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Herbal treatments for non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: With the rising prevalence of non-alcoholic fatty liver disease (NAFLD), there is a growing need to explore alternative therapeutic interventions. This study aimed to comprehensively evaluate the available evidence from randomized controlled trials (RCTs) for the use of herbal medications in NAFLD.

Methods: A literature search was conducted in PubMed, Web of Science and Scopus databases using appropriate keywords for studies published before the 6th of July 2023. RCTs involving humans, with confirmed NAFLD, the intervention group (IG) receiving herbal treatment, the control group (CG) given a placebo, participants aged \geq 18 years, published in English, and a Jadad score \geq 6 were included. Coffee and green tea as interventions were excluded. A meta-analysis of studies examining the effects of herbal supplementation on clinical and biochemical parameters in patients with NAFLD was performed. Analysis was done with the "meta" package in R programming language version 4.3.

Results: In this analysis encompassing 48 articles, study durations varied from 6 weeks to 12 months, with sample sizes ranging between 36 and 226 patients. The study included a total of 3741 patients, (IG=2013, CG=1728). Predominant single herbal medicines identified were *Phyllanthus niruri, Beta vulgaris, Allium sativum* L., Silymarin (*Silybum marianum*), *Portulaca oleracea L., Nigella sativa, and Cynara cardunculus L.* Meanwhile, Cynara cardunculus and curcumin were the most common ingredients in polyherbal compounds. Meta-analysis outcomes revealed a higher reduction in alanine aminotransferase (ALT), aspartate aminotransferase (AST), liver stiffness, waist circumference (WC), weight, body mass index (BMI), triglycerides (TG), and fasting blood glucose (FBG) in the IG compared to the CG. Notably, the reductions in ALT and weight were more pronounced in single herb compounds compared to polyherbal compounds. No differences were observed between the two groups regarding HbA1c levels.

Conclusion: These findings highlight the potential benefits of herbal interventions with regard to improvements in anthropometry, metabolic profiles, and liver enzymes in study participants.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, with an estimated prevalence of 30 % world-wide[1]. The highest reported NAFLD prevalence in 2023 was in Latin America (44.4 %) while the prevalence in South Asia was 33.8 % (22.9 %-46.8 %) [2]. NAFLD denotes a spectrum of diseases, which includes all disease grades and stages. NAFLD is defined as ≥ 5 % of

hepatocytes displaying macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis such as medications, starvation, or monogenic disorders, in individuals who drink little or no alcohol (defined as <20 g/d for women and <30 g/d for men) [3]. The progression of NAFLD can be divided into three stages: non-alcoholic fatty liver (NAFL), which involves fat accumulation and mild inflammation but no liver cell injury; non-alcoholic steatohepatitis (NASH), marked by inflammation and liver cell injury (ballooning); and cirrhosis,

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D.W. Rathnayake et al.

the most severe stage characterized by liver scarring and potential liver failure [4]. According to recent evidence, the development of NAFLD is associated with lipid accumulation, oxidative stress, endoplasmic reticulum stress, and lipotoxicity [5].

NAFLD is closely associated with metabolic disorders, including central obesity, dyslipidaemia, hypertension, and hyperglycaemia [6]. Histological evaluation with liver biopsy is the gold standard used for diagnosing and staging NAFLD in doubtful cases [7]. With the epidemics of obesity and type 2 diabetes mellitus, the prevalence of NAFLD continues to rise parallelly. NAFLD causes potentially progressive chronic liver disease, which can eventually result in cirrhosis, hepatocellular carcinoma, need for liver transplantation and death. Furthermore, NAFLD is associated with extrahepatic manifestations such as cardiovascular disease, sleep apnoea and chronic kidney disease. Altogether, NAFLD contributes to a large economic burden and poor health-related quality of life [8].

Despite the growing health impact of NAFLD, it is still a diagnostic and therapeutic challenge for clinicians. Currently, there is no approved specific treatment for NAFLD [9]. Therefore, lifestyle modifications such as diet and physical activity remain the cornerstone of its management [9]. These treatment strategies are mainly targeted at reducing body weight and associated metabolic disorders. A dose-dependent relationship is observed in physical activity in NAFLD, and vigorous physical activity is shown to be much more beneficial than moderate physical activity [10]. A calorie-deficit diet with limited carbohydrates and saturated fat, and rich in fibre and unsaturated fats, such as a Mediterranean diet is recommended [11].

However, not all patients can achieve substantial enhancements in their liver health through lifestyle changes alone. Only a minority of the patients can achieve adequate weight loss from these means, and even fewer can maintain the achieved weight loss [12]. Also, these options may be less effective in patients with advanced fibrosis or cirrhosis and long-term adherence to lifestyle changes can be poor [13]. Bariatric surgery is considered a novel therapeutic option which results in a significant reduction of mortality from cardiovascular disease and malignancy in eligible NAFLD patients [14]. So far, there are only a few pharmacological treatment options such as vitamin E and pioglitazone, recommended by international guidelines [15]. Therefore, effective drugs are urgently needed for the treatment of NASH.

Over the past few decades, the use of herbal medications in the treatment of NAFLD has been studied increasingly, due to its evidence of potential therapeutic mechanisms, wide availability, and lower side effects. Herbal medications have been shown to have favourable effects during the initiation and progression of NAFLD in both pre-clinical and clinical trials [16]. There is promising evidence from randomized controlled trials on the efficacy and safety of traditional Chinese medicines for NAFLD [17]. In the recent past, several Chinese herbal medicines have proven effective in treating NAFLD by modulating the intestinal microbiota, thereby affecting the gut-liver axis [18]. Herbal extracts are shown to inhibit inflammation, and antioxidant stress and improve lipid metabolism and insulin sensitivity [19].

On this background, the present systematic literature review and meta-analysis aimed to comprehensively evaluate the available evidence from randomized controlled trials (RCTs) regarding the use of herbal medicines in the treatment of NAFLD and provide an evidencebased assessment of the efficacy and safety of herbal medicines, helping to inform clinical practice and future research directions.

2. Methodology

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines were followed in reporting this systematic review and meta-analysis [20].

2.1. Literature search strategy

A comprehensive search of the literature was conducted in the following databases: PubMed® (U.S. National Library of Medicine, USA), Web of Science® (Thomson Reuters, USA) and SciVerse Scopus® (Elsevier Properties S.A, USA) for studies published before the 6th of July 2023 from their inception. In the PubMed® database, an "advanced" search was performed on article titles and abstracts using keywords. Similarly, the Web of Science® database was searched using the advanced search operator TS (Title, Abstract, Author Keywords, Keywords Plus) and in the SciVerse Scopus® database in the article title, abstract or keywords. The detailed search strategy is shown in Supplementary File 1. The cited references of retrieved articles and previous reviews were also manually checked to identify any additional eligible studies. All citations were imported into a bibliographic database (EndNote X8; Thomson Reuters) and duplicates were removed. This search process was conducted independently by two reviewers (WR and PS) and the final group of articles to be included in the review was determined after an iterative consensus process.

2.2. Study selection, data extraction

The title, abstracts and full text of all articles were screened for eligibility. The studies that met the following criteria were included in the study using the populations, interventions, comparison, outcome, and study (PICOS) design strategy [21].

Population (P): Individuals aged ≥ 18 years with a confirmed diagnosis of non-alcoholic fatty liver disease (NAFLD), determined by ultrasonography or histology.

Interventions (I): Randomized controlled trials (RCTs) involving herbal treatment for NAFLD.

Comparison (C): Control groups receiving a placebo.

Outcome (O): Studies with a Jadad score \geq 6, published in English, and reporting relevant health variables of interest such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), liver stiffness, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), high density lipoprotein (HDL) cholesterol, triglycerides (TG), waist circumference (WC), weight, and body mass index (BMI).

Study Design (S): Eligible studies must be RCTs involving human participants, while excluding non-RCTs, animal experiments, pilot studies, case reports, conference proceedings, commentaries, editorials, book chapters/book reviews, and duplicated publications. Additionally, studies investigating coffee and green tea as herbal interventions were excluded.

2.3. Data extraction

The following data were extracted from the included articles by one author (WR) by using a standardized form. A second author rechecked the accuracy of the data extracted (PS), and discrepancies were corrected by the involvement of a third author where necessary (JP). The following details were extracted from each study: a) details of the study (study setting, year of publication, study design, duration), b) study population, sample size, gender and average age of the subjects, c) primary intervention(s) and CG, d) co-interventions, outcome measures and (e) results of the main outcomes.

2.4. Assessment of quality

The study quality assessment for RCTs was done by two independent investigators (WR and PS) using the Modified Jadad Scale. Each study could achieve a score ranging from zero to eight [22]. Studies were then classified as high-quality (scoring 6–8 points), moderate quality (4–5 points), or poor quality (less than 4 points) from a maximum possible score of eight. Only studies achieving a score of six or higher were considered for inclusion in this review. The Jadad scale score of each

D.W. Rathnayake et al.

included study is reported in the Supplementary File 2.

2.5. Data analysis

We used the mean and standard deviations of each variable of interest (ie. ALT, AST, liver stiffness, FBG, HDL, TG, HbA1c, waist circumference, weight, and BMI) of the IG and CG for the analysis. We simulated pre- and post-assessment realization from normal distribution using their respective means, standard deviations, and sample sizes, for both IG and CG. This process was repeated 1000 times to account for random variability. For each simulation, we calculated the difference between the pre- and post-assessment realisations for each variable of interest in the IG and CGs. The mean and standard deviation of these differences were then calculated to obtain an estimate of the true effect size. This simulation-based approach allowed us to make inferences about the population effect size without relying on assumptions about the underlying distribution of the data. It also allowed us to assess the precision of our estimates by considering the variability of the simulated differences.

We considered mean difference (MD) for effect size calculations, as our objective was to estimate the effect of intervention in the original Advances in Integrative Medicine xxx (xxxx) xxx

scale of measurement to enable clinical interpretation. Meta-analyses were conducted using a random-effects model to account for heterogeneity between studies. Subsequently, a subgroup analysis was done to evaluate effect size differences between single and polyherb interventions for each variable of interest. Heterogeneity was assessed using the I² statistic and Cochran's Q test. A significance level of α =0.05 was used for all statistical tests. Analysis was done with "meta" package in R programming language version 4.3.

