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Review

Effect of caper fruit (Capparis spinosa L.) consumption on liver enzymes, lipid profile, fasting plasma glucose, and weight loss. A systematic review and a preliminary meta-analysis of randomized controlled trials

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ABSTRACT

This systematic review and meta-analysis aimed to evaluate the overall effect of caper fruit on the modulation of glycemic, lipid profile, liver enzymes, and body mass. Google Scholar, PubMed, and Scopus were explored to collect relevant studies in the last 10 years. RCTs with caper fruit supplementation or consumption in different cohorts of subjects with non-alcoholic fatty liver disease (NAFLD), Type-2-Diabetes (T2D), metabolic syndrome, and hyperlipidemia were included in this systematic review with a mean intervention duration from 2 to 12 weeks. The outcomes measured in this meta-analysis were liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), the lipid profile represented by triglycerides, total cholesterol (TC) with LDL and HDL and also, weight, and fasting blood glucose. Five randomized controlled trials, which involved a total of 178 adults, were included. According to the results, caper fruit seems to decrease liver enzymes ALT −12.29 U/L [−24.47, −0.11], AST −2.20 U/L [−4.70, 0.31]. Furthermore, the lipid profile seems to improve with a decrease in triglycerides. −11.89 mg/dL [−33.73, 9.95], LDL −4.80 mg/dL [−16.34, 6.74], HDL 0.72 mg/dL [0.10, 1.34], total cholesterol −7.83 mg/dL [−20.04, 4.38], FPG −17.93 [−42.66, 6.79], weight −1.00 kg [−1.44, −0.56]. Significant modulations were found only for ALT, HDL, and weight. In conclusion, this systematic review and meta-analysis showed the paucity of data available on the topic while showing the potential role of caper fruit as a promising food for improving the liver-lipid profile axis in patients with metabolic syndrome and diabetes. Further studies are required to confirm these results.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common and chronic liver disease characterized by excessive fat accumulation in the liver, not caused by alcohol consumption [1]. It is one of the most common causes of chronic liver disease worldwide, affecting approximately 25% of the general population [2]. NAFLD is a significant public health concern, as it can progress to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventually hepatocellular carcinoma, a type of liver cancer [3]. The pathogenesis of NAFLD is complex and multifactorial, involving various mechanisms such as insulin resistance, oxidative stress, mitochondrial dysfunction, and inflammation [4]. Insulin resistance is thought to be a key factor in the development of NAFLD. In the setting of insulin resistance, the liver is unable to properly metabolize glucose, leading to the accumulation of fatty acids in the liver. This accumulation of fatty acids triggers oxidative stress, mitochondrial

Abbreviations: RCT, Randomized control trial; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; NAFLD, Non-alcoholic fatty liver disease; CFP, Caper Fruit Pickle; T2D, Type 2 Diabetes; MetS, Metabolic Syndrome; TG, Triglycerides LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; TC, Total Cholesterol; FPG, Fasting Plasma Glucose; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HbA1c, Hemoglobin A1C; BMI, Body Mass Index; WC, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BUN, Blood Urea Nitrogen; CRP, C-Reactive Protein.

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dysfunction, and inflammation, which ultimately leads to liver damage [5]. It has been suggested that oxidative stress and chronic inflammation play a significant role in the development and progression of NAFLD [6]. Although there is no specific treatment for NAFLD, lifestyle modifications, including weight loss and exercise, are recommended as the first-line therapy [7].

Phytochemicals, the bioactive compounds present in plant-based foods, have gained attention as potential agents for the prevention and management of chronic diseases, including T2D and NAFLD [8]. Capparis spinosa L. (caper), a plant species belonging to the family Capparaceae, is widely distributed in the Mediterranean region and has been traditionally used for culinary and medicinal purposes [12–15]. Caper fruits, buds, and leaves contain several bioactive compounds such as flavonoids, alkaloids, and phenolic acids, which seem to possess antioxidant, anti-inflammatory, and anti-diabetic properties [9–11]. Caper fruit is consumed fresh in specific countries such as Iran and Bahrain by the elderly, whereas in Eastern India, fresh raw caper berries are consumed as an appetizer [16].

The major phytochemicals identified in Caper were flavonoids (rutin, quercetin, and catechin), alkaloids (indoles and spermidines), and glucosinolates (glucocapparin) [12,13]. It also contains, in minor quantity, several beneficial compounds like spermidine, kaempferol, stigmasterol, campesterol, tocopherols, and carotenoids [12,14,15]. The plant contains moderate levels of vitamin C and carbohydrates, dietary fiber, protein, and lipids [13]. The major phytochemicals identified. Glucoraphanin is the main component in non-fermented caper berries, and fermentation causes the epicatechin amounts to decrease, and free quercetin is observed [16]. Capparis spinosa also contains various elements like fiber (3–4 g for 100 g) but also several minerals such as Al, P, S, K, Ca, Cl, Ti, Mn, Fe, Ni, Cu, Zn, Br, Rb, Sr, and Pb [17,18]. The volatile oils of the leaf, ripe fruit, and root of Capparis spinosa var. mucronifolia consist of isothiocyanates, n-alkanes, terpenoids, a phenylpropanoid, an aldehyde, and a fatty acid [19]. The product is used as a traditional Iranian medicinal plant due to its activity against carbon tetrachloride and paracetamol-induced hepatotoxicity *in vivo* and thioacetamide and galactosamine-induced hepatotoxicity in isolated rat hepatocytes evaluated using *in vitro* technique [20,21]. The main phytoconstituents of Capparis spinosa include flazin, guanosine, capparine A, capparine B, 1H-indole-3-carboxaldehyde, 4-hydroxy-1H-indole-3-carboxal-dehyde, chrysoeriol, apigenin, kaempferol, thevetia-flavone, 5-hydroxymethylfuraldehyde, vanillic acid, and cinnamic acid [12].

