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Effects of Artichoke Supplementation on Liver Enzymes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Studies examining the effect of artichoke on liver enzymes have reported inconsistent results. This systematic review and meta-analysis aimed to assess the effects of artichoke administration on the liver enzymes. PubMed, Embase, the Cochrane Library, and Scopus databases were searched for articles published up to January 2022. Standardized mean difference (Hedges' g) were analyzed using a random-effects model. Heterogeneity, publication bias, and sensitivity analysis were assessed for the liver enzymes. Pooled analysis of seven randomized controlled trials (RCTs) suggested that the artichoke administration has an effect on both alanine aminotransferase (ALT) (Hedges' g, −1.08; 95% confidence interval [CI], −1.76 to −0.40; p = 0.002), and aspartate aminotransferase (AST) (Hedges' g, −1.02; 95% CI, −1.76 to −0.28; p = 0.007). Greater effects on ALT were detected in trials that lasted ≤8 weeks. Also, greater effects on AST were detected in trials using > 500 mg artichoke. Overall, this meta-analysis demonstrated artichoke supplementation decreased ALT and AST.

Keywords: Artichoke; Liver enzymes; Alanine aminotransferase; Aspartate aminotransferase

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver disorders in developed countries and its incidence continues to increase [1,2]. Furthermore, the general term is known as nonalcoholic steatohepatitis (NASH) which is caused by increasing oxidative stress, hepatocellular inflammation, and insulin resistance [3,4]. There are routine approaches for the treatment of this disorder such as weight loss, changes in dietary

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Amini MR; Data curation: Amini MR; Formal analysis: Amini MR; Methodology: Sheikhhossein F; Project administration: Hekmatdoost A; Supervision: Hekmatdoost A; Writing - original draft: Djafari F, Bazshahi E, Talebyan A; Writing - review & editing: Sheikhhossein F, Amini MR.

composition, and lifestyle modifications However, herbal substances have always received a lot of attention as an alternative approach to treating chronic diseases such as NASH [5,6].

Based on some evidence, one of the plants used for the protection of hepatocytes is artichoke (*Cynara scolymus*) [7-9]. It is grown in countries in the Mediterranean region that have a high concentration of natural antioxidants such as mono-caffeoylquinic acid and dicaffeoylquinic acid (cynarin and chlorogenic acid), caffeic acid, and the volatile sesquiterpine and flavonoids [10] and it also has an antimicrobial [11] and cholesterol decreasing effects [12]. Artichoke can have protective effects against NAFLD by reducing the production of reactive oxygen species [13], lipid peroxidation [9], and protein oxidation and increasing the activity of glutathione peroxidase [14].

Some in vitro, animal, and human studies evaluated the potential antioxidant effect of artichoke on hepatocytes [15-18]. In a study conducted by Panahi et al. [17], treatment with artichoke leaf extract (ALE) significantly lowered aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and improved AST/ALT ratio compared with the placebo group. However, Fallah Huseini et al. [19] did not find any significant effects on ALT and AST for ALE group in comparison with the control group.

Therefore, since studies were inconsistent in this regard, this systematic review and meta-analysis aimed to assess the effect of artichoke on liver enzymes function.

MATERIALS AND METHOD

Literature search and selection

The present study was performed using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [20]. Electronic databases including PubMed, Cochrane library, Scopus, and Embase were searched for articles published up to January 2022. We used Medical Subject Headings (MeSH) terms, abstracts, and keywords without any limitation in the search. **Supplementary Table 1** provides details of the search terms. The reference lists of the retrieved articles were also reviewed to avoid missing any publication. The literature search procedure was developed and performed by two reviewers (MRA and FS) separately and in duplicate. Any differences were resolved by a discussion with the principal investigator (AH).

Inclusion and exclusion criteria

Two of the authors identified eligible publications independently via reading titles, abstracts, and their full texts, if necessary. The PICOS model [21] for the definition of the inclusion criteria was applied: Population (adults aged > 18 years), intervention (artichoke), comparator (placebo), outcome (ALT and AST), and study design (parallel and cross-over clinical trial). Studies were included if they: 1) were RCT studies conducted on the human population; 2) reported mean and standard derivation (SD) of ALT and AST. We also included only English-language publications in the present study. We excluded studies with less than 2 weeks' intervention duration and publications without any comparing control group. We also excluded letters, books, comments, conference papers, animal and observational studies, non-interventional studies, and reviews. If the same dataset had been published in more than one article, we included the one with the greatest number of participants. Any disagreements about the article choice process were resolved by direct discussion.