3. Results

3.1. Literature selection

Through our search strategy, 2575 articles were retrieved: 452 from PubMed, 1429 from Scopus and 694 from Web of Science. After removing 943 duplicates, 1632 articles were selected. After initial screening, based on titles and abstracts, 70 articles were selected for further full-text review. After careful reading of the full-text articles, 24 studies were excluded for the following reasons: not meeting the highquality Jadad score (n=14), full text-article not available in English (n=2), the full-text article being not available (n=8). By manually



Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for study selection.

D.W. Rathnayake et al.

searching, two additional articles were discovered. Finally, 48 articles were included in this systematic review and meta-analysis. The study selection protocol conducted per the PRISMA guidelines is shown in Fig. 1.

3.2. Study characteristics

A summary of the included articles is presented in Tables 1 and 2. Out of the 48 eligible articles identified, five studies were conducted in Italy [23–27], two each in Korea [28,29], China [30,31], Malaysia [32, 33], and one each in Pakistan [34], USA[35] and India[36]. The remaining 34 trials were conducted in Iran [37–73]. The review included all double or single-blinded, randomized controlled trials published between 2010 and 2022. The study durations ranged from 6 weeks to 12 months. A total of 3741 patients (2013 in IG and 1728 in CG) were eligible for inclusion, with individual sample sizes ranging from 36 to 226 patients. Two trials did not identify the gender of participants [20,21], whereas the rest of the studies included both males (n=1978) and females (n=1740).

Out of the included studies, 38 were on single herbal/herb-derived compound preparations and 10 studies were on polyherbal preparations [23–27,31,36,69–71]. The key study characteristics of the studies on single herbal preparations are shown in Table 1. The most common single herbal medicinal materials found in the 36 studies included: *Phyllanthus niruri, Beta vulgaris, Allium sativum* L. Silymarin (*Silybum marianum*), *Portulaca oleracea L. Nigella sativa and Cynara cardunculus* L. *etc.* In 42 RCTs, the single herbal preparation was given in the form of a tablet/capsule in the treatment group, in five as an oral liquid [28,51,55, 60], and one as a powder.[38] The composition of the formulation of polyherbal preparations is depicted in Table 2. The most common herbs used in polyherbal formulations were *Cynara cardunculus*, and *Curcuma longa*.

Among the selected studies, 18 of them had included cointerventions; dietary modifications, physical activity [38], or both [39]. The most measured outcomes were related to response measures of liver biochemistry including AST and ALT levels (n=45), ultrasound scan findings (n=18), body weight (n=22) and biochemical response measures of glycaemic control (n=28) and blood lipids (n=31). Body mass index, waist circumference, hip circumference and waist-to-hip ratio were measured as other anthropometric parameters. The commonest parameter measured for the assessment of glycaemic control was fasting blood glucose level, while HbA1c, fasting insulin, insulin resistance, HOMA- β , HOMA-IR, and QUICKI were used as other parameters. Only three studies measured histological parameters related to NAFLD before and after the intervention.

3.3. Meta-analysis

3.3.1. ALT

Thirty-nine studies (44 interventions) assessed the impact on ALT levels, encompassing 3333 patients [23–29,31,32,34,36–40,42,43,47, 49,52,55–57,59,62,64–67,69,70–74]. Data showed high levels of heterogeneity (I² = 99 %, P < 0.001). The herbal compounds showed a greater reduction in ALT levels compared to the CG, with an average excess decrease of 7.23 units (95 % CI: 4.82 – 9.64 units, P < 0.0001) (Fig. 2.A).

3.3.2. AST

A total of 29 studies, including 34 interventions, incorporating 2564 patients, evaluated the impact on AST levels [23,25,26,31,32,34,36–39, 42,43,45,47,49,52,55,57,59,62,64–67,69,70–73]. Data showed high levels of heterogeneity (I² = 76 %, P < 0.001). Herbal interventions showed a higher AST reduction over the controls (P = 0.005). AST levels were 3.08 (95 % CI: -0.92; -5.23) IU/L lower on average in the herb group than in the CG (Fig. 2.B). Among herbal interventions, 19 used a single herb compound and 10 used polyherbal compounds. There was no

difference in AST reduction between single and polyherbal compounds (-4.8349 [95 % CI: -7.9802; -1.6895] vs -1.8522 [95 % CI: -4.1910; 0.4867], P = 0.1011).

3.3.3. Liver stiffness

There were 7 studies assessing liver stiffness using fibro scan readings of 724 patients [25,26,32,42,44,72,73]. Data showed low levels of heterogeneity (I2 = 24 %, P = 0.23). There was a significant difference in liver stiffness readings between the IGs and CGs (liver stiffness difference = 15.49 (95 %CI: 6.86 – 24.12), P=0.0004) (Fig. 2.C).

3.3.4. Waist Circumference (WC)

Eighteen studies, evaluating 20 interventions, analysed the effects of WC, encompassing 1487 patients [23,25,32,38–40,42,43,49,52,57,59, 62,63,69,70,71,73]. Data showed low heterogeneity ($I^2 = 0.0$, P = 0.91). Herbal interventions showed a higher WC reduction over the controls (P = 0.002). WCs was 1.99 (95 % CI:-0.71; -3.27) cm lower on average in the herb group than in the CG (Fig. 3.A). Among these studies, 14 used a single herb compound and 6 used polyherbal compounds. There was no significant difference in WC reduction between single and polyherbal compounds (-1.4174 [95 % CI: -3.1370; 0.3022] vs -1.3176 [95 % CI: -2.8935; 0.2584], P = 0.1011).

3.3.5. Weight

The impact on weight was investigated across 18 studies, including 18 interventions, and 1430 patients [23,25,26,34,38,40,42–44,49,52, 57,59,62,63,66,70,71]. Data showed low heterogeneity ($I^2 = 0.0 \%$, P = 0.99). Herbal interventions showed a higher weight reduction than the controls (P = 0.03). Weight measurements were 1.77 (95 % CI: -0.13; -3.41) kg lower on average in the herb group compared to the CG (Fig. 3.B). Among these studies, 12 used a single herb compound and six used polyherbal compounds. Single herb compounds showed a significantly higher weight reduction compared to polyherbal compounds -2.4094 [95 % CI: -4.0046; -0.8141] vs -0.3083 [95 % CI: -0.8791; 0.2625], P = 0.0051).

3.4. BMI

There were 23 studies, incorporating 27 interventions, assessing BMI levels of 2066 patients [23,25,26,32,34,38–40,42,44,45,47,49,52,55, 57,62,64,65,69,71,73]. Data showed low heterogeneity ($I^2 = 0.0 \%$, P =1.0000). Herbal interventions showed a higher BMI reduction than the controls (P = 0.03). BMI levels were 0.38 (95 % CI:0.05; 0.71) units lower on average in the herb group than in the CG (Fig. 3.C). Among these studies, 16 used a single herb compound and seven used polyherbal compounds. There was no difference in BMI reduction between single and polyherbal compounds (-0.3682 [95 % CI: -0.6310; -0.1055] vs -0.3186 [95 % CI: -0.4767; -0.1606], P = 0.7216).

3.5. TG

There were 18 studies (21 interventions) assessing TG levels of 1542 patients [25,26,36,37–39,44,49,55,57,62,64–66,69,71–73]. Data showed moderate levels of heterogeneity ($I^2 = 60$ %, P = 0.0002). Herbal interventions showed a higher TG reduction over the controls (P < 0.0001). TG levels were 20.05 (95 % CI:10.42; 29.67 mg/dL lower on average in the herb group than in the CG (Fig. 4.A). Among these studies, 12 used a single herb compound and 6 used polyherbal compounds, there was no difference in TG levels between herbal interventions over the controls (-12.9318 [95 % CI: -22.1286; -3.7349] vs -8.8687 [95 % CI: -18.6922; 0.9548], P = 0.4665).

3.6. HDL

There were 19 studies (22 interventions) assessing HDL levels of 1762 patients [23,25,26,32,36–40,44,49,55,57,64,66,69,71–73]. Data

D.W. Rathnayake et al.