Therefore, Capparis spinosa has attracted scientific interest, as a potential dietary supplement for the prevention and management of T2D and NAFLD; thus, several studies have been investigating the effect of its consumption on various metabolic parameters in this type of patients.

Therefore, this systematic review and meta-analysis aimed to assess the current evidence on the potential health benefits of Capparis spinosa consumption. Specifically, we reviewed the effects of Capparis spinosa consumption on glycemic, lipid profile, liver function tests, and other metabolic parameters in patients with T2D and NAFLD. In addition, we have tried to underline the mechanisms of action of Capparis spinosa bioactive compounds and their potential role in the prevention and management of these diseases.

2. Materials and methods

The protocol of the systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) - CRD42023427411.

2.1. Search strategy

English-written articles, published between 2013 and 2023, were identified by searching Google Scholar, PubMed, and ScienceDirect databases. The search strategy on PubMed was based on the following MESH search terms (updated on 1st of May 2023): Caper fruit (MeSH Terms) OR Capparis spinosa (MeSH Terms) AND obesity (MeSH Terms) OR liver enzymes (MeSH Terms) or lipid (MeSH Terms) OR glucose (MeSH Terms) OR inflammation (MeSH Terms). A manual search was performed by 2 independent senior researchers, experienced in clinical nutrition, through the revision of reviews and research articles on caper fruit and metabolic and inflammatory makers.

2.2. Study selection

The selection process of the studies was based on PRISMA guidelines [21]. All randomized control trials conducted on humans within the last 10 years (from 2013 to 2022) were included.

Non-English language, animal-based studies, *in vitro* studies, non-RCTs in overweight and obese patients, and RCTs in adults with BMI < 18.5 kg/m^2, were excluded. Studies based on adolescent subjects, those not including a control group, and measured outcomes of interest other than required were also excluded.

A more detailed list of criteria adopted is reported. In particular, a structured approach using five components was adapted to construct the research question and to select available studies. The five components (PICOS) include 1. Participants, 2. Interventions, 3. Comparators, 4. Outcomes, 5. Study design.

2.2.1. Participants

Studies including adult participants (age $\geq$ 18 years), normal, overweight, and obese adults (BMI = 30.0 and Above kg/m^2), [22]. diagnosed with different conditions such as NAFLD, T2D or Metabolic Syndrome, and hyperlipidemia were selected.

No constraints were assigned concerning gender, diseases, race, and geographical distribution of the individuals enrolled in the study.

2.2.2. Intervention

RCT investigating the effect of caper fruit or powder consumption on glycemic and lipid profile, liver enzymes, and body mass was selected.

2.2.3. Outcomes

Eligible studies were required to report baseline and follow-up values, the mean change (Δ-change) and relative standard deviation from baseline, and/or the mean difference among intervention groups vs. control group concerning glycaemic and lipid profile, liver enzymes, and body mass indexes.

2.2.4. Study design

Randomized controlled trials (RCTs) with caper fruit consumption as primary treatment and different controls have been considered in patients with NAFLD, Type-2-Diabetes or with Metabolic Syndrome, and hyperlipidemia.

2.3. Data extraction and analysis

Two authors (S.P. and M.M.) independently analyzed studies for their eligibility based on the following inclusion and exclusion criteria. Disagreement between reviewers was resolved by consulting a third independent reviewer (P.R). For each study, the following data were collected by another researcher (A.R.): first author, publication year, study setting, study design, eligibility criteria, number of subjects, gender, age, race-country, intervention methods, treatment duration, and the main outcomes.

2.4. Risk of bias in individual studies

Two authors from Bahrain independently assessed the risk of bias. Disagreements were solved by a third author (S.P.). The risk of bias in each study was assessed using the Cochrane Collaboration Risk of Bias

tool [23] and considering factors contributing to the study quality, the generation of the allocation sequence, the allocation concealment, the blinding of outcome data, the presence of incomplete data and the selective reporting.

These factors were classified as low risk of bias, high risk of bias, or unclear risk of bias. Studies with a low risk of bias for at least three items were held as good, studies with a low risk of bias for at least two items were considered fair and studies with a low risk for no item or only for one item were regarded as poor.

2.5. Statistical analysis

Study authors were contacted to gather missing or unclear data. For continuous outcome data, the method used in the original study to account for missing data, usually mixed model repeated measures or the last observation carried forward was used. Missing SD was calculated from p values; to combine the two outcomes in our meta-analysis, the mean difference (MD) with 95% confidence intervals (CI) as the pooled effect size was used. Heterogeneity across the included studies was confirmed using checking Higgins' I2 statistic. A fixed-effects model for data pooling was used if the I2 statistic was below 50%, which meant that there was acceptable heterogeneity across the included studies. Publication basis was checked for through a meta-analysis or subgroup analysis including five or more studies. The level of significance was set at $p < 0.05$ for all statistical analyses performed. Procedures related to data pooling were carried out in Review Manager 5.4.

3. Results

3.1. Database search

The databases' literature searches yielded a total of 16 potentially pertinent studies. A total of 9 studies were found after reference networking of earlier systematic reviews revealed two additional pieces of research. After duplicates were eliminated, 2 studies were ultimately found. Specifically, 2 articles were still excluded after the second round of eligibility screening, mostly because the research design was not a randomized control trial, the study participants were not adults, the intervention and outcome did not meet the inclusion criteria, the combined intervention did not follow the MD exactly, there was no parallel control group, or there was no intervention at all.