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Data extraction

Two investigators (MAR and FS) independently extracted data from the studies. The main data were extracted from the included publication using a pre-designed abstraction from general features of studies, reported. When the outcomes were reported at different intervention duration, only the final results were included in the analysis. When necessary, the corresponding author was contacted by the investigators to acquire missing information. Any differences were resolved by a discussion with the principal investigator (AH).

Quality assessment of the studies

We assessed the quality of the included studies using Cochrane Collaboration's tool [22]. This tool divided quality into 5 domains: randomization process, deviations from the intended interventions, missing data, outcome measurement, and selection of the reported result (**Table 1**). Quality of individual publications were conducted by two independent investigators (MAR and FS). Any differences were resolved by a discussion with the principal investigator (AH).

Statistical analysis

Bias-corrected standardized mean difference (Hedge's g method) and its 95% confidence interval (CI) was computed to quantify the effects of artichoke on liver enzymes. Mean and SD values of the baseline and the end of the trials in both intervention and control groups were pooled to estimate the effect of artichoke on ALT and AST. When studies did not report mean and SD, the available statistical data was converted into mean and SD using the suitable formula: $SD_{difference}$ = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2 \times R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) 0.8 as it is a conservative estimate for an expected range of 0–1 [23]. When means (± SD) of outcome measures were not directly available and a standard error of the mean (SEM) was reported in place of SD, we converted it to SD using this formula: SD = SEM × √n, being "n" the number of participants in each group. Numerical data were extracted from graphs GetData Graph Digitizer version 2.24 [24].

Firstly, we performed a fixed-effect model to determine the effect with a forest plot. The I-squared statistic was used to define the degree of heterogeneity. I^2 values greater than 50% were considered as significant heterogeneity between studies. If there was significant between-study heterogeneity, a random-effects model (DerSimonian and Laird) was applied; otherwise, a fixed-effect model was performed [25]. Subgroup analysis was performed to detect potential sources of heterogeneity. These analyses were based on intervention and duration of supplementation, sample size, dosage, and mean age. Any publication bias was investigated by visually inspecting funnel plots and quantitatively evaluated using the Egger's test [26]. Meta-analysis was conducted using Stata software, version 14.0 (Stata Corp LP, College Station, TX, USA). The p values less than 0.05 were considered to be statistically significant.

Table 1. Risk of bias for randomized controlled trials, assessed according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Publications	Year	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
1. Englisch et al. [27]	2000	L	L	L	L	L	L
2. Roghani-Dehkordi and Kamkhah [30]	2009	L	L	L	L	L	L
3. Fallah Huseini et al. [19]	2012	L	L	L	L	S	L
4. Rangboo et al. [29]	2016	L	L	S	L	L	L
5. Panahi et al. [17]	2018	L	L	L	L	L	L
6. Musolino et a. [28]	2020	L	L	L	L	L	L
7. Rondanelli et al. [31]	2020	L	L	L	L	L	L

L, Low risk of bias; H, High risk of bias; S, Some concerns.

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RESULTS

Selection and identification of studies

We found 1,507 studies through database searching plus one publication through hand searching, of which 168 records were duplicates. After exclusion of duplicate publications, a total of 1,340 publications were screened by title and abstract. We excluded animal studies (n = 135), unrelated studies (n = 1,074), and reviews (n = 114). Finally, 17 publications remained for full-text review. After a full-text review, ten studies were excluded: 3 with an irrelevant intervention, 1 without a placebo-controlled group, 2 with insufficient data, and 3 with conference abstracts. We also excluded another study with complex intervention. Finally, seven studies were included in the systematic review and meta-analysis [27-33]. **Figure 1** shows a flow diagram of study selection.

Characteristics of the studies

In total, 8 effect sizes were extracted from 7 clinical trials conducted on 575 participants (**Table 2**). The mean age of participants ranged from 42.5 to 51.5 years. The studies on hypercholesterolemia [27,30], NAFLD [17,28], type 2 diabetes [19], NASH [29] and overweight patients [31] were included. The clinical trials were released in the period from 2000 to 2020. The studies were conducted in Iran [17,19,29,30], Italy [29,33], and