Table 1

Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
Abu Hassan et al. [32], 2023; Malaysia	R, DB, PC; 12 months; 8 points	NAFLD patients with mild-to- moderate stages; $105/100; M=107, F=119; \ge 18$ years	Phyllanthus niruri extract of 3000 mg/ day (12 capsules)	Placebo (12 capsules containing lactose and corn starch/ day)	-	CAP and fibrosis scores, AST, ALT, ALP, GGT, FBS, HbA1C, TC, LDL, HDL, BMI, WC	No significant difference in the change of CAP score or liver enzyme levels between the groups. IG showed a significant reduction in fibrosis score (p = 0.001).
Afzali N. et al. [37], 2020; Iran	R, DB, PG; 6 months; 7 points	NAFLD patients diagnosed with USS and liver transaminases; 60/ 57; M=62, F=55; 18–70 years	Beta vulgaris capsule (400 mg/daily), including vitamin E pearl (300 IU/twice daily), Livergol tablet (140 mg/ daily)	Same dosages of vitamin E pearl, Livergol tablet, and a placebo instead of Beta vulgaris extract	-	AST, ALT, ALP, PT, ALB, FBS, TG, TC, LDL, HDL, grade of fatty liver,	AST significantly reduced in the IG compared to the CG ($P = 0.04$). ALT reduction was not significant in the groups. But <i>Beta</i> <i>vulgaris</i> on ALT increased over time ($P < 0.001$). ALP, FBS, LDL, and HDL significantly improved in the IG compared to the CG.
Akbari S. et al. [38], 2022; Iran	R, DB, PC; 8 weeks; 7 points	NAFLD patients with BMI of 25–40 kg/ m ² ; 57/53; M=87, F=31; 20–65 years	4 g rosemary (<i>Rosmarinus</i> <i>officinalis</i> Linn) leaf powder/day	Placebo (starch)	weight loss diet & physical activity	AST, ALT, ALP, GGT, FBG, HbA1c, Fasting insulin, Insulin resistance, HOMA-β, HOMA-IR, QUICKI, TC, TG, LDL-C, Weight, BMI, WC	Liver enzymes, FBG, fasting insulin, insulin resistance, TC, TG, LDL, and anthropometric indices decreased significantly in both groups with weight loss. No significant difference between the 2 groups, except in HOMA-6.
Askari F. et al. [39], 2014; Iran	R, DB, PC; 12 weeks; 6 points	NAFLD diagnosed in the previous 6 months, with USS and ALT; 23/22; M=21, F=24; 20–65 years	750 mg Cinnamon capsule (2 capsules/ day)	2 placebo capsules/day	balanced diet and physical activity	ALT, AST, GGT, insulin, HOMA-IR, FBS, QUICKI, TC, TG, LDL, HDL, hs-CRP	IG showed significant decreases in HOMA -index, FBS, TC, TG, ALT, AST, GGT and hs-CRP, but no significant change in serum HDL. In both groups, LDL decreased
Cheraghpour et al. [72], 2019; Iran	R, DB, PC; 12 weeks; 7 points	AFLD grades 2 and 3 (at least 35 % of hepatocytes, CAP >263) on FibroScan; 25/24; M=22, F=25; 18–70 years	2 capsules of hesperidin(each contains 500 mg),	2 capsules of placebo (starch)	healthy lifestyle habits including dietary and physical activity recommendations	ALT, AST, GGT, FBS, Insulin, HOMA-R, TC, TG, LDL-C, HDL-C, Weight, BMI, WHR, Energy, MET, TNF- α , NF- κ B steatosis, fibrosis	signineanity. Hesperidin supplementation accompanied with lifestyle modification is superior to lifestyle modification alone in management of NAFLD at least partially through inhibiting NF-xB activation and improving lipid profile.
Damavandi RD. et al. [40], 2021; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD by USS (hepatic steatosis grade 1-3) with BMI 25-40 kg/m ² ; 37/ 34: M=43 F=31; ≥18 years	300 mg purslane (Portulaca oleracea L.) extract 1 capsule/day	Placebo- filled with 300 mg toast powder. 1 capsule/day	-	ALT, AST, ALP, GGT, total bilirubin, FBS, insulin, HOMA-IR, QUICKI, TC, TG, LDL, HDL, Liver steatosis grade, Weight, BMI, WC	ALT, AST, GGT, FBG, insulin resistance, TG, LDL, decreased significantly in the IG. No significant changes were observed in liver steatosis grade, insulin, liver enzymes, total bilirubin, libid

profile, and blood (continued on next page)

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Table 1 (continued)							
Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
Daneshi-Maskooni M. et al. [41], 2019; Iran	R, DB, PC; 3 months; 8 points	NAFLD by USS (mild to severe fatty infiltration), & 25 =/ <bmi<35 <br="" kg="">m²; 43/44; M=54, F=33; 30–60 years</bmi<35>	Two 500 mg capsules 3 times/day with meals. Ingredient - <i>Elettaria</i> <i>cardamonum (L.)</i> <i>Maton</i>	Placebo	-	FBS, FBI, HOMA-IR, QUICKI TC, TG, LDL, HDL, Liver steatosis grade, BMI, Serum irisin	pressure between the two groups. IG significantly increased irisin, HDL- c, and QUICKI and decreased FBI, TG, LDL-c, HOMA-IR, and the grade of fatty liver. After adjustment for confounders, the changes were similar except for LDL. No significant
Darand M. et al. [42], 2019; Iran	R, DB, PC; 12 weeks; 8 points	NAFLD CAP score > 263 (dB/m); 22/21; M=21, F=22 ≥18 years	4 capsules/day (2 g/ day) <i>Nigella sativa</i> seed	Placebo - 2 g/ day starch	-	AST, ALT, GGT, TNF- a, hs-CRP, NF-kB, Weight, BMI, WC, HC, WHR, Fibro scan exam - CAP score, steatosis, fibrosis	differences in FBS, TC, and BMI TNF- α decreased significantly in both, hs-CRP and NF- κ B only decreased significantly in IG, reduction in TNF- α was significantly more in IG. Hepatic steatosis and its percentage decreased significantly only in the IG; the changes were not significantly different between
Ebrahimi-Mameghani M. et al. [43], 2017; Iran	R, DB, PC; 8 weeks; 7 points	NAFLD by USS, obese 29/26; M=30, F=25 20–50 years	400 mg/day vitamin E + 4 tablets of 300 mg/day of <i>Chlorella vulgaris</i> - before breakfast (1 tablet), lunch (2 tablets) and dinner (1 tablet)	Vitamin E 400 mg/day and 4 tablets of placebos/ day		AST, ALT, GGT, total bilirubin FBS, Insulin, HOMA- IR Weight, WC, HC, TNF-α, hs-CRP, Fibro Scan score	two groups. Both groups had significant anthropometric reductions, with higher weight reduction in the IG. In the IG, liver enzymes, FSG, and hs-CRP significantly decreased, and serum insulin and HOMA-IR increased significantly. Mean changes in serum glucose and TNF-α
Ehsani S. et al. [44], 2022; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD stage 1 diagnosed by FibroScan with 25 ≤BMI< 30 kg/m ² 40/40; M=46, F=34 20–60 years	500 mg sumac powder capsule, 4 times a day Ingredient - <i>Rhus</i> <i>coriaria Linn,</i>	Equal amounts of placebo capsule containing dextrin for the same period	-	AST, ALT, ALP, GGT TC, TG, LDL, HDL, leptin, steatosis status, Weight, BMI, WHR, SBP, DBP	differed significantly between groups. SBP decreased, but DBP did not change in IG. AST, ALT, ALP, TC, TG, LDL were decreased but HDL was increased in the IG compared to the CG. No change in GGT and Leptin between two groups. The status of steatosis was improved in the
Ghaffari A. et al. [45], 2019; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD, BMI 24.9–40 kg/m ² Turmeric(T)= 21, Chicory seed(C)= 21, T+C=22, Placebo=21 M=46, F=46 20–60 years	Group T consumed 3 g/d turmeric; group C infused 9 g/ d of powdered chicory seed; T+C consumed (3 g/ d turmeric + infused 9 g/d chicory seed). Turmeric- <i>Curcuma</i> <i>longa</i> L. Chicory	Placebo (6 × 500 mg corn starch capsules)	-	AST, ALT, Total antioxidant capacity (TAC), Malon- dialdehyde (MDA), hs-CRP, IL -6 and TNF- α , BMI, Trans- abdominal USS- Degree of hepatic steatosis	IG compared to CG Significant decreases in BMI of subjects in C and T+C groups, compared with CG. Serum levels of TAC were increased in T and C groups. Chicory seed and combination of chicory seed and turmeric significantly (continued on next page)

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Table 1 (continued)							
Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
			seeds- Cichorium intybus				reduced serum levels of MDA compared to CG. Combination of turmeric and chicory seed marginally reduced serum level of II = 6
Hajiaghamohammadi AA. et al. [46], 2012; Iran	R, DB, PC; 2 months; 6 points	NAFLD with elevated liver enzymes and increased liver echogenicity on USS; M=38, F=28; I= 28-52 y, C= 21-56 y	1 capsule containing 2 g aqueous licorice root extract per day. Glycyrrhizin - major bioactive component of licorice root extract	Placebo (2 g starch)	-	AST, ALT, Weight, BMI	In the IG, ALT and AST decreased which were statistically significant. In the CG, drops in ALT and AST was not statistically significant. The BMI difference before and after the study was not statistically significant in both erroups.
Han B. et al. [28], 2020; Korea	R, DB, PC; 8 weeks; 6 points	NAFLD patients with borderline and mild liver dysfunction with elevated AST or ALT; 38/41; M=58, f=21 19–73 years	SPB–201 (powdered-water extract of Artemisia annua L.) twice a day in the morning and evening	Placebo with crystallin cellulose twice a day in the morning and evening	-	AST, ALT, BMI, Multidimensional Fatigue Scale score (MFS)	SPB-201 can improve liver function in subjects with NAFLD at mild to moderate levels. A significant decrease of AST and ALT was observed in the IG as compared to the CG. MFS of the IG decreased but that of the CG increased, implicating that SPB-201 also eliminated overall fatime
Hosseini SMR. Et al. [47], 2018, Iran	R, OL, PC; 3 months; 6 points	NAFLD (grade 1–3) diagnosed by USS and BMI>27 kg/m ² 24/23; M=23, F=24 20–60 years	TPM based diet plus Hepatomelis capsules (herbal tea consisting of intact seeds of <i>Nigella sativa</i> and dry leaf of <i>Melissa officinalis</i>) (10 mg twice per day)	Low fat low- calorie diet plus Orlistat capsules (500 mg twice per day)	TPM based diet/ low fat low-calorie diet	AST, ALT, grade of fatty liver (fatty tissue infiltration in the liver by USS), BMI	A significant decrease in the AST, ALT, BMI, and grade of fatty liver in both groups after the intervention compared with baseline. A more significant reduction in the grade of fatty liver over the study period in the IG
Hussain M. et al. [34], 2017; Pakistan	R, SB, PC; 12 weeks; 6.5 points	NAFLD with USS fatty liver grading 0–3, mild to moderate elevation of transaminases, BMI \geq 25 kg/m ² ; 35/35; M=44, F=26; 20–45 years	Nigella sativa 1 g twice a day	Placebo twice a day		AST, ALT, GGT, USS finding of fatty liver, Weight, BMI	Significant reduction in body weight, BMI AST, ALT in the IG vs CG.57.14 % patient had normal fatty liver grading on USS after 12 weeks in the IG, compared to placebo (n=0.002).
Jazayeri SF. et al. [48], 2021; Iran	R, DB, PC; 12 weeks; 8 points	NAFLD with elevated liver enzymes USS grades 1 or 2 31/32; M=60, F=3 12–80 years	2 capsules (each containing 500 mg <i>Plantago major</i> seed) at 10 a.m. and 2 capsules at 6 p.m.	Placebo capsules (Two 500 mg capsules, 2 times a day)	dietary recommendations and walking exercise	AST, ALT, FBS, TC, TG, HDL, LDL, WC, BMI, USS grade	IG showed significant reduction in ALT, AST, TG, WC, and grade of fatty liver in USS. No significant difference between the two groups regarding serum levels of FBS, HDL, LDL, cholesterol, and other outcomes.
Jazayeri-Tehrani SA. Et al. [49], 2019; Iran	R, DB, PC; 3 months; 7 points	overweight/obese patients with NAFLD diagnosed using USS, BMI	Two 40 mg capsules/day after meals, 1 capsule at	Placebo capsules	low-calorie diet, and moderate-intensity aerobic exercise	ALT, AST, FBS, FBI, HbA1c, HOMA-IR, QUICKI, TC, TG, LDL, HDL, BMI, WC,	IG compared with CG significantly increased HDL, QUICKI, and nesfatin (continued on next page)