As a result, 5 RCTs were chosen to be part of the current systematic

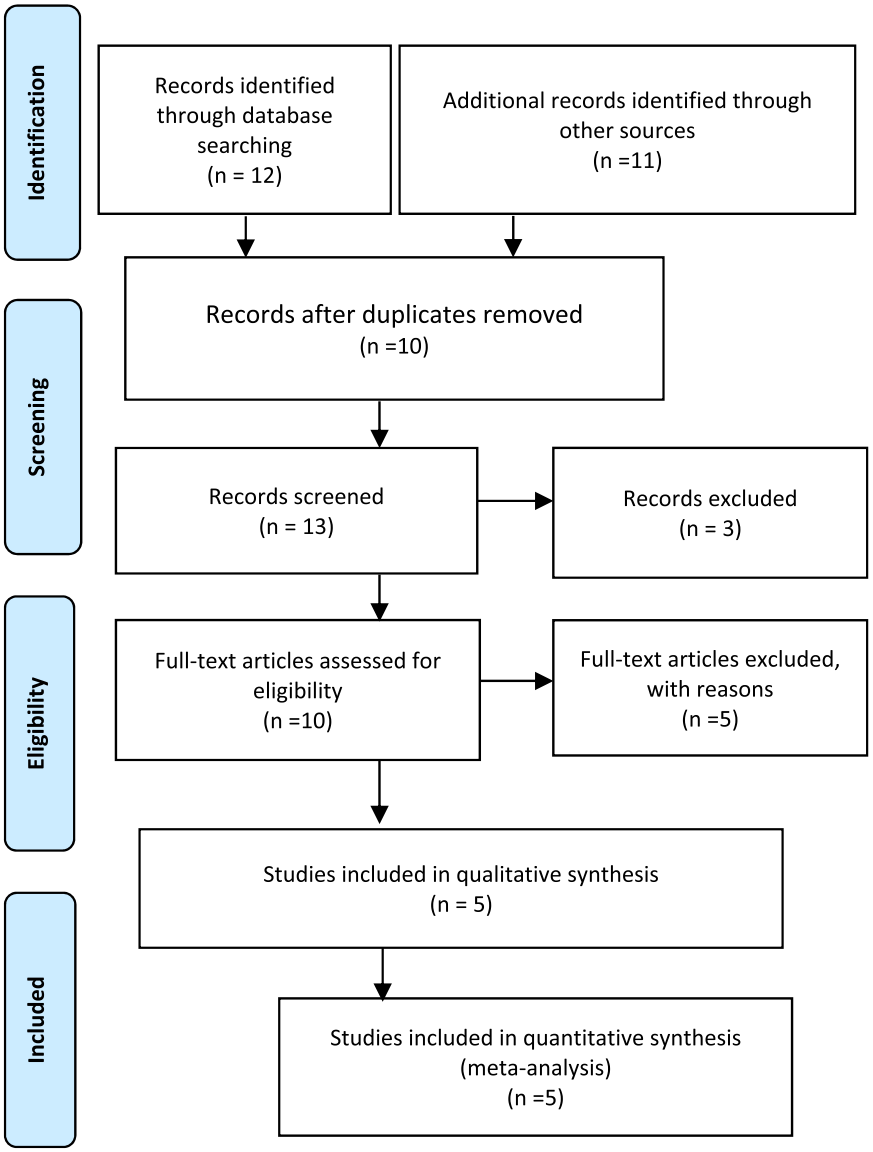

Fig. 1. PRISMA flowchart of studies' selection process.

review and meta-analysis. Fig. 1 shows the study selection procedure.

3.2. Study characteristics

The studies that were chosen for this systematic review are listed in Table 1.

Except for three studies involving populations from the center town (Zanjan), each study's geographic origin was distinct (Tehran and Mashhad), but they were all from the same country (Iran). Additionally, different type of intervention was used, with the chosen studies placing particular emphasis on capsules containing caper fruit extract powder or a dietary intake of 40–50 g of caper fruit pickles (CFP) with meals. Only one study considered a specific vinegar-containing product called C. spinosa oxymel (10 mL/thrice daily). Regarding the study design, 5 papers were double-blind RCTs, the intervention lasted between 2 and 12 weeks, and the population age ranged between 18 and 80 years. There were 178 individuals in all 5 studies, including both males and females (Table 1). The control groups were set to consume a conventional diet alone or with statins or were given dietary instructions and counseling in order to fix macronutrients to be consumed and improve compliance.

3.3. Effect on liver enzymes

Of the five studies selected for this review, four measured the liver function tests (LFTs), mainly measuring ALT and AST [25–28]. A total of 168 patients were assessed on ALT and AST for a duration ranging between 8 and 12 weeks. Two studies by Khasavi et al. (2017) and Khasavi et al. (2018) evaluated the same data but for different outcome measures [25,26]. A total of 44 NAFLD patients were randomly assigned to a control and an intervention group receiving 40–50 g of CFP with their meals throughout the day for 12 weeks. This group was also provided with counseling on lifestyle changes. In comparison with the control group, a significant reduction in ALT [25,26], and in AST after adjustment [25] was reported in the CFP group post-intervention. Vahid et al. (2019) randomly distributed 30 T2D patients with MetS into three groups of 10 each; placebo, oxymel, and caper fruit oxymel. Comparing the placebo group and caper fruit oxymel group, it was not found any significant change in ALT and AST among other liver markers after a period of 3 months [27]. Sardari et al. (2019) reported a statistically significant reduction in ALT and no significant change in AST after treatment for 8 weeks with atorvastatin and 40 – 50 g CFP per day in males with hyperlipidemia [28]. Fallah Huseini et al. (2013) reported no significant differences in SGOT, SGPT, and ALP [24]. Meta-analysis results showed a statistically significant decrease in ALT and a trend toward a decrease in AST after treatment with CFP (Fig. 2).