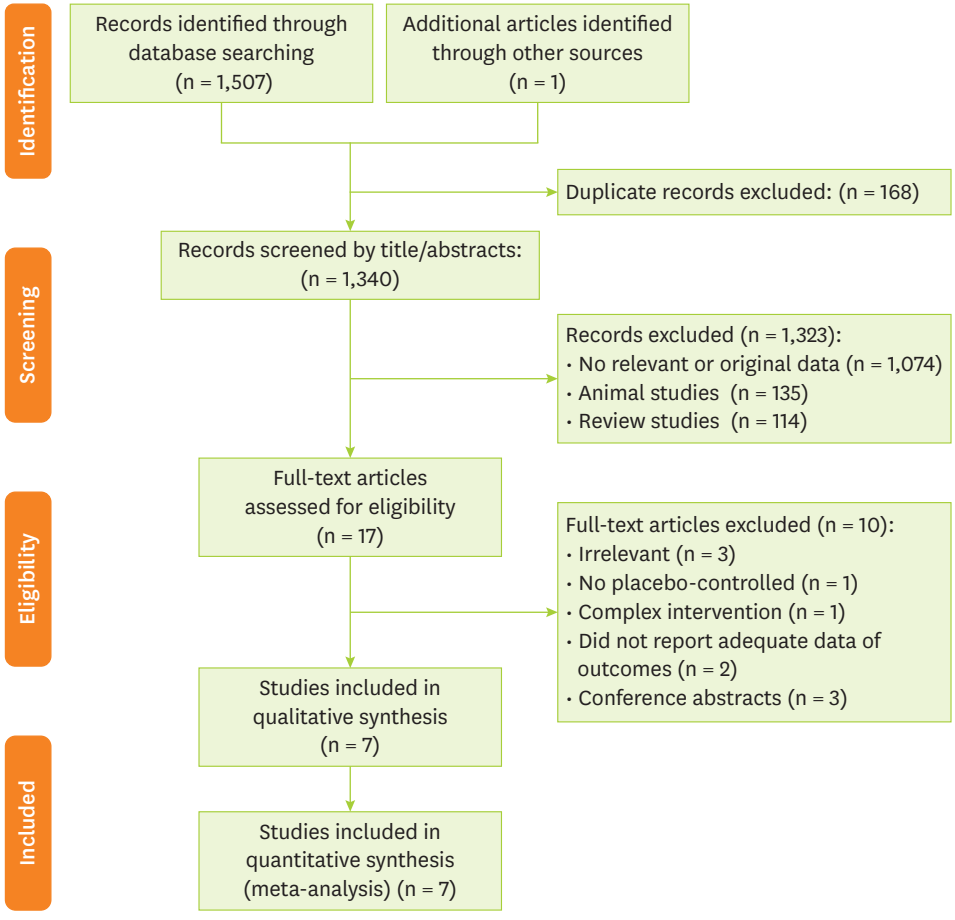

Figure 1. Flow chart of the number of studies identified and selected into the meta-analysis.

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Table 2. Demographic characteristics of the included studies

First author (year)	Location	Study design	Health status	Sex	Sample size (male/female)	Duration (wk)	Mean age (yr)	Baseline BMI (kg/m^2)	Intervention		Outcome
									Treatment group	Control group	
Englisch (2000)	Russia	Randomized, single-blind, placebo-controlled, parallel trial	Moderate to severe hypercholesterolemia	Both	143 (47/96)	6	44	28.2	1,800 mg ALE	Placebo	ALT/AST
Roghani-Dehkordi (2009)	Iran	Randomized, double-blind, placebo-controlled, parallel trial	Non or mild hypercholesterolemic	Male	56	12	42.5	24.5	50 mg ALE	Placebo	ALT/AST
Roghani-Dehkordi (2009)	Iran	Randomized, double-blind, placebo-controlled, parallel trial	Non or mild hypercholesterolemic	Male	51	12	42.5	24.5	100 mg ALE	Placebo	ALT/AST
Fallah Huseini (2012)	Iran	Randomized, double-blind, placebo-controlled, parallel trial	Mild to moderate hypercholesterolemia in type 2 diabetes	Both	76 (18/58)	8	50	NA	1,200 mg ALE	Placebo	ALT/AST
Rangboo (2016)	Iran	Randomized, double-blind, placebo-controlled, parallel trial	Non or mild hypercholesterolemic NASH patients	Both	60 (42/18)	8	48.9	NA	2,700 mg ALE	Placebo	ALT/AST
Panahi (2018)	Iran	Randomized, double-blind, placebo-controlled, parallel trial	Patients with NAFLD	Both	89 (50/39)	8	46.2	29.1	600 mg ALE	Placebo	ALT/AST
Musolino (2020)	Italy	Randomized, double-blind, placebo-controlled, parallel trial	Type 2 diabetes and NAFLD	Both	40 (NA)	16	50.5	25.7	300 mg ALE	Placebo	ALT/AST
Rondanelli (2020)	Italy	Randomized, double-blind, placebo-controlled, parallel trial	Overweight and obese with newly detected IFG	Both	54 (28/26)	8	51.5	30	500 mg ALE	Placebo	ALT/AST