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Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
		25–35 kg/m ² 42/42; M=46, F=38 25–50 years	breakfast and another at dinner			SBP, DBP, Fatty liver degree, anthropometrics, TNF-a, hs-CRP, IL–6 Nesfatin	and decreased fatty liver degree, liver transaminases, WC, FBS, FBI, HbA1c, TG, TC, LDL, HOMA-IR, TNF-alpha, hs-CRP, and IL-6 (P < 0.05). The mean changes in weight, BMI, body composition (BC), and blood pressure were not significant (P > 0.05).
Jeong JY. et al. [29], 2017; South Korea	R, DB, PC; 12 weeks; 6 points	NAFLD diagnosed by USS high dose =22, low dose=23 placebo=23; M=54, F=14 19–75 years	High dose group (400 mg) HL tablet, low dose group (133.4 mg) HL tablet daily. Active ingredients- Honokiol and magnolol extracted from Magnolia officinalis	Placebo daily		AST, ALT, HOMA-IR, TC, TG, HDL, LDL, VLDL, FFA, BMI, post-Treatment change of hepatic fat content (HFC)	The mean HFC of the high dose HL group, but not of the low dose group, declined significantly (high dose vs placebo, P = 0.033; low dose vs placebo, P = 0.386). Serum ALT levels decreased in the groups receiving HL tablet while other factors were unaffected
Kashkooli RI. et al. [50], 2015; Iran	R, SB, PC; 3 months; 7.5	NAFLD with USS evidence of liver steatosis and increased liver enzymes; 40/40; M=32, F=48; I=43.65 years, C=42.97 years	2 capsules (750 mg) of <i>Berberis vulgaris</i> extract daily, one before breakfast and one before dinner	Placebo two capsules every day, one before breakfast and one before dinner	-	ALT, AST, FBG, TC, TG, HDL, LDL, Weight	In the IG, the ALT and AST decreased which was statistically significant compared to the CG. In the CG, the ALT and AST decreased, but not significantly. Also, in CG a significant decrease in weight, TG, and TC, while no significant change was found in FBS, URL WIN
Kavyani M. et al. [51], 2021; Iran	R, DB, PC; 12 weeks; 8 points	NAFLD by a USS, BMI 25–35 kg/m2; 18/18; M=19, F=17; 20–50 years	20 g d ⁻¹ <i>Camelina</i> sativa oil (CSO) + resistant dextrin 5 g at breakfast and 5 g at dinner	20 g d ⁻¹ CSO + maltodextrin At breakfast and dinner	calorie-restricted diet & limited consumption of nuts and fish	FBG, insulin, hs-CRP, endotoxin, antioxidant enzyme activity, TAC, MDA, 8-iso prostaglandin F2α, Serum uric acid	Significantly decreased insulin concentration, HOMA-IR, hs-CRP, endotoxin, cortisol, GHQ, DASS, MDA and increased levels of TAC and superoxide dismutase in the IG compared with the CG. No significant changes of other biomarkers
Kazemi S. et al. [52], 2020; Iran	R, DB, PC; 12 weeks; 8 points	NAFLD with BMI 25–30 40/40; M=34, F=46 20–60 years	500 mg sumac powder capsule, 4 times/day (preferably after each meal). Active ingredient- <i>Rhus</i> <i>coriaria</i> L.	Equal amounts of placebo capsule containing dextrin for the same period.	500-calories deficit diet plan	AST, ALT, FBS, serum insulin, HbA1c, QUICKI MDA hs-CRP	IG showed a greater decrease in hepatic fibrosis, liver enzymes and FBS, serum insulin, HbA1c, HOMA-IR, MDA, hs-CRP, compared to the placebo; while the QUICKI was significantly higher in the IG at the end of intervention.
Kelardeh BM. et al. [53], 2020; Iran	R, DB, PC; 12 weeks; 7 points	obese older women with NAFLD diagnosed with USS M=0, F=45 Resistance training	RT and RTC groups received nonlinear resistance training while the C and P groups had a normal	placebo (P) normal sedentary lifestyle	-	AST and ALT, Total bilirubin liver structure	In the RT and RTC groups, AST and ALT significantly decreased (P <= 0.05), unlike the C (continued on next page)

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Advances in Integrative Medicine xxx (xxxx) xxx

Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
		(RT)=12, Curcumin (C) =11, RT + C (RTC)=11, Placebo (P)=11 60-71 years	sedentary lifestyle. C and RTC groups received daily curcumin capsule				and P groups (P > 0.05). ALP, total bilirubin, platelet counts, and liver structure remained unchanged in all groups (P > 0.05). Resistance training, with or without curcumin supplementation, improved liver function significantly, while curcumin alone had
Khavasi N. et al., [54], 2018; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD with BMI 25–35 kg/m ² ; 22/ 22; 12–80 years	40–50 g of the caper fruit pickle (CFP) with daily meals Active ingredient - <i>Capparis spinosa</i>	Placebo	lifestyle changes	Weight, WC, AST, ALT, FBS, insulin, HOMA-IR, LDL/HDL, TG/HDL, TC/HDL, non-HDL.C, hs-CRP	ho significant effect. Weight and WC significantly decreased both in the IG and CG ($P = 0.001$ and $P = 0.03$). Adjusted to the baseline measures, a mean difference of ALT ($P = 0.04$), LDL/ HDL ($P = 0.001$), TG/HDL ($P = 0.001$) and TC/HDL ($P = 0.001$)
Khonche A. et al., [55], 2019; Iran	R, DB, PC; 3 months; 8 points	NAFLD diagnosed by USS 60/60; M=64, F=56 20–70 years	2.5 mL fully standardized <i>Nigella</i> <i>sativa</i> seed oil every 12 hourly	placebo		AST, ALT, LDL, HDL, TG ultrasound grade- 0, 1, 2, 3 hepatic steatosis, blood urea nitrogen, creatinine, BMI	fine for than the CG. Grade of hepatic steatosis was significantly reduced in the IG compared to the CG ($P = 0.004$). Significant reduction of variables in the oil and placebo groups in ALT, AST, TG, LDL-C, HDL-C. The oil did not significantly affect the other outcome variables compared to the alcoche
Mojiri-Forushani H. et al. [56], 2022; Iran	R, DB, PC; 2 months; 7 points	NAFLD with BMI of 30 – 40 kg/m2; 45/ 45; M=52, F=38; 20–50 years	Grape seed extract (GSE) capsules (200 mg, 2 times a day Active ingredient - <i>Vitis vinifera</i>	200 mg starch		AST, ALT, FBS, TG, HDL, LDL, TC, HDL/ LDL ratio, BMI	AST, ALT, FBS, TG, HDL, LDL, and cholesterol significantly decreased, (P-value < 0.05), and HDL significantly increased in the IG (P-value < 0.05) compared to PG, but BMI and weight did not change significantly
Musazadeh V. et al. [57], 2022; Iran	R, DB, PC; 12 weeks; 8 points	NAFLD with BMI: 25–35 kg/m2; 22/ 21; M=21, F=22; 20–50 years	Camelina sativa oil (CSO) supplement	Placebo	Calorie-restricted diet, minimal intake of nuts and fish and avoid antioxidants and omega-3 supplements.	AST, ALT, TG, TC, LDL-c, TC/HDL, LDL/HDL, atherogenic index, weight, BMI, WC, HC, WHR, adiponectin concentrations	Significant differences in weight, BMI, WC, WHR, TG, TC, LDL, TC/HDL, LDL/HDL, atherogenic index, ALT, and adiponectin concentrations in the IG compared with the CG. No significant differences in HC, neck circumference, HDL, and other liver (continued on next page)

9

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Author; Published Year;	Study design;	Study population; Sample size (I/C);	Intervention; Dose/Frequency	Control; Dose/	Co-intervention	Outcome measures	Significant outcome
Country	Duration; Jaded score	Male/Female; Age (years)		Frequency			
Navarro VJ. et al. [35], 2019; USA	R, DB, PC; 48 weeks; 7 points	NASH without cirrhosis and a NAFLD Activity Score (NAS) of >/=4 on the baseline biopsy; Legalon 420 mg = 26; Legalon 700 mg = 27; placebo = 25; M=45, F=33; >18 yrs	Legalon® 420 mg, 700 mg three times daily Active ingredient - <i>Silybum marianum</i>	Placebo three times daily	Dietary restriction of saturated and total fats, maintain a target weight/BMI of $ %change of bodyweight.$	Histological improvement in NAS ALT and AST, ALP, FBG, HOMAr, TG, TC, BMI	enzymes in the IG compared with the CG. No benefit from silymarin in the intention to treat analysis. A substantial number of participants (49, 63 %) did not meet histological entry criteria and that fibrosis stage improved most in the PG, although not cimiferantly different
Parsi A. et al. [58], 2020; Iran	R, DB, PC; 8 weeks; 7 points	NAFLD diagnosed by USS and BMI 24.9–40 kg/m2 30/ 30; M=33, F–27 20–60 years	15 mg crocin once a day. Active ingredient - <i>Crocus</i> <i>sativus</i> extract	Placebo capsules once a day	-	AST, ALT, TG, HDL, LDL, BMI, WC	from other groups. TG (p = 0.0008), AST (p = 0.03) and ALT (p = 0.0001) were significantly decreased in the IG. Changes in HDL-C and LDL-C levels were not statistically significant in the two
Pour,F.K et al. [59], 2020,Iran.	R, DB, PC; 12 weeks; 8 points	NAFLD with USS grade of 1–3; 36/36; M=43, F=33; 18–65 years	Daily supplementation of either one tablet of 100 mg saffron (<i>Crocus sativus</i>)	Placebo	Healthy diet and physical activity	AST, ALT, Weight, BMI, WC, HC, WHR, body fat percent (BFP), Muscle mass, TNF-α, MDA, TAC, hs- CRP, leptin, adiponectin	groups. In the IG, significant decreases in hs-CRP, leptin, MDA and significant increase in TAC were observed compared to the PG. No significant changes in serum ALT, AST, TNF- α , body composition, and anthropometric
Rashidmayvan, M. et al. [60], 2022; Iran	R, DB, PC; 8 weeks; 7 points	NAFLD diagnosed by USS 22/22; 20–60 years	1000 mg of Nigella sativa oil per day	Placebo		Weight, BMI, WC, HC, WHR Serum levels of adiponectin, leptin, SBP, DBP	No statistically significant differences in serum levels of adiponectin, leptin, SBP, and DBP between the two groups. No significant changes were observed in leptin, adiponectin, SBP, and DBP within the two groups
Rostamizadeh P. et al. [61], 2022; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD diagnosed by USS and liver transaminases, and BMI \geq 25 kg/m ² ; 28/24; M=0, F=60; 18-65 years	1000 mg/day powder of licorice root extract (<i>Glycyrrhiza glabra</i>) 2 capsules daily (each containing 500 mg) before breakfast and at bedtime	placebo	weight loss diet and healthy lifestyle	AST, ALT, GGT, FBS, Insulin, HOMA-IR, TC, TG, HDL, LDL, Weight, BMI, MDA, Grade of fatty liver	women in the IG experienced a statistically significant improvement in ALT, insulin, insulin resistance, MDA serum levels, and ultrasonographic findings of liver steatosis, compared to the CG.
Sangouni AA. et al. [62], 2020; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD diagnosed by USS with grade 1–3 fatty liver; 45/43; M=57, F=31 aged ≥18 years	4 tablets of garlic (<i>Allium sativum</i> L.) daily (each tablet contained 400 mg garlic powder)	4 tablets of placebo (each placebo contained 400 mg starch)	-	AST, ALT, FBS, Insulin, HOMA-IR, Weight, BMI, WC, BFP, skeletal muscle mass, TAC, SOD, MDA	Significant decrease was seen in the IG compared to the PG in WC, BFP, serum FBS, insulin, HOMA- IR, and MDA. significant increase (continued on next page)

