. Treatment of patients with cirrhosis. N Engl J Med 2016;375(8):767-777. [CrossRef]
19. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. Drugs 2001;61(14):2035-2063. [CrossRef]
20. Valková V, Ďúranová H, Bilčíková J, Habán M. Milk thistle (Silybum marianum): a valuable medicinal plant with several therapeutic purposes. J Microbiol Biotechnol and Food Sci 2021;9(4):836-843. [CrossRef]
21. Adetuyi BO, Omolabi FK, Olajide PA, Oloke JK. Pharmacological, biochemical and therapeutic potential of milk thistle (silymarin): a review. World News Nat Sci 2021;37:75-91.
22. Gillesen A, Schmidt HHJ. Olacak. Silymarin as supportive treatment in liver diseases: A narrative review. Adv Ther 2020;37(4):1279-1301. [CrossRef]

23. Federico A, Dallio M, Loguercio C. Silymarin/silybin and chronic liver disease: a marriage of many years. Molecules 2017;22(2):191. [CrossRef]
24. Zaidi SNF, Mahboob T. Prevention of liver cirrhosis by Silymarin. Pak J Pharm Sci. 2017;30(4):1203-1211.
25. Ferenci P. Silymarin in the treatment of liver diseases: What is the clinical evidence? Clin Liver Dis (Hoboken) 2016;7(1):8-10. [CrossRef]
26. Kim SH, Oh DS, Oh JY, Son TG, Yuk DY, Jung YS. silymarin prevents restraint stress-induced acute liver injury by ameliorating oxidative stress and reducing inflammatory response. Molecules 2016;21(4):443. [CrossRef]
27. Abenavoli L, Izzo AA, Milić N, Cicala C, Santini A, Capasso R. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytother Res 2018;32(11):2202-2213. [CrossRef]
28. Bahmani M, Shirzad H, Rafieian S, Rafieian-Kopaei M. Silybum marianum: beyond hepatoprotection. J Evid Based Complementary Altern Med 2015;20(4):292-301. [CrossRef]
29. Soleimani V, Delghandi PS, Moallem SA, Karimi G. Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review. Phytother Res 2019;33(6):1627-1638. [CrossRef]
30. Fehér J, Lengyel G. Silymarin in the prevention and treatment of liver diseases and primary liver cancer. Curr Pharm Biotechnol 2012;13(1):210-217. [CrossRef]
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10(1):89. [CrossRef]
32. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions. New York: John Wiley & Sons; 2019. [CrossRef]
33. Begg CB. Publication bias. The Handbook of Research Synthesis. New York: Russell Sage Foundation; 1994. p. 299-409.
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-634. [CrossRef]
35. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions. New York: Wiley Online Library; 2019. p. 241-284. [CrossRef]
36. Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. Hepatology 1989;9(1):105-113. [CrossRef]
37. Velussi M, Cernigoi A, Viezzoli L, Dapas F, Caffau C, Zilli M. Silymarin reduces hyperinsulinemia, malondialdehyde levels, and daily insulin need in cirrhotic diabetic patients. Curr Ther Res 1993;53(5):533-545. [CrossRef]
38. Velussi M, Cernigoi AM, De Monte A, Dapas F, Caffau C, Zilli M. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. J Hepatol 1997;26(4):871-879. [CrossRef]
39. Parés A, Planas R, Torres M, Caballería J, Viver JM, Acero D, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol 1998;28(4):615-621. [CrossRef]
40. Angulo P, Patel T, Jorgensen RA, Therneau TM, Lindor KD. Silymarin in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. Hepatology 2000;32(5):897-900. [CrossRef]
41. Lucena MI, Andrade RJ, de la Cruz JP, Rodriguez-Mendizabal M, Blanco E, Sánchez de la Cuesta F. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. Int J Clin Pharmacol Ther 2002;40(1):2-8. [CrossRef]
42. Fallah Huseini H, Alavian S, Toliat T, Jamshidi A, Heshmat R, Naghdi Badi H, et al. The efficacy of herbal medicine Khar Maryam (Silybum marianum (L.) Gaertn.) on liver cirrhosis in chronic hepatitis B patients. J Med Plants 2005;4(13):1-6.