NASH, nonalcoholic Steatohepatitis; NAFLD, non-alcoholic fatty liver disease; IFG, impaired fasting glucose; BMI, body mass index; NA, not reported; ALE, artichoke leaf extract; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Russia [27]. The dose of artichoke ranged from 50 mg/day to 2,700 mg/day. The length of supplementations varied from 6 to 16 weeks.

Meta-analysis of data

Effects of artichoke on ALT

Artichoke administration significantly reduced the serum levels of ALT (Hedges' g, −1.08; 95% CI, −1.76 to −0.40; p = 0.002). There was evidence of considerable heterogeneity among studies (I^2 = 92.2%; p < 0.001) (**Figure 2**).

The stratified analyses based on the duration of intervention revealed that the effect of artichoke supplementation on ALT was significantly greater in trials that lasted ≤ 8 weeks (Hedges' g, −0.69; 95% CI, −0.89 to −0.49; p < 0.001). More subgroup analysis for dosage and mean age did not indicate different results of artichoke supplementation efficacy on ALT (**Table 3**).

Effects of artichoke on AST

Compared to that of the control participants, a significant effect of artichoke administration on AST was reached (Hedges' g, −1.02; 95% CI, −1.76 to −0.28; p = 0.007). An extreme level of heterogeneity was seen in the studies (I^2 = 93.6%; p < 0.001) (**Figure 3**). The stratified analysis based on the intervention dose showed that > 500 mg/day of artichoke supplementation significantly reduced the AST levels (Hedges' g, −0.81; 95% CI, −1.02 to −0.59; p < 0.001). More stratified analysis for the duration and mean age did not indicate different results of artichoke supplementation efficacy on AST (**Table 3**).

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Table 3. Subgroup analysis of included randomized controlled trials in meta-analysis of the effect of artichoke supplementation on liver enzymes

Group	No. of trials	WMD (95% CI)	p value	I^2 (%)	P-heterogeneity	p for between subgroup heterogeneity
ALT						
Dosage (mg)						0.407
≤ 500	3	−0.49 (−0.82, −0.16)	0.003	95.5	< 0.001	
> 500	4	−0.66 (−0.87, −0.44)	< 0.001	86.3	< 0.001	
Duration (wk)						0.070
≤ 8	5	−0.69 (−0.89, −0.49)	< 0.001	82.3	< 0.001	
> 8	2	−0.27 (−0.68, 0.13)	0.184	96.9	< 0.001	
Mean age (yr)						0.079
< 50	4	−0.51 (−0.72, −0.31)	< 0.001	87.1	< 0.001	
≥ 50	3	−0.88 (−1.23, −0.53)	< 0.001	96.4	< 0.001	
AST						
Dosage (mg)						0.001
≤ 500	3	−0.17 (−0.49, 0.15)	0.301	95.0	< 0.001	
> 500	4	−0.81 (−1.02, −0.59)	< 0.001	92.1	< 0.001	
Duration (wk)						0.448
≤ 8	5	−0.64 (−0.84, −0.44)	< 0.001	92.6	< 0.001	
> 8	2	−0.47 (−0.86, −0.07)	0.020	96.3	< 0.001	
Mean age (yr)						0.288
< 50	4	−0.66 (−0.88, −0.45)	< 0.001	91.9	< 0.001	
≥ 50	3	−0.45 (−0.79, −0.11)	0.010	96.6	< 0.001	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; WMD, weight mean difference.

Publication bias and sensitivity analysis

To examine the influence of each study on the overall effect estimate, we excluded every single study from the analysis. Sensitivity analysis for ALT and AST indicated that exclusion of each study one at a time did not materially alter the pooled estimate. Egger's regression test was conducted to find the publication bias. There was no evidence of publication bias for ALT (p = 0.155) and AST (p = 0.315).