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Table 1 (continued)							
Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
Sangouni, A.A. et al. [63], 2021; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD with grade 1–3 fatty liver 45/43; M=57, F=31; aged ≥ 18 years	4 tablets of garlic (<i>Allium sativum</i> L.) daily (400 mg garlic powder/tablet)	4 tablets of placebo (400 mg starch/tablet)	-	AST, ALT, GGT, ALP, TC, TG, HDL, LDL, Weight, BMI, WC Hepatic steatosis by USS	in skeletal muscle mass, serum concentration of SOD, and TAC. Hepatic steatosis, ALT, AST, GGT, TC, TAG, HDL, and LDL were significantly reduced in the IG compared with the CG. No significant difference between the two groups in
Shafiezadeh R. et al. [64], 2020; Iran	R, DB, PC; 8 weeks; 8 points	grades of 1–3 of NAFLD 32/36; M=48, F=20; 18–60 years	Aqueous extracts of Ajwain seeds 500 mg capsules. Active ingredient - <i>Carum copticum</i> (or <i>Trachyspermum</i> <i>ammi</i>) Seeds	Placebo		AST, ALT, FBS, TC, TG, HDL, LDL, grade of fatty liver, BMI, WC, Leeds score	In the IG compared to the CG, significant changes were observed in Leeds questionnaire, TG, and ALT, while AST, FBS, and BMI changed similarly in both groups. Cholesterol, HDL, and LDL remained unchanged in both groups. USS findings showed significantly greater improvements in the IG compared to the CG
Shavakhi A. et al. [65], 2015; Iran	R, DB, PC; 6 months; 8 points	NASH with histopathological diagnosis, BMI 30–35 kg/m2 and HbA1c level ≤7 in presence of diabetes; 40/41; M=32, F=49 18–60 years	Oral cumin capsule (<i>Cuminum cyminum</i>) thrice daily	Placebo		AST, ALT, FBS, TC, TG, HDL, LDL, BMI, Grade of steatosis	No significant differences in baseline and post- treatment health markers between groups. Post- treatment reductions in BMI, TG, TC, ALT, AST, LDL, and FBS were not statistically significant, and mean changes and steatosis grade showed no significant differences. However, significant differences were observed in AST and HDL changes between groups (P < 0.05)
Soleimani,D,et al. [66], 2020; Iran	R, DB, PC; 15 weeks; 8 points	NAFLD with USS diagnosis and elevated liver transaminases 51/47; M=46, F=64 20–70 years	800 mg garlic (<i>Allium sativum</i> L.) per day	Placebo		ALT, AST, FBS, Hb A1C, TC, TG, LDL, HDL, USS - hepatic steatosis, Weight, BMI, Body fat mass	0.05). Significant improvement in the hepatic steatosis, and significant reductions in weight and ALT, AST, FBS, Hb A1C, TC, LDL, and TG in the IG compared to the CG. The results were significant after adjusting for weight change, energy intake, and physical activity.
Solhi H. et al. [67], 2014; Iran	R, DB, PC; 8 weeks; 8 points	NASH diagnosed with USS and persistently elevated liver enzymes.	210 mg/day silymarin (Silybum marianum) orally	Placebo	low-fat, low carb diet, regular sport activity to lose weight up to 4 Kg in 8 weeks	AST, ALT, Weight, BMI	Serum concentrations of both AST and ALT were reduced in the IG. (continued on next page)

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Advances in Integrative Medicine xxx (xxxx) xxx

Table 1 (continued)							
Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co-intervention	Outcome measures	Significant outcome
		I=43.6±8.3 y,					
Wah Kheong, C. et al. [33], 2017; Malaysia	R, DB, PC; 48 weeks; 8 points	$C=39.4\pm10 \text{ y}$ Biopsy-proven NASH and a NAFLD activity score (NAS) of 4 or more and ALT and AST levels \geq 40 IU/L 49/50; M=46, F=53 > 18 years	Silymarin (<i>Silybum</i> <i>marianum</i>) 700 mg 3 times a day	Placebo 3 times a day		AST, ALT, GGT, FBS, HbA1c, HOMA-IR, TC, TG, HDL, LDL Liver biopsy, NAS and fibrosis score, Liver stiffness, Weight, BMI, WC, Central obesity	No significant difference in primary efficacy outcome achievement between groups. The IG showed higher rates of reduced fibrosis than the CG, along with significant reductions in AST to platelet ratio index, fibrosis–4 score, and NAFLD fibrosis score,
Wong VW. Et al. [30], 2013; China	R, DB, PC; 24 weeks; 8 points	histology-proven NASH 40/20; M=33, F=27; 18–70 years	400 mg of Phyllanthus urinaria together with inactive ingredients	Placebo	-	AST, ALT, FBS, HbA1c, TC, TG, HDL, LDL, BMI, WC, NAFLD activity score, histological parameters	not seen in the CG. Phyllanthus is not superior to placebo regarding improvement of NAFLD activity score, histology, liver transaminases, FBS and lipid profile in improving NAFLD activity score in NASH batients.
Yari et al. [73], 2021; Iran	R, PG, OL; 12 weeks; 6 points	patients with more than 37 % hepatic fat (CAP \geq 260, grade \geq 2); Hesperidin(H)=22, Flax(F)=24, H+F=25, Control=21; M=49, F=43 18–70 years	H: 500 mg hesperidin capsule twice daily; F: 30 g brown milled flaxseed daily; H+F: 2 capsules of hesperidin and 30 g of flaxseed.	No intervention	All participants were instructed to lifestyle changes	ALT, AST, GGT, FBS, Insulin, HOMA-IR, QUICKI, hs-CRP TC, TG, LDL-C, HDL-C, BMI, WC, WHR, Energy, MET, TNF- α , NF- κ B steatosis, fibrosis	Hesperidin and flaxseed supplementation improved glucose and lipid metabolism, while reduced inflammation and hepatic steatosis in NAFLD patients. The synergistic effects of their combination were observed on plasma glucose concentration and HOMA IP
Zamani, N.et al. [68], 2018; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD with USS evidence, elevated liver transaminases and BMI 18–35 45/35; M=61, F=24 18–65 years	1400 mg Zataria multiflora Boiss. (Shirazi thyme) ZM powder daily. 350 mg tablets 2 twice daily	Placebo twice daily	Dietary modifications -eliminate fast foods and soft drinks	AST, ALT, GGT, FBS, serum insulin, HOMA-IR, lipid profiles, weight, WC, HC, WHR, SBP, DBP, hs-CRP, TNF- α , grade of fatty liver in USS	ZM resulted in a significant reduction in serum insulin level, insulin resistance, SBP, DBP compared to CG. No significant difference between two groups regarding ALT, hs- CRP, TNF- α , grade of fatty liver in USS, lipid profiles, and

(PC-placebo controlled; PG-parallel group; AST- aspartate transaminase; ALB-albumin; ALT-alanine transaminase; ALP-alkaline phosphatase; BFP- Body fat percentage; BMI-Body mass index; CAP- Continuation attenuation parameter; CK-18-cytokeratin 18; DB-double blind; DL- Dyslipidaemia; DM-diabetes mellitus; F- female; FBS-fasting blood sugar; FGF21-fibroblast growth factor 21; FLI- Fatty Liver Index; GGT- gamma glutamyl transferase; HbA1C-percentage of glycated haemoglobin; HC- hip circumference; HDL-high-density lipoprotein; HFC- hepatic fat content; HOMA-β- homeostasis model assessment of β-cell dysfunction, HTN- hypertension; IG-Intervention group; LDL-low-density lipoprotein; M-male; NAFLD-non-alcoholic fatty liver disease; NAS-NAFLD Activity Score; NFS- NAFLD fibrosis score; OL-Open label; PC-Placebo-controlled; PG-placebo group, PT-prothrombin time; QUICKI- Quantitative Insulin Sensitivity Check Index; R- randomized; RT- Resistance training; SOD- superoxide dismutase; TAC-total antioxidant capacity; TC- Total cholesterol; TG- triglyceride; USS-Ultrasound scan; WHR-Waist: hip ratio; WC- Waist circumference; MET- metabolic equivalent of tasks; NF-κB- nuclear factor-κB).

showed moderate levels of heterogeneity ($I^2 = 51$ %, P = 0.003). There was a significant difference in HDL levels between herbal interventions over the controls (HDL difference = 0.53 [95 % CI: 1.02; 0.04] mmol/L, P = 0.03) (Fig. 4.B).