43. Fathalah WF, Abdel Aziz MA, Abou el Soud NH, El Raziky MES. High dose of silymarin in patients with decompensated liver disease: a randomized controlled trial. J Interferon Cytokine Res 2017;37(11):480-487. [CrossRef]
44. Czaja AJ. Hepatic inflammation and progressive liver fibrosis in chronic liver disease. World J Gastroenterol 2014;20(10):2515-2532. [CrossRef]
45. Forbes SJ, Newsome PN. Liver regeneration - mechanisms and models to clinical application. Nat Rev Gastroenterol Hepatol 2016;13(8):473-485. [CrossRef]
46. Dhande D, Dhok A, Anjankar A, Nagpure S. Silymarin as an antioxidant therapy in chronic liver diseases: A comprehensive review. Cureus 2024;16(8):e67083. [CrossRef]
47. Cacciapuoti F, Scognamiglio A, Palumbo R, Forte R, Cacciapuoti F. Silymarin in non alcoholic fatty liver disease. World J Hepatol 2013;5(3):109-113. [CrossRef]
48. Calderon Martinez E, Herrera D, Mogan S, Hameed Z, Jangda AA, Khan TJ, et al. Impact of silymarin supplements on liver enzyme levels: A systematic review. Cureus 2023;15(10):e47608. [CrossRef]
49. Clichici S, Olteanu D, Nagy A-L, Oros A, Filip A, Mircea PA. Silymarin inhibits the progression of fibrosis in the early stages of liver injury in CCl4-treated rats. J Med Food 2015;18(3):290-298. [CrossRef]
50. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol 2014;4(4):302-311. [CrossRef]
51. Kalas MA, Chavez L, Leon M, Taweesedt PT, Surani S. Abnormal liver enzymes: A review for clinicians. World J Hepatol 2021;13(11):1688-1698. [CrossRef]
52. Poupon R. Liver alkaline phosphatase: a missing link between choleresis and biliary inflammation. Hepatology 2015;61(6):2080-2090. [CrossRef]
53. Vargas-Mendoza N, Madrigal-Santillán E, Morales-González A, Esquivel-Soto J, Esquivel-Chirino C, García-Luna Y, et al. Hepatoprotective effect of silymarin. World J Hepatol 2014;6(3):144-149. [CrossRef]
54. Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, et al. Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. Arterioscler Thromb Vasc Biol 2005;25(1):193-197. [CrossRef]
55. Yang Y, Nemoto E, Harvey S, Subbotin V, Gandhi C. Increased hepatic platelet activating factor (PAF) and PAF receptors in carbon tetrachloride induced liver cirrhosis. Gut 2004;53(6):877-883. [CrossRef]
56. Zhao Y, Chen Y-Q, Bonacci TM, Bredt DS, Li S, Bensch WR, et al. Identification and characterization of a major liver lysophosphatidylcholine acyltransferase. J Biol Chem 2008;283(13):8258-8265. [CrossRef]
57. Harayama T, Shindou H, Ogasawara R, Suwabe A, Shimizu T. Identification of a novel noninflammatory biosynthetic pathway of platelet-activating factor. J Biol Chem 2008;283(17):11097-11106. [CrossRef]
58. Stanca E, Serviddio G, Bellanti F, Vendemiale G, Siculella L, Giudetti AM. Down-regulation of LPCAT expression increases platelet-activating factor level in cirrhotic rat liver: potential antiinflammatory effect of silybin. Biochim Biophys Acta 2013;1832(12):2019-2026. [CrossRef]

59. Guo Y, Wang S, Wang Y, Zhu T. Silymarin improved diet-induced liver damage and insulin resistance by decreasing inflammation in mice. Pharm Biol 2016;54(12):2995-3000. [CrossRef]
60. Freitag AF, Cardia GF, da Rocha BA, Aguiar RP, Silva-Comar FM, Spironello RA, et al. Hepatoprotective effect of silymarin (Silybum marianum) on hepatotoxicity induced by acetaminophen in spontaneously hypertensive rats. Evid Based Complement Alternat Med 2015;2015:538317. [CrossRef]
61. Gracia-Sancho J, Laviña B, Rodríguez-Vilarrupla A, García-Calderó H, Fernández M, Bosch J, García-Pagán JC. Increased oxidative stress in cirrhotic rat livers: a potential mechanism contributing to reduced nitric oxide bioavailability. Hepatology 2008;47:1248-1256. [CrossRef]
62. Wagner GM, Lubin BH, Chiu DT-Y. Oxidative damage to red blood cells. In Chow CK (editor). Cellular Antioxidant Defense Mechanisms. Boca Raton, Florida: CRC Press; 2019. p. 185-196. [CrossRef]
63. Girón-González JA, Martínez-Sierra C, Rodriguez-Ramos C, Macías MA, Rendón P, Díaz F, et al. Implication of inflammation-related cytokines in the natural history of liver cirrhosis. Liver Int 2004;24(5):437-445. [CrossRef]
64. Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, et al. The systemic inflammation hypothesis: towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol 2021;74(3):670-685. [CrossRef]
65. Geetha A, Priya ML, Jeyachristy SA, Surendran R. Level of oxidative stress in the red blood cells of patients with liver cirrhosis. Indian J Med Res 2007;126(3):204-210.