3.4. Effect on lipid profile

Four RCTs reported lipid profile markers [24,25,27,28]. A total of 178 patients were assessed for the lipid profile mainly measuring TGs, LDL-C, HDL-C, and TC. Treatment by Fallah Huseini et al. (2013), on a total of 28 T2D patients for 2 months with 1200 mg caper fruit extract powder per day showed a significant decrease in TGs, while no significant difference in other parameters [24]. Khasavi et al. (2017) reported a significant decrease in TGs, LDL-C, and TC among the control group as opposed to the CFP-treated group [25]. Similarly, Vahid et al. (2019) reported a not significant decrease in the progression of TGs and no difference in the other parameters [27]. Sardari et al. (2019) reported statistically significant improvement in TGs, LDL-C, HDL-C, and TC in the treatment group of atorvastatin and CFP [28]. Our meta-analysis results showed a significant increase in HDL-C (Fig. 3C). Reductions in TGs, LDL-C, and TC were also found but without significance (Figs. 3A, 3B, 3D).

3.5. Effect on glycemia

The parameters measured in all studies were insulin, HOMA-IR, PPBG, FPG, and HbA1c. A total of 102 participants were tested in the studies. Three studies measured the FBS [24,26,28]. Fallah Huseini et al. (2013) reported a significant decrease in FPG and HbA1c in the caper-treated group [24]. Khavasi et al. (2018) reported no statistically significant difference in serum FPG, insulin, and HOMA-IR post-CFP treatment [26]. Vahid et al. (2019) reported the inhibition of

Table 1
Characteristics of the studies.

First Author/ Year of Publication	Sample, Gender (Control, intervention groups)	Country	Population (Age, BMI)	Treatment Duration	Parallel treatments	Intervention strategies
Fallah Huseini et al., 2013 [24]	Total: 54 26-placebo 28-caper	Tehran, Iran	• 45–65 years T2D patients • 150 mg/dl < FPG < 250 mg/dl • HbA1c: 7–9% • Disease duration: 2–8 years • Normal BP and blood lipid levels • Taking > / two 5 mg glibenclamide and two 500 mg metformin tablets per day	2 months	Placebo capsules- 400 mg toast powder	Caper capsules- 400 mg caper fruit extract powder (3 times a day). (Total: 1200 mg /day). Conventional oral anti-hyperglycemic agent treatments in two groups
Khavasi et al., 2017 [25]	Total: 44 22-control 22-caper	Zanjan, Iran	• 12–80 years NAFLD patients with BMI of 25–35 kg/m^2 • Willingness to consume CFP as a food additive	12 weeks	Not mentioned	• 40–50 g of CFP with meals • Instructed by a nutritionist to promote lifestyle changes
Khavasi et al., 2018 [26]	Total: 44 22-control 22-caper	Zanjan, Iran	• 12–80 years NAFLD patients with BMI of 25–35 kg/m^2 • Willingness to consume CFP as a food additive	12 weeks	Not mentioned	• 40–50 g of CFP with meals • Instructed by a nutritionist to promote lifestyle changes
Vahid et al., 2019 [27]	Total: 30 10-Placebo 10-caper	Mashhad, Iran	• 30–65 years T2D with MetS • FPG) > 130 mg/dL or blood glucose > 180 mg/dL or glycosylated hemoglobin (HbA1c) > 7%, and • Did not want to start insulin therapy	3 months	Diluted lactulose in distilled water.	C. spinosa oxymel (10 mL/ thrice daily) (1 g per 10 mL)
Sardari et al., 2019 [28]	Total: 60, M 30-Atrovastatin 30-Atorvastatin+CFP	Zanjan, Iran	• 40–60 years old newly diagnosed with hyperlipidemia and prescribed low-dose atorvastatin	8 weeks	Atorvastatin	10 mg atorvastatin plus 40–50 g of CFP per day

M: Male; T2D: Type-2-Diabetes; FPG: Fasting Plasma Glucose; HbA1c: Hemoglobin A1c, BP: Blood Pressure; TG: Triglycerides; NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: Body Mass Index; MetS: Metabolic Syndrome; CFP: Caper Fruit Pickle; >/: not more than

A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fallah Huseini et al., 2013	0	0	0	0	0	0		Not estimable
Khavasi et al., 2017	-28.91	7.3	22	-7.36	2.12	22	25.8%	-21.55 [-24.73, -18.37]
Khavasi et al., 2018	-29.2	4.6	22	-7.4	1.3	22	26.1%	-21.80 [-23.80, -19.80]
Sardari et al., 2019	-6.21	1.94	30	-2.3	1.3	30	26.2%	-3.91 [-4.75, -3.07]
Vahid et al., 2019	-2.3	5.51	10	-2.2	16.16	10	21.9%	-0.10 [-10.68, 10.48]
Total (95% CI)			**84**			**84**	**100.0%**	**-12.29 [-24.47, -0.11]**

Heterogeneity: Tau² = 147.05; Chi² = 344.70, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.98 (P = 0.05)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours [experimental] Favours [control]

B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fallah Huseini et al., 2013	0	0	0	0	0	0		Not estimable
Khavasi et al., 2017	-11.41	2.25	22	-7.78	3.92	22	28.4%	-3.63 [-5.52, -1.74]
Khavasi et al., 2018	-11.9	2.2	22	-8	1.8	22	31.5%	-3.90 [-5.09, -2.71]
Sardari et al., 2019	-0.93	1.14	30	-0.4	0.8	30	33.4%	-0.53 [-1.03, -0.03]
Vahid et al., 2019	-1.5	6.34	10	-5.1	12.53	10	6.7%	3.60 [-5.10, 12.30]
Total (95% CI)			**84**			**84**	**100.0%**	**-2.20 [-4.70, 0.31]**

Heterogeneity: Tau² = 4.82; Chi² = 34.30, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.72 (P = 0.09)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours [experimental] Favours [control]

Fig. 2. Effect of caper fruit on liver enzymes. A: Effect of caper fruit on ALT. B: Effect of caper fruit on AST.