3.6.1. FBG

There were 18 studies assessing FBG levels of 1600 patients [25,26, 28,32,37–39,43,49,52,62,64–66,69,71–73]. Data showed moderate levels of heterogeneity ($I^2 = 66 \%$, P <0.0001). Herbal interventions showed a higher FBG reduction over the controls (P = 0.05). FBG levels

D.W. Rathnayake et al.

Table 2

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Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co- intervention	Outcome measures	Significant outcome
Cerletti C. et al. [23], 2020; Italy	R, DB, PC; 3 months; 7 points	NAFLD, confirmed by USS, AST/ALT/ GGT; 55/58; M=74, F=39; 18–80 years	Soft gel capsules - mixture of active ingredients: fish oil, phosphatidylcholine, silymarin (<i>Cardo</i> <i>marianum</i>), choline bitartrate, curcumin and D-a-tocopherol, total of 830 mg/day	Formulation excipients and the same amount of choline present in the active mixture (in the form of bitartrate salt).	Mediterranean diet	NAFLD fibrosis score (NFS), AST, ALT, GGT, direct and indirect bilirubin, cholesterol, TG, glucose and insulin, CRP, changes in plasma coagulation–fibrinolysis assay	AST, ALT, GGT decreased, but only AST was significant. But no inter-group difference. Metabolic and inflammatory variables and Coagulation- fibrinolytic parameters were unchanged, except for a slight (<10 %) increase in cholesterol and glucose levels after the active treatment.
Faghihzadeh F. et al. [69], 2015; Iran	R, DB, PC; 12 weeks; 8 points	NAFLD by USS, ALT and Fibro scan 24/24; M=35, F=13; ≥18 years	500-mg resveratrol (A polyphenolic phyto- oestrogen) 1 capsule/ day for 12 weeks	Placebo (edible paraffin) as 1 capsule/ day	Energy- balanced diet & exercise	AST, ALT, GGT, T. bilirubin, insulin sensitivity index, TC, TG, HDL, Apo a1, Steatosis grade – USS, Fibrosis degree – Fibro Scan, BMI, WC, WHR, BP	ALT and hepatic steatosis reduced significantly in IG more than PG.BMI, WC, AST, Total bilirubin, HDL, apo a1 reduced significantly in both. No significant differences between the two groups no significant changes in BP, insulin resistance markers and TG in either group
Ferro Y. et al. [24], 2022, Italy	R, DB, PC; 6 weeks; 7 points	NAFLD diagnosed on the CAP value >216 dB/m by transient elastography; 42/47; M=54, F=40; 30-75 years	One daily capsule of nutraceutical containing 150 mg of Bergamot polyphenol fraction (BPF), 150 mg of <i>Cynara cardunculus</i> extract (CyC) plus 300 mg of excipients (i. e., polyunsaturated fatty acid, and a mixture of bergamot pulp and albedo derivative)	One capsule daily of the placebo. Placebo pill contains maltodextrin and the same excipients	Mediterranean diet without energy intake restriction. overweight/ obese subjects received a restriction of 400–500 calories	AST, ALT, GGT, Glucose, HOMA-IR, TC, TG, HDL, LDL, CAP Score, IQR, Weight, BMI, WHR, SBP, DBP, SUA, Serum creatinine, Total bilirubin	The IG showed significant SUA reduction, especially in those with moderate/ severe hepatic steatosis. The highest baseline SUA demonstrated a more substantial reduction, establishing a significant association between absolute SUA change and nutraceutical treatment.
Ferro Y. et al. [25], 2020; Italy	R, DB, PC; 12 weeks; 8 points	NAFLD only long- term lipid-lowering drugs users; 41/45; 30–75 years	Nutraceutical containing a Bergamot polyphenol fraction and <i>Cynara cardunculus</i> L. extract, 300 mg/day	Placebo daily		AST, ALT, GGT, Total bilirubin, Glucose, Insulin, HOMA-IR, TC, TG, HDL, LDL, non-HDL, Weight, BMI, WC, HC, Fat mass, SBP, DBP, transient elastography - CAP score, Stiffness (kPa), Liver fat content, Creatinine, SUA	The IG had a significantly greater reduction in liver fat content, particularly in android obesity, overweight/ obesity, and women. After adjusting for weight change, the percentage CAP score reduction remained significant only in

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Advances in Integrative Medicine xxx (xxxx) xxx

D.W. Rathnayake et al.

Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co- intervention	Outcome measures	Significant outcome
Ferro Y. et al. [26], 2022; Italy	R, DB, PC; 12 weeks; 8 points	Hepatic steatosis diagnosed by fibroscan; 65/62 M=70, F=70; 30–75 years	Six soft gel capsules daily (Livogen Plus®) containing a combination of natural bioactive components	Six soft gel capsules daily	-	AST, ALT, GGT, albumin, Serum glucose, insulin, HOMA-IR, TC, TG, HDL, LDL, CRP, TNF- α , IL -1β , IL -6 , biological antioxidant potential (BAP), WC, HC, BMI SBP, DBP, Creatinine	individuals over 50 years old. After adjustment for confounding variables (i.e., CAP score and triglyceride at baseline, and changes of GGT, and vegetable and animal proteins, cholesterol intake at the follow-up), found a greater CAP score reduction in the IG rather than placebo. CAP score reduction was higher in those aged 60 or less, with low baseline HDL-C, reduced AST, and among
Hormati A. et al. [70], 2019; Iran	R, DB, PC; 3 months; 8 points	NAFLD diagnosis via USS with elevated liver enzymes; 37/39; M=24, F=52; 18–65 years	2 tablets of Dava Al- Balgham (a combination of Nigella sativa, Zataria multiflora, Pistacia lentiscus, Trachyspermum ammi) consumed with each meal	2 placebo tablets with each meal	-	ALT, AST, ALP, blood urea, serum creatinine Weight, WC, BMI	men The levels of liver enzymes, weight, and WC decreased in both groups. The mean reduction in ALT in the IG was significant compared to PG (P = 0.008). The mean weight loss in the IG and PG was 2.69 kg and 0.9 kg, respectively (P = 0.003). Mean reduction in WC in the IG and PG was 3.43 cm and 0.33 cm, respectively (P =
Li L. et al. [31], 2010; China	R, OL, PC; 6 months; 6 points	NAFLD 45/43 M=55, F=33 18-65 years	Qianggan Capsule (QGC) 3 capsules in the morning, 3 at noon and 4 in the evening, with 1 day pause after every 6 days.QGC includes - Radix Astragali, Radix Salviae militorrhizae, Radix Angelicae sinensis, Radix Paeoniae Alba, Radix Curcumae, Radix Codonopsis, Rhizoma Polygonati, Rhizoma Alismatis, Radix Rehmanniae, Rhizoma Dioscoreae, Fructus Crataegi, Massa Fermentata Medicinalis, Herba Artemisiae scopariae, Radix Gentianae Macrophyllae, Radix Isatidis and Radix Glycyrrhizae	Polyene phosphatidylcholine capsule (PPC) thrice a day.		AST, ALT, GGT, TC, TG Plane CT scan, iconographic indexes	0.001). In the IG, ALT was lowered significantly, and CT liver/spleen ratio significantly increased, ($P < 0.05$). But, the corresponding changes of the two indexes in the control group showed insignificant difference ($P > 0.05$).
Musolino V. et al. [27], 2020; Italy	R, DB, PC; 16 weeks; 6 points	Adult with a history of at least 12 months of T2DM and NAFLD	BPF (300 mg/day), Cyc (300 mg/day), separately or formulated in	Placebo all containing 300 mg of bergamot albedo fibers	-	AST, ALT, GGT, ALP, weight, BMI, SOD, glutathione peroxidase (GPx), MDA, TNF-a	BPF+CyC (Bergacyn) demonstrated significant

(continued on next page)

Advances in Integrative Medicine xxx (xxxx) xxx

D.W. Rathnayake et al.

Author; Published Year; Country	Study design; Duration; Jaded score	Study population; Sample size (I/C); Male/Female; Age (years)	Intervention; Dose/Frequency	Control; Dose/ Frequency	Co- intervention	Outcome measures	Significant outcome
		(diagnosed by USS and echo) Bergamot Polyphenolic Fraction (BPF)=20, <i>Cynara cardunculus</i> (Cyc)=20, BPF+CyC=20, Placebo=20	combination 50/50 % (Bergacyn; BPF+CyC 300 mg/daily) capsules. All containing 300 mg of bergamot albedo fibers micronized and co- grinded as excipients.	micronized and co- grinded as excipients		serum liver fibrosis markers: hyaluronic acid (HA), type III precollagen (PC III), and type IV collagen (IVeC), Endothelial function.	improvement in NAFLD biomarkers and a substantial reduction in oxidative stress/ inflammatory biomarkers. The synergistic effect of both extracts suggests a novel therapeutic strategy for countering vascular inflammation and endothelial dysfunction in individuals with T2DM and NAFLD.
Pothula Rajendra VK. et al. [36], 2022; India	R, DB, PC; 84 days; 8 points	Elevated Fatty Liver Index (FLI) between 31 and 59, BMI 23–29 kg/m ² ; CL16049F1=30, Silymarin=30, Placebo=29; M=46, F=44; 25–60 years	Daily dose of 300 mg CL16049F1, 320 mg Silymarin capsules. CL16049F1 is a blend of aqueous extracts of <i>Terminalia chebula</i> fruit and <i>Sphaeranthus</i> <i>indicus</i> flower heads at a 2:1 ratio. Silymarin contained Silybum marianum	Placebo daily	-	AST, ALT, ALP, GGT, Albumin/globulin, Fatty Liver Index, HOMA-IR, Cystatin C, TC, TG, LDL, HDL, VLDL, SOD, MDA, TBARS, GSH, 36-Item Short-Form Health Survey (SF–36), Gastrointestinal symptoms (GIS) score	Post-trial, CL16049F1 supplementation resulted in a 13.81 % and 16.08 % reduction in FLI score compared to baseline and placebo, respectively (p < 0.05). Additionally, CL16049F1 significantly improved liver enzymes, lipid profile, and oxidative markers, with changes in secondary efficacy measures comparable to the Silumacing group
Rafie, R. Et al. [71], 2020; Iran	R, DB, PC; 12 weeks; 7 points	NAFLD with elevated liver enzymes and USS evidence and 24.9 <bmi<35 <br="" kg="">m²; 23/23; M=20, F=26; 20–70 years</bmi<35>	3 capsules daily, each containing 500 mg of ginger (<i>Zingiber</i> <i>officinale</i>). Active ingredients- polyphenolic compounds as <i>gingerol</i> and curcumin	Placebo 3 capsules daily, each containing 500 mg wheat flour	Energy balanced diet and exercise	AST, ALT, GGT, FBS, Fasting insulin, HOMA-IR, TC, TG, HDL, LDL, LDL/ HDL, SBP, DBP, Weight, BMI, WC, HC, WHR, hs- CRP, TAC, Adiponectin TNF- α and fetuin-A	HOMA, hs-CRP, and fetuin-A in the IG significantly decreased compared to PG. No significant difference between the two groups in body weight, fasting insulin, HDL, TG, adiponectin, TNF- α , TAC, GGT, AST, FLI, fatty liver grade and blood pressure