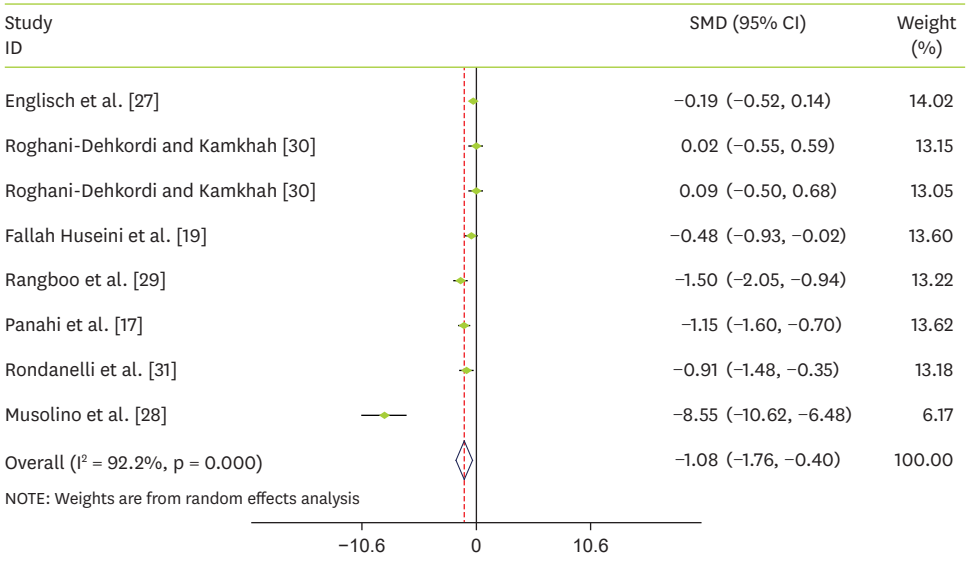

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of artichoke supplementation on ALT.
SMD, standardized mean difference; CI, confidence interval.

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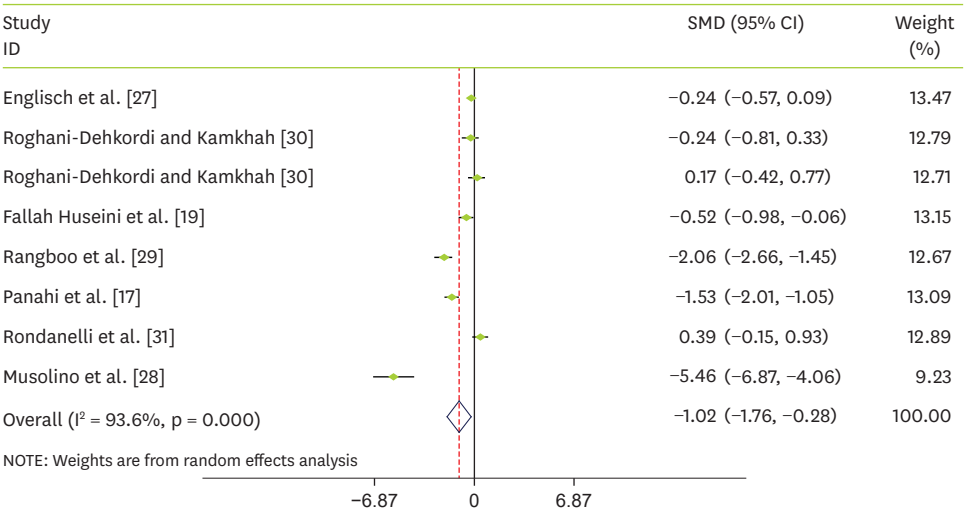

Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of artichoke supplementation on AST.
SMD, standardized mean difference; CI, confidence interval.