A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fallah Huseini et al., 2013	-60.1	16	28	-36.8	29	26	26.1%	-23.30 [-35.92, -10.68]
Khavasi et al., 2017	1.57	23.87	22	-9.32	3.04	22	27.0%	10.89 [0.83, 20.95]
Khavasi et al., 2018	0	0	0	0	0	0		Not estimable
Sardari et al., 2019	-55.7	15.4	30	-27.4	6.6	30	28.0%	-28.30 [-34.30, -22.30]
Vahid et al., 2019	9.1	39	10	13.4	27	10	18.9%	-4.30 [-33.70, 25.10]
Total (95% CI)			**90**			**88**	**100.0%**	**-11.89 [-33.73, 9.95]**

Heterogeneity: Tau² = 433.71; Chi² = 44.53, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.07 (P = 0.29)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours [experimental] Favours [control]

B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fallah Huseini et al., 2013	-7.9	3.3	28	-4.8	0.7	26	26.7%	-3.10 [-4.35, -1.85]
Khavasi et al., 2017	-8.95	2.4	22	-12.41	3.8	22	26.6%	3.46 [1.58, 5.34]
Khavasi et al., 2018	0	0	0	0	0	0		Not estimable
Sardari et al., 2019	-50.6	4.1	30	-30	2.5	30	26.6%	-20.60 [-22.32, -18.88]
Vahid et al., 2019	5.5	16	10	2.58	13	10	20.2%	2.92 [-9.86, 15.70]
Total (95% CI)			**90**			**88**	**100.0%**	**-4.80 [-16.34, 6.74]**

Heterogeneity: Tau² = 129.64; Chi² = 396.89, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.81 (P = 0.42)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours [experimental] Favours [control]

C

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fallah Huseini et al., 2013	-0.5	1.1	28	-1.9	1.2	26	31.7%	1.40 [0.78, 2.02]
Khavasi et al., 2017	0.6	0.34	22	0.09	0.82	22	39.6%	0.51 [0.14, 0.88]
Khavasi et al., 2018	0	0	0	0	0	0		Not estimable
Sardari et al., 2019	0.6	1.9	30	0.4	0.7	30	28.3%	0.20 [-0.52, 0.92]
Vahid et al., 2019	4.6	12.5	10	-0.38	10.5	10	0.4%	4.98 [-5.14, 15.10]
Total (95% CI)			**90**			**88**	**100.0%**	**0.72 [0.10, 1.34]**

Heterogeneity: Tau² = 0.22; Chi² = 8.43, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.27 (P = 0.02)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours [experimental] Favours [control]

D

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fallah Huseini et al., 2013	-12.1	1	28	-3.5	1	26	26.7%	-8.60 [-9.13, -8.07]
Khavasi et al., 2017	-7.41	2.4	22	-14.23	1.2	22	26.7%	6.82 [5.70, 7.94]
Khavasi et al., 2018	0	0	0	0	0	0		Not estimable
Sardari et al., 2019	-61.4	5.1	30	-35.2	3.1	30	26.5%	-26.20 [-28.34, -24.06]
Vahid et al., 2019	0.2	17	10	2.2	14	10	20.0%	-2.00 [-15.65, 11.65]
Total (95% CI)			**90**			**88**	**100.0%**	**-7.83 [-20.04, 4.38]**

Heterogeneity: Tau² = 145.03; Chi² = 927.88, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.26 (P = 0.21)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours [experimental] Favours [control]

Fig. 3. Effect of caper fruit on lipid profile. A: Effect of caper fruit on triglycerides. B: Effect of caper fruit on LDL. C: Effect of caper fruit on HDL. D: Effect of caper fruit on cholesterol.

hyperglycemia through a reduction in FPG and PPBG but without significant differences in HbA1c [27]. The meta-analysis performed showed a not significant difference in FBG levels post-CFP treatment (Fig. 4).

3.6. Effect on weight loss

Only three studies, for a total of 108 participants measured body weight [25–27]. Khavasi et al. (2017) reported a statistically significant reduction in weight and BMI among caper-treated NAFLD patients [25]. Similarly, weight and WC decreased significantly in the CFP group as reported by Kavasi et al. (2018) [26]. Vahid et al. (2019) also reported a significant decrease in weight and BMI and no significant differences in WC [27]. The results of our meta-analysis also showed a statistically significant decrease in weight in the CFP group (Fig. 5).

3.7. Effect on blood pressure

Only one study measured the blood pressure parameters. The study by Vahid et al. (2019) showed a reduction in SBP and DBP, however, the difference was not statistically significant [27].

3.8. Effect on kidney function

Only two studies measured the BUN [24,27]. Both Fallah Huseini et al. (2013) and Vahid et al. (2019) did not report statistically significant differences in serum creatinine [24,27].

3.9. Effect on inflammation

Only one study measured the inflammation marker CRP [26]. The study by Khavasi et al. (2018) showed a slight reduction in CRP, however, the difference was not statistically significant [26].