(PC-placebo controlled; PG-parallel group; AST- aspartate transaminase; ALB-albumin; ALT-alanine transaminase; ALP-alkaline phosphatase; BFP- Body fat percentage; BMI-Body mass index; CAP- Continuation attenuation parameter; CK-18-cytokeratin 18; DB-double blind; DL- Dyslipidaemia; DM-diabetes mellitus; F- female; FBS-fasting blood sugar; FGF21-fibroblast growth factor 21; FLI- Fatty Liver Index; GGT- gamma glutamyl transferase; HbA1C-percentage of glycated haemoglobin; HC- hip circumference; HDL-high-density lipoprotein; HFC- hepatic fat content; HOMA-β- homeostasis model assessment of β-cell dysfunction, HTN- hypertension; IG-Intervention group; LDL-low-density lipoprotein; M-male; NAFLD-non-alcoholic fatty liver disease; NAS-NAFLD Activity Score; NFS- NAFLD fibrosis score; OL-Open label; PC-Placebo-controlled; PG-placebo group, PT-prothrombin time; QUICKI- Quantitative Insulin Sensitivity Check Index; R- randomized; RT- Resistance training; SOD- superoxide dismutase; TAC-total antioxidant capacity; TC- Total cholesterol; TG- triglyceride; USS-Ultrasound scan; WHR- Waist: hip ¹ratio; WC- Waist circumference)

1. Hormati A, et al. Effect of an Herbal Product on the Serum Level of Liver Enzymes in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Placebo-Controlled Trial. Iranian Red Crescent Medical Journal 2019;21(7).

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Medicine xxx (xxxx) xxx



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SD | Total
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IV, Random, 95% Cl | | | | | | | |
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| Δ | Abu Hassan et al. 2023
 | -9.79
 | 29.82 | 105
 | -4.83

 | 29.62 | 100
 | 2.3% | -4.96 [-13.10, 3.18] | | | | | | | | |
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| - | Afzali et al. 2020
 | -19.9
 | 30.1938 | 60
 | -9.2

 | 19.7806 | 57
 | 2.1% | -10.70 [-19.91, -1.49] | | | | | | | | |
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| | Askari et al. 2022
Askari et al. 2014
 | -0.12
 | 14.0038 | 23
 | -5.97

 | 16.0506 | 22
 | 2.2% | -25.10 [-33.92, -16.28] | | | | | | | | |
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| | Cerletti et al. 2020
 | -1.7
 | 36.4825 | 74
 | -8.3

 | 48.6111 | 39
 | 1.2% | 6.60 [-10.77, 23.97] | | | | | | | | |
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| | Cheraghpour et al. 2019
Demourpediet al. 2021
 | -8.22
 | 8.0673 | 25
 | -7.91

 | 16.6484 | 24
 | 2.4% | -0.31 [-7.68, 7.06] | | | | | | | | |
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| | Darrand et al. 2019
 | -1.68
 | 16.6047 | 22
 | -4.5

 | 11.715 | 21
 | 2.3% | -0.28 [-8.84, 8.28] | | | | | | | | |
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| | Ebrahimi-Mameghani et al.2016
 | -13.21
 | 28.3609 | 29
 | -6.92

 | 43.8509 | 26
 | 1.0% | -6.29 [-26.05, 13.47] | | | | | | | | |
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| | Faghihzadeh et al. 2015
Ferro et al 2020
 | -32.38
 | 25.63 | 24
 | -13.54

 | 45 | 24
 | 0.9% | -18.84 [-39.56, 1.88]
1.50 L8 20, 11 20] | | | | | | | | |
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| | Ferro et al. 2022
 | -2.7
 | 6 | 42
 | -6.1

 | 13 | 47
 | 2.8% | 3.40 [-0.74, 7.54] | <u>+-</u> | | | | | | | |
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| | Ferro Y. et al. 2022
Choffori et al. 2019 (CHI)
 | 0
 | 19.8493 | 65
 | -1

 | 30 | 62
 | 2.2% | 1.00 [-7.89, 9.89] | | | | | | | | |
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| | Ghaffari et al. 2018 (TUR)
 | -4.84
 | 9.2865 | 21
 | -0.82

 | 12.6789 | 21
 | 2.5% | -2.38 [-9.10, 4.34] | | | | | | | | |
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| | Ghaffari et al. 2018 (TUR+CHI)
 | -4.08
 | 11.8077 | 22
 | -0.82

 | 12.6789 | 21
 | 2.4% | -3.26 [-10.59, 4.07] | | | | | | | | |
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| | Han et al.2020
Hormati et al 2019
 | -0.24
-28.3
 | 22.8 | 38
 | -0.14

 | 55.9302 | 41
 | 3.0% | -13.60 [-32.63, 5.43] | | | | | | | | |
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| | Hosseini et al. 2018
 | -14.83
 | 27.4129 | 24
 | -32.95

 | 46.5409 | 23
 | 0.9% | 18.12 [-3.84, 40.08] | | | | | | | | |
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| | Hussain et al. 2017
Jazaveri et al. 2021
 | -25.45
 | 7.898 | 35
42
 | -2.16

 | 7.3511 | 35
 | 2.9% | -23.29 [-26.86, -19.72]
-7 70 [-8 53 -6 87] | | | | | | | | |
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| | Jeong et al. 2017 (high dose)
 | -12.73
 | 29.3 | 22
 | -0.17

 | 19.58 | 23
 | 1.4% | -12.56 [-27.19, 2.07] | | | | | | | | |
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| | Jeong et al. 2017 (low dose)
Kazemi et al. 2020
 | -13.65
 | 39.56 | 23
 | -0.17

 | 19.58 | 23
 | 1.1% | -13.48 [-31.52, 4.56] | | | | | | | | |
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| | Khonche et al. 2019
 | -32.6
 | 72.9146 | 60
 | -14.2

 | 31.7603 | 60
 | 1.0% | -18.40 [-38.52, 1.72] | | | | | | | | |
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| | Li et al. 2010
Maiiri Fanyahani et al. 2022
 | -17.75
 | 38.5804 | 45
 | -6.89

 | 36.8822 | 43
 | 1.3% | -10.86 [-26.63, 4.91] | | | | | | | | |
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| | Mojiri-Forusnani et al. 2022
Musazadeh et al. 2022
 | -12
 | 8.4705 | 45
 | -0.27

 | 5.7078
4.7655 | 45
 | 2.8% | -15.00 [-16.67, -13.33]
-2.18 [-6.26, 1.90] | | | | | | | | |
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| | Musolino et al. 2020 (BPF)
 | -9
 | 1.1 | 20
 | -0.3

 | 0.6 | 20
 | 3.0% | -8.70 [-9.25, -8.15] | - | | | | | | | |
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| | Musolino et al. 2020 (BPF+CyC)
Musolino et al. 2020 (CyC)
 | -15.41
 | 2.6 | 20
 | -0.3

 | 0.6 | 20
 | 3.0% | -15.11 [-16.28, -13.94] | ~ | | | | | | | |
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| | Pour et al. 2020
 | -8.14
 | 15.3686 | 36
 | -5.19

 | 7.6548 | 36
 | 2.6% | -2.95 [-8.56, 2.66] | | | | | | | | |
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| | Rafie et al. 2020
Rejendre et al. 2022 (CL16040E)
 | -9.83
 | 10.5892 | 23
 | -3.31

 | 7.8889 | 23
 | 2.6% | -6.52 [-11.92, -1.12] | | | | | | | | |
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| | Rajendra et al.2022 (CE10043)
Rajendra et al.2022 (Silymarin)
 | -1.21
 | 8.3403 | 29
 | 3.63

 | 10.3823 | 30
 | 2.7% | -4.84 [-9.64, -0.04] | | | | | | | | |
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| | Rostamizadeh et al. 2022
 | -6.62
 | 3.8168 | 28
 | -3

 | 1.8946 | 24
 | 3.0% | -3.62 [-5.22, -2.02] | | | | | | | | |
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| | Sangouni et al. 2020
Shafiezadeh et al. 2020
 | -4.9
-14.71
 | 6.5
50.0834 | 45
32
 | -4.79

 | 8.4
28.5375 | 43
36
 | 2.9% | -8.46 [-11.61, -5.31]
-9.92 [-29.62, 9.78] | | | | | | | | |
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| | Shavakhi et al. 2015
 | -30
 | 34.2854 | 40
 | -23.2

 | 44.4057 | 41
 | 1.2% | -6.80 [-24.05, 10.45] | | | | | | | | |
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| | Soleimani et al.2020
Solbi et al. 2014
 | -10.5
 | 13.5 | 51
 | 0.25

 | 15.2 | 47
 | 2.6% | -10.75 [-16.46, -5.04]
-20.60 [-36.32 -4.88] | | | | | | | | |
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| | Wah Kheong et al. 2017
 | -20
 | 50.5868 | 49
 | -21