DISCUSSION

The current evidence shows that artichoke supplementation significantly affects serum ALT and AST. The prevalence of NAFLD, most commonly caused by sedentary lifestyles and high dietary calorie intakes, is on the rise in industrialized nations [32]. The American Association for the Study of Liver Diseases [33] recommends liver biopsy only in patients with elevated serum markers and non-invasive serum markers for screening liver dysfunction, especially in those with metabolic risk factors. The serum markers ALT and AST can be used to diagnose hepatic damage. Severe liver damage was commonly detected by elevated levels of serum ALT and AST [34]. Due to its multifaceted mechanisms of action, herbal medicine offers possible benefits as an alternative remedy [5,6,35]. Artichoke has been used as a remedy that is rich in natural antioxidants and is frequently grown in Mediterranean countries [10]. Artichoke extracts have shown antimicrobial, hepatoprotective, choleretic, hypocholesterolemic, hypoglycemic, and anticancer effects in previous in vitro and in vivo studies [36-43]. These are the main actions of artichoke that is used as an herbal drug: liver and gallbladder bile stimulation, hepatoprotective, antihepatotoxic, and hypocholesterolemic [44]. The antioxidative and free radical scavenging ability of artichoke extracts in to protect hepatocytes from oxidative stress has been evaluated in several in vitro and animal studies [15,16,18], but there are limited number of human studies in this area. However, the results are controversial. In line with other findings, in two studies from Iran, ALE supplementation significantly improved the serum levels of ALT and AST in NAFLD [17] and NASH [29] patients. Although in another study, Fallah Huseini et al. [19] showed that artichoke extract supplementation has a significant reduction effect on AST no effect was seen with ALT in hypercholesterolemic type 2 diabetic patients. In return, Rondanelli et al. [31] study of overweight IFG individuals reported a statistically significant reduction between time and group for ALT level. Meanwhile, the study by Musolino et al. [28] reported that a combination of bergamot polyphenolic fraction and *Cynara cardunculus* significantly increased AST and ALT levels in patients with type 2 diabetes mellitus. Since these studies were conducted on different subjects, direct comparisons of their findings are not possible.

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Several studies have documented that artichoke extracts can exert antioxidant activity in the prevention and treatment of oxidative stress related diseases [14,45-48]. The most active antioxidant ingredients in artichoke extract including mono- and dicaffeoylquinic acid (cynarin and chlorogenic acid), caffeic acid, and chlorogenic acid could explain the therapeutic effects of artichoke on biochemical and liver biomarkers [49]. The main compounds of flavonoids in artichoke extract combinations are glycosides luteolin-7-β-rutinoside (scolymoside), luteolin-7-β-D-glucoside, and luteolin-4-β-D-glucoside that [50-52]. The result of Saffa et al. study in determining the efficacy of *Cynara scolymus* total methanolic extract (CSM) and its fraction (CSF) in rats showed that CSF is more active in comparison with CSM. Due to the high concentration of chlorogenic acid in CSF [53]. Several mechanisms could explain the beneficial effects of artichoke supplementation on liver enzymes. Artichoke bioactive compounds inhibit lipid peroxidation [54], These components also modulate reactive oxygen species (ROS)-dependent cell functional signaling. Intercepting free radicals and ROS at the level of critical signaling pathways involving various protein kinases, phosphatases, and transcription factors may be responsible for the modulation effects [55]. Finding from a meta-analysis showed that animals with hepatotoxicity compared with animals with other diseases may benefit more from artichoke extract [56]. However, the high dose and duration of intervention with artichoke extract in patients with hepatitis C did not have a remarkable reduction in serum ALT and AST levels [57]. Also, the Englisch et al.'s study [27] which was performed on patients with severe hypercholesterolemia did not show an improvement in AST and ALT levels despite the larger sample size and higher dose of artichoke, than the Roghani-Dehkordi and Kamkhah's study [30], which was performed on hypocholesterolemia patients. It seems that the ineffectiveness of artichoke extract on ALT and AST was caused by microbial agents and severe damage to hepatocytes.

A previous meta-analysis revealed Artichoke supplementation reduced liver enzymes, especially among patients with NAFLD [32]. In comparison to the previous review, we included two more related studies, also we did a subgroup analysis based on dose and duration which showed that artichoke extract in high dosage (> 500 mg) for a short duration (≤ 8 weeks) was suggested as potent antioxidant effect on AST and ALT levels.

Our meta-analysis has several strengths. First, we involved only RCTs in the meta-analysis, therefore the causal inference of our findings is strong. Second, different subgroup analyses were performed to explore the effect of intervention across different subgroups and detect possible sources of heterogeneity. Limitations of our study include the relatively small sample size. Moreover, there was evidence of significant between-study heterogeneity in some of our analyses. Thus, high-quality randomized-controlled trials with different durations and dosages are needed. In addition, most of the included studies was conducted in Asian countries which limits the extrapolation of our findings.

CONCLUSION

In conclusion, this systematic review and meta-analysis of intervention trials suggests that artichoke supplementation may reduce the serum levels of AST and ALT. However, further large, high-quality clinical trials in different regions are needed to provide definite conclusion. Our findings provide additional evidence for physicians and medical researchers on the efficacy of alternative treatments for hepatic patients.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Search syntax

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