3.10. Meta-analysis of randomized control trials

Fig. 2A shows the forest plot for randomized controlled trials of caper fruit studies included in the ALT (IU/L) subgroup meta-analysis (n = 178). Meta-analyzed data showed a statistically significant decrease in ALT −12.29 U/L [−24.47, −0.11] in the intervention group compared with the control group. Fig. 2B shows the forest plots for randomized controlled trials of caper fruit studies included in the AST (IU/L) subgroup meta-analysis (n = 178). As shown in Fig. 2B, intervention decreased AST −2.20 U/L [−4.70, 0.31] but was not statistically significant compared with the control group.

Fig. 3A shows the forest plots for randomized controlled trials of caper fruit studies included in the TG (mg/dL) subgroup meta-analysis (n = 178). Meta-analysis has shown that caper affects (but not statistically) TG. The mean difference in TG across all the studies was −11.89 mg/dL [−33.73, 9.95] compared with the control group. Fig. 3B shows the forest plots for randomized controlled trials of caper fruit studies included in LDL cholesterol (mg/dL) subgroup meta-analysis (n = 178). Meta-analysis has shown that caper fruit did not significantly affect LDL but tends to decrease compared with the control group LDL −4.80 mg/dL [−16.34, 6.74]. Fig. 3C shows the forest plots for randomized controlled trials of caper fruit studies included in HDL (mg/dL) subgroup meta-analysis (n = 178). Meta-analysis has shown that caper fruit significantly affects HDL cholesterol. The mean difference in HDL across all the studies was an increase of 0.72 mg/dL [0.10, 1.34] (p = 0.00001). The test for overall effect was Z: 11.21 (p = 0.04). The heterogeneity was I2 = 64%. Fig. 3D shows the forest plots for randomized controlled trials of caper fruit studies included in the total cholesterol (TC) (mg/dL) subgroup meta-analysis (n = 178). Meta-analysis has shown that caper fruit did not significantly affect the TC. The mean difference in TC across all the studies was −7.83 mg/dL [−20.04, 4.38].

Fig. 4 displays the forest plots for randomized controlled trials of caper fruit studies included in the FPG (mg/dL) subgroup meta-analysis (n = 102). Meta-analysis has shown that caper fruit did not affect significantly the FPG (mg/dL). The mean difference of FPG (mg/dL) across all the studies was −17.93 [−42.66, 6.79]. The heterogeneity was $I^2 = 99\%$.

Fig. 5 shows the forest plots for randomized controlled trials of caper fruit studies included in the weight (kg) subgroup meta-analysis (n = 108). As shown in Fig. 5, caper fruit affects statistically significant weight loss of −1.00 kg [−1.44, −0.56] compared with the control group.

3.11. Risk of bias analysis

All trials were classed as having a low risk or unclear risk of bias based on one or more of the components. Overall, only 2 studies had over 75% low risk of bias (Fig. 6).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the effect of caper fruit consumption on NAFLD and related clinical conditions. The following systematic review and meta-analysis revealed that, based on the 5 studies identified, caper fruit consumption or extract supplementation (from 2 to 12 weeks) seems to have favorable effects on different metabolic outcomes. Particularly, it was found to reduce significantly liver enzymes (ALT), improve HDL cholesterol levels and reduce body weight. Furthermore, the caper fruit has been shown to promote a tendency towards the improvement of most of the other markers of lipid profile (total cholesterol, triglycerides, and LDL) and fasting blood glucose level. The beneficial findings were observed following the consumption of 40–50 g of caper fruits or as 400 mg supplement. The caper fruits used were from Iran. Specifically, the genetics of Iranian caper fruit shows an important quantity of quercetin content, which demonstrates the effect of different climatic situations on the plant metabolites. In addition, all subjects enrolled in the included trials were following a dietetic regimen based on the Iranian diet, following the recommendation of Food-based dietary guidelines – Iran (WHO).

The beneficial effect of caper fruit intervention on liver enzymes could be attributed to the presence of specific bioactive compounds such as flavonoids. In particular, the high level of quercetin and kaempferol

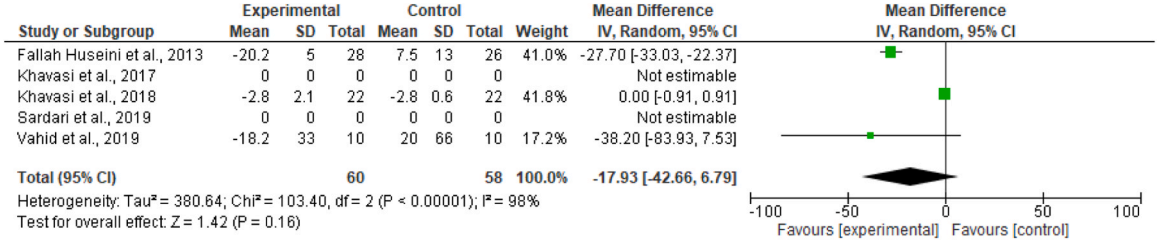

Fig. 4. Effect of caper fruit on FBG.

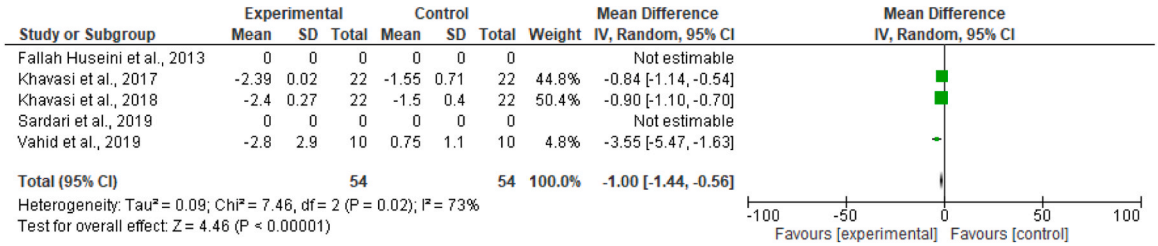

Fig. 5. Effect of caper fruit on weight loss.