66. Park GJH, Lin BP, Ngu MC, Jones DB, Katelaris PH. Aspartate aminotransferase: alanine aminotransferase ratio in chronic hepatitis C infection: is it a useful predictor of cirrhosis? Journal of gastroenterology and hepatology 2000;15(4):386-390. [CrossRef]
67. Nyblom H, Björnsson E, Simrén M, Aldenborg F, Almer S, Olsson R. The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver Int 2006;26(7):840-845. [CrossRef]
68. Alempijevic T, Krstic M, Jesic R, Jovanovic I, Milutinovic AS, Kovacevic N, et al. Biochemical markers for non-invasive assessment of disease stage in patients with primary biliary cirrhosis. World J Gastroenterol 2009;15(5):591-594. [CrossRef]
69. Bernardi M, Caraceni P. Novel perspectives in the management of decompensated cirrhosis. Nat Rev Gastroenterol Hepatol 2018;15:753-764. [CrossRef]
70. Shaker E, Mahmoud H, Mnaa S. Silymarin, the antioxidant component and Silybum marianum extracts prevent liver damage. Food Chem Toxicol 2010;48(3):803-806 [CrossRef]
71. El-Lakkany NM, Hammam OA, El-Maadawy WH, Badawy AA, Ain-Shoka AA, Ebeid FA. Anti-inflammatory/anti-fibrotic effects of the hepatoprotective silymarin and the schistosomicide praziquantel against Schistosoma mansoni-induced liver fibrosis. Parasit Vectors 2012;5:9. [CrossRef]
72. Camini FC, Costa DC. Silymarin: not just another antioxidant. J Basic Clin Physiol Pharmacol 2020;31(4):/j/jbcpp.2020.31.issue-4/jbcpp-2019-0206/jbcpp-2019-0206.xml. [CrossRef]
73. Abdel-Moneim AM, Al-Kahtani MA, El-Kersh MA, Al-Omair MA. Free radical-scavenging, anti-inflammatory/anti-fibrotic and hepatoprotective actions of taurine and silymarin against CCl4 induced rat liver damage. PLoS One 2015;10(12):e0144509. [CrossRef]
74. Tsai JH, Liu JY, Wu TT, Ho PC, Huang CY, Shyu JC, et al. Effects of silymarin on the resolution of liver fibrosis induced by carbon tetrachloride in rats. J Viral Hepat 2008;15(7):508-514. [CrossRef]
75. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: a systematic review. J Viral Hepat 2005;12(6):559-567. [CrossRef]
76. de Avelar CR, Pereira EM, de Farias Costa PR, de Jesus RP, de Oliveira LPM. Effect of silymarin on biochemical indicators in patients with liver disease: Systematic review with meta-analysis. World J Gastroenterol 2017;23(27):5004-5017. [CrossRef]
77. Chen IS, Chen YC, Chou CH, Chuang RF, Sheen LY, Chiu CH. Hepatoprotection of silymarin against thioacetamide-induced chronic liver fibrosis. J Sci Food Agric 2012;92(7):1441-1447. [CrossRef]
78. Tighe SP, Akhtar D, Iqbal U, Ahmed A. Chronic liver disease and silymarin: A biochemical and clinical review. J Clin Transl Hepatol 2020;8(4):454-458. [CrossRef]
79. Freedman N, Curto T, Morishima C, Seeff L, Goodman Z, Wright E, Sinha R, et al. Silymarin use and liver disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Aliment Pharmacol Ther 2011;33(1):127-137. [CrossRef]
80. Kalopitas G, Antza C, Doundoulakis I, Siargkas A, Kouroumalis E, Germanidis G, et al. Impact of Silymarin in individuals with nonalcoholic fatty liver disease: A systematic review and meta-analysis. Nutrition 2021;83:111092. [CrossRef]