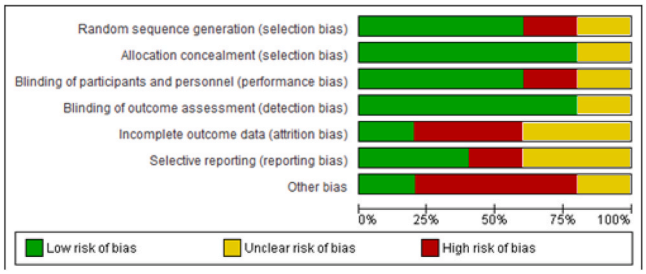

Fig. 6. Risk of bias summary.

have been reported in several studies [29] [30]. The antioxidant and anti-inflammatory properties of these flavonoids have been extensively studied, and their potential health benefits have been reported in various studies, including those by Manach et al. [31] and Panche et al. [32]. Several studies have investigated the effects of quercetin and kaempferol on liver enzymes such as ALT and AST. A study by Pasdar et al. [33] investigated the effects of quercetin supplementation on liver function in patients with non-alcoholic fatty liver disease (NAFLD). The study found that quercetin supplementation significantly reduced ALT and AST levels compared to the placebo group. Another study by Wang et al. [34] examined the effects of kaempferol on liver damage induced by alcohol and found that kaempferol treatment significantly reduced ALT and AST levels in rats. A systematic review and meta-analysis by Mahmoodi et al. [35] analyzed the effects of flavonoids on liver enzymes in patients with NAFLD. The study found that flavonoid supplementation significantly reduced ALT and AST levels compared to the control group. Overall, these studies suggest that quercetin and kaempferol may have beneficial effects on liver enzymes such as ALT and AST, particularly in individuals with liver disease or damage.

The beneficial effects of kaempferol-3 rutinoside, and quercetin-3-O rutinoside (rutin) are mainly associated with its antioxidant, anti-inflammatory, and antiapoptotic effects. The antioxidant effect of rutin has been reported to involve the enhancing activity of enzymes such as SOD, GST, GGT, CAT, and GPx GR, and the induction of the Nrf2/HO-1 pathway [36].

Along with other flavonoids like quercetin and kaempferol, caper fruit contains also isorhamnetin [15]. The presence of this flavonoid could explain the significant effect observed on HDL-C levels following caper fruit consumption. Studies suggest that isorhamnetin may have a positive effect on HDL cholesterol levels. For example, a study by Sirikanchanarod et al. [37] found that supplementation with isorhamnetin-rich mulberry extract increased HDL cholesterol levels in hyperlipidemic patients. Another study by Matboli et al. [38] reported that isorhamnetin supplementation improved lipid metabolism in high-fat diet-induced obese rats, including increasing HDL cholesterol levels. The study by Ressaissi et al. [39] investigated the effects of isorhamnetin derivatives and piscidic acid on hypercholesterolemia. The study included *in vitro* experiments to evaluate the cholesterol permeability and HMG-CoA reductase inhibition of these compounds, as well as docking studies to predict their potential binding interactions. While the study did not directly investigate the effects of isorhamnetin on HDL cholesterol levels, it did find that some of the iso-rhamnetin derivatives tested showed promising results in terms of inhibiting HMG-CoA reductase, a key enzyme involved in cholesterol synthesis. Additionally, the study reported that some of the compounds tested showed good cholesterol permeability, which could potentially lead to increased cholesterol efflux and improved lipid metabolism. However, it's important to note that the research on the specific effects of isorhamnetin on HDL cholesterol levels is limited, and further studies are needed to confirm these potential benefits *in vivo*.

Regarding the effect of caper fruit consumption on weight loss, despite it having been observed to a lower extent, the presence of a considerable amount of quercetin may provide a plausible explanation. Quercetin has been studied for its potential effects on obesity and weight loss. A recent study [40] investigated the effects of quercetin supplementation on obesity in mice fed a high-fat diet. The study found that quercetin supplementation decreased body weight gain and reduced adipose tissue mass in the mice. Another study [41] examined the effects of quercetin supplementation on body weight, body mass index (BMI), and other metabolic parameters in overweight and obese subjects. The study found that quercetin supplementation reduced body weight, BMI, and waist circumference, as well as improved lipid profiles. The study by Hossain et al. [42] discussed the findings of previous studies that demonstrated the dose- and time-dependent increases in lipolysis in rat adipocytes caused by quercetin. The effect was observed in combination with epinephrine, which is involved in regulating energy homeostasis by promoting triglyceride breakdown and the release of fatty acids and glycerol from adipocytes. However, it is important to note that these studies were conducted on animal or human subjects with specific conditions, and more research is needed to fully understand the potential effects of quercetin on obesity and weight loss in the general population.

Aside from the major effects of quercetin and kaempferol, also rutin and chlorogenic acid were detected as dominant compounds in caper aqueous infusion. [16]. In this regard, as shown by Choo et al., (2010) the chlorogenic acid significantly inhibited the fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase, and acyl-CoA: cholesterol acyltransferase activities improving body weight, lipid metabolism, and obesity-related hormones levels [43].

4.1. Potential mechanisms

The pathogenesis of T2D and NAFLD is multifactorial, involving insulin resistance, inflammation, oxidative stress, and mitochondrial dysfunction. As already reported, caper fruit extract contains several compounds that may target these mechanisms of action and improve metabolic parameters.

Insulin resistance: One of the primary mechanisms underlying T2D and NAFLD is insulin resistance, which impairs glucose uptake and leads to hyperglycemia and hyperinsulinemia. Caper fruit extract may improve insulin sensitivity by increasing glucose uptake and enhancing insulin signaling pathways. Fallah Huseini et al. (2013) reported that caper fruit extract supplementation for eight weeks decreased fasting blood glucose and HbA1c levels in T2D patients, suggesting improved insulin sensitivity [24]. Vahid et al. (2019) also found that caper extract

supplementation for eight weeks reduced fasting blood glucose, insulin, and HOMA-IR index in T2D patients, indicating improved insulin sensitivity [27].

Inflammation: Chronic inflammation plays a critical role in the development and progression of NAFLD and T2D. Caper fruit extract contains various anti-inflammatory compounds that may reduce inflammation and oxidative stress. Khavasi et al. (2018) found that caper fruit extract supplementation for eight weeks decreased serum levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, in patients with NAFLD, suggesting anti-inflammatory effects [26]. Sardari et al. (2019) also reported that caper fruit extract supplementation for eight weeks in combination with atorvastatin decreased serum levels of CRP, a marker of inflammation, and improved lipid profiles in hyperlipidemic patients [28].

Oxidative stress: Oxidative stress is a key factor in the development of NAFLD and T2D, leading to damage to cellular components and inflammation. Caper fruit extract contains various antioxidants that may reduce oxidative stress and improve metabolic parameters. Khavasi et al. (2017) reported that caper fruit pickle consumption for eight weeks decreased serum levels of malondialdehyde (MDA), a marker of lipid peroxidation, in patients with NAFLD, suggesting reduced oxidative stress [25].

Mitochondrial dysfunction: Mitochondrial dysfunction is a hallmark of NAFLD and T2D, leading to impaired energy metabolism and oxidative stress. Caper fruit extract contains various bioactive compounds that may improve mitochondrial function and energy metabolism. Khavasi et al. (2018) found that caper fruit extract supplementation for eight weeks increased serum levels of adiponectin, a hormone that regulates energy metabolism and insulin sensitivity, in patients with NAFLD, suggesting improved mitochondrial function [26].

4.2. Strengths and limitations

The selection of RCTs for the systematic review and meta-analysis was the main strength of the study. However, the review is not without limitations. Likely, some included studies had different interventions.

The geographical locations of the studies may also have affected the analysis since they were performed on the same populations (Iran), for this reason, generalization of our results in other populations is not suitable. Since adherence to the consumption of caper fruit was not measured, the inaccuracy risk increases further. In addition, a deep analysis of dietary intake in the studied population is not available. The small study sample size of the selected studies was another limitation. Larger study samples with longer intervention periods may provide better results. Finally, all studies considered fresh caper fruits or extracts. This is a huge limitation since the worldwide consumption of caper fruits is dried, dehydrated and salted, but not fresh. Reaching a consumption of 40/50 g of fresh fruit consumption daily could be a challenge.

4.3. Future perspectives

The studies included in this systematic review and meta-analysis used either caper fruit powder as a tablet or pickled caper fruit. Some nutrients of the fruit may likely have diminished during the processing to optimize the dose administration. Adopting a more universally applicable extraction method would prove advantageous since the dissimilar amounts of caper fruit administered to the participants in the included studies may have contributed to disparate outcomes. Future studies are needed to explore various aspects of enhancing the methodology employed for caper fruit extraction. Future research shall also target people of different geographical locations to obtain a better understanding of the effects of caper fruit on the metabolic markers of different populations. Increasing the sample size, participants of varied age groups, and duration of intervention are other important perspectives to keep in check. While caper fruit provides promising results, there are many potential areas of improvement to analyze the benefits of caper fruit on diet and disease management. Our results showed significant improvements only in ALT, HDL, and weight, but more research on the underlying mechanisms of action may help improve the implementation of caper fruit as a safe complementary therapeutic drug for the treatment of many diseases.

5. Conclusions

In conclusion, this systematic literature review and meta-analysis revealed preliminary data showing that the consumption of caper fruit can have favorable effects on different metabolic outcomes, particularly in individuals with NAFLD. The study found that caper fruit consumption significantly reduced liver enzymes (ALT) and improved HDL cholesterol levels. Additionally, caper fruit showed a tendency to improve overall markers of lipid profile and fasting blood glucose. The beneficial effects of caper fruit consumption on liver enzymes and HDL cholesterol levels can be attributed to the presence of specific bioactive compounds such as flavonoids, including quercetin, kaempferol, and isorhamnetin. Furthermore, the presence of quercetin in caper fruit may explain the observed effect on weight loss. However, further studies are necessary. These findings overall suggest that caper fruit consumption may be a promising dietary intervention for individuals with NAFLD and may have potential health benefits for the general population. However, further studies are needed to confirm these findings and to identify the actual caper fruit bioactive compounds and their mechanisms of action. Moreover, the optimal dose and duration of caper fruit consumption to enable the putative health benefit observed should be investigated.

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CRediT authorship contribution statement

Simone Perna and **Mirko Marino:** Conceptualization, Methodology, Software. **Simone Perna** and **Mirko Marino,Ayesha Rafique:** Data curation, Writing – original draft preparation. **Simone Perna:** Visualization, Investigation. **Ayesha Rafique:** Supervision. **Sabika Allhedan:** Software, Validation. **Mariangela Rondanelli, Patrizia Riso:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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