 | 42.421 | 50
 | 1.1% | 1.00 [-17.41, 19.41] | | | | | | | | |
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| | Wong et al. 2013
 | -5
 | 38 | 40
 | -5

 | 12.66 | 20
 | 1.2% | 0.00 [-16.69, 16.69] | | | | | | | | |
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| | Yari et al. 2021 (Hes+Flax)
 | -11.12
 | 5.76 | 24
 | -4.87

 | 13.66 | 21
 | 2.5% | -1.13 [-7.39, 5.13] | | | | | | | | |
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| | Yari et al. 2021 (Hesperidin)
Zemeni et al. 2019
 | -7.2
 | 6.55 | 22
 | -4.87

 | 13.66 | 21
 | 2.5% | -2.33 [-8.78, 4.12] | | | | | | | | |
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| | Zamani et al. 2010
 | -30.7
 | 4.0 | 40
 | -22.5

 | 0.0 | 55
 | 5.0 % | -13.00[-13.33,-12.07] | | | | | | | | |
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| | Total (95% CI)
Hotorogonoity: Touã = 49,72: Chiã
 | - 2164.44
 | If = AG /D | 1712
 | 013-18-

 | 0.00% | 1621
 | 100.0% | -7.23 [-9.64, -4.82] | ◆ | | | | | | | |
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| | Test for overall effect: Z = 5.88 (P
 | < 0.00001)
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Favours fexperimentally Favours fcontroll | | | | | | | |
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 | Control |
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| D | Study or Subgroup
 | Exp
Mean
-4.95
 | perimenta
SD
19 6943 | Total
 | Mean
-2.69

 | Control
SD | Total
 | Weight
3.3% | Mean Difference
IV, Random, 95% Cl | Mean Difference
IV, Random, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Afzali et al. 2020
 | Exp
Mean
-4.95
-13.83
 | perimenta
SD
19.6943
23.8157 | 1
Total
105
60
 | Mean
-2.69
-11.43

 | Control
SD
23.016
20.3066 | Total
100
57
 | Weight
3.3%
2.7% | Mean Difference
IV, Random, 95% Cl
-2.26 [-8.14, 3.62]
-2.40 [-10.41, 5.61] | Mean Difference
IV, Randorn, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Afzali et al. 2020
Akbari et al. 2022
 | Exp
Mean
-4.95
-13.83
-5.07
-5.57
 | 0erimenta
SD
19.6943
23.8157
20.3924
17.4117 | Total
105
60
57
 | Mean
-2.69
-11.43
-2.56

 | Control
SD
23.016
20.3066
37.767 | Total
100
57
53
 | Weight
3.3%
2.7%
2.0% | Mean Difference
IV, Random, 95% CI
-2.26 [-8.14, 3.62]
-2.40 [-10.41, 5.61]
-2.51 [-13.97, 8.95] | Mean Difference
IV, Random, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Afzali et al. 2020
Akbari et al. 2022
Askari et al. 2014
Certetti et al. 2020
 | Exp
-4.95
-13.83
-5.07
-25.53
-3.92
 | 23.8157
20.3924
17.4117
26.8895 | Total
105
60
57
23
74
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11

 | Control
23.016
20.3066
37.767
27.6963
29.1629 | Total
100
57
53
22
39
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0% | Mean Difference
N, Random, 95% Cl
-2.26 [-8.14, 3.62]
-2.40 [-10.41, 5.61]
-2.51 [-13.97, 8.95]
-23.79 [-37.38, -10.20]
2.19 [-8.82, 13.20] | Mean Difference
IV, Random, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Afzali et al. 2020
Akbari et al. 2020
Askari et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
 | Exp
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
 | berimentai
SD
19.6943
23.8157
20.3924
17.4117
26.8895
6.323 | Total
105
60
57
23
74
25
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914 | Total
100
57
53
22
39
24
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8% | Mean Difference
IV, Random, 95% CI
-2.26 [-8.14, 3.62]
-2.40 [-10.41, 5.61]
-2.51 [-13.97, 8.95]
-23.79 [-37.38, -10.20]
2.19 [-8.82, 13.20]
2.86 [-1.12, 6.84] | Mean Difference
IV, Random, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzail et al. 2020
Akbari et al. 2020
Askari et al. 2014
Cerietti et al. 2014
Cheraghpour et al. 2019
Darand et al.2019
 | Exp
<u>Mean</u>
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
 | serimentai
SD
19.6943
23.8157
20.3924
17.4117
26.8895
6.323
17.1985
15.0086 | Total
105
60
57
23
74
25
22
29
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258 | Total
100
57
53
22
39
24
21
26
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
2.7% | Mean Difference
IV, Random, 95% Cl
-2.26 [-8.14, 3.62]
-2.40 [-10.41, 5.61]
-2.51 [-1.397, 8.95]
-23.79 [-37.38, -10.20]
2.19 [-8.82, 13.20]
2.19 [-8.62, 13.20]
2.86 [-1.12, 6.84]
2.03 [-5.67, 9.73]
-24.56 [-0.74, 5.81] | Mean Difference
IV, Random, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzali et al. 2020
Akbari et al. 2020
Akbari et al. 2020
Cheraghpour et al. 2019
Darand et al.2019
Ebrahimi-Mameghani et al.2016
 | Exp
4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
 | berimenta
SD
19.6943
23.8157
20.3924
17.4117
26.8895
6.323
17.1985
15.0086
15.4824 | Total
105
60
57
23
74
25
22
29
24
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.892 | Total
100
57
53
22
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 | Weight
3.3%
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3.8%
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2.8% | Mean Difference
IV, Randorn, 95% CI
-2.26 [-8.14, 3.62]
-2.40 [-10.41, 6.61]
-2.51 [-1.397, 8.95]
-23.79 [-37.38, -10.20]
2.19 [-8.82, 13.20]
2.86 [-1.12, 6.84]
2.03 [-5.67, 9.73]
-2.45 [-10.71, 5.81]
-3.23 [-10.80, 4.34] | Mean Difference
IV. Random, 95% CI
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzali et al. 2020
Akbari et al. 2020
Askari et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Ebrahimi-Mameghani et al. 2016
Faghitzaden et al. 2015
Ferro et al. 2020
 | Exp
<u>Mean</u>
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-2
 | berimenta
SD
19.6943
23.8157
20.3924
17.4117
26.8895
6.323
17.1985
15.0086
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15.4824
15.4824
15.4824
15.4824
15.4824
15.4824
15.4824
15.4824
15.4824 | Total
105
60
57
23
74
25
22
29
24
41
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.892
10.1864 | Total
100
57
53
22
39
24
21
26
24
45
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
2.8%
2.8%
3.9% | Mean Difference V, Random, 95% CI -2.26 [+8.14, 3.62] -2.30 [+13.47, 8.95] -2.37 [+3.78, -10.27] -2.86 [+1.12, 6.84] -2.35 [+1.307, 8.95] -2.37 [+3.39, 10.20] 2.86 [+1.12, 6.84] -2.35 [+1.307, 8.95] -3.35 [+0.08, 0.434] -0.94 [+4.64, 2.76] | Mean Difference
IV, Random, 95% C1 | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzali et al. 2020
Akkari et al. 2020
Cheraghpour et al. 2014
Cerletti et al. 2020
Cheraghpour et al. 2019
Ebrahimi-Mameghani et al. 2016
Faghihzadeh et al. 2015
Ferro et al. 2020
Ferro Y. et al. 2020
Ferro Y. et al. 2018
CHD
 | Exp
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-1.06
0.08
 | berimenta
50
19.6943
23.8157
20.3924
17.4117
26.8895
6.323
17.1985
15.0086
15.4824
7.191
9.9435
14.3226 | Total
105
60
57
23
74
25
22
29
24
41
65
21
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33

 | Control
3D
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.892
10.892
10.892
10.864
15.5314
14.5138 | Total
100
57
53
22
39
24
21
26
24
24
45
62
42
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
2.8%
3.9%
3.7%
2.9% | Hean Difference V, Random, 95% CI -2.26 [F8.14, 362] -2.40 [-10.41, 561] -2.51 [-13.97, 8.95] -23.79 [-37.38, -10.20] 2.86 [-1.12, 6.84] 2.08 [-57, 973] -2.45 [-10.71, 5.81] -3.34 [-10.86, 4.376] -0.94 [-46, 2.76] 0.86 [-3.71, 5.41] 0.85 [-3.71, 5.41] 0.86 [-3.71, 5.41] 0.86 [-3.71, 5.41] | Mean Difference
IV, Random, 95% C1 | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbar et al. 2020
Akbar et al. 2024
Cerletti et al. 2024
Cheraghpour et al. 2019
Darand et al.2019
Ebrahim-Mameghani et al.2016
Faghihzadeh et al. 2015
Ferro Y. et al.2022
Ghaffari et al. 2018 (CHB)
Ghaffari et al. 2018 (CHB)
 | Exp
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-1.06
0.08
-0.84
 | sp 19.6943 23.8157 20.3924 17.4117 26.8895 6.323 17.1985 15.0086 15.4824 7.191 9.9435 14.3226 9.7213 | Total
105
60
57
23
74
25
22
29
24
41
65
21
21
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33
-0.26

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.892
10.1864
15.5314
14.5138
14.6253 | Total
100
57
53
22
39
24
21
26
24
24
45
62
42
42
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
2.8%
3.9%
3.7%
2.8%
3.3% | Mean Difference V., Random, 95% CI -226 [83:43, 362] -240 [10.41, 561] -251 [13.97, 8.95] -23.79 [47:38, 10.20] 2.19 [482, 13.20] 2.86 [11.2, 684] 2.03 [-567, 9.73] -24.5 [-10.71, 5.81] -0.94 [464, 276] 0.85 [-371, 541] 0.45 [-10.71, 5.81] -0.94 [465, 2.76] 0.85 [-371, 541] 0.45 [-10.71, 5.81] | Mean Difference
IV, Random, 95% C1 | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzail et al. 2020
Akbari et al. 2020
Akbari et al. 2020
Cheraghpour et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Earbinni-Mameghani et al. 2016
Ferro et al. 2020
Ferro Y. et al. 2020
Chaffari et al. 2018 (CHR)
Chaffari et al. 2018 (CHR)
Chaffari et al. 2018 (CHR+CHI)
 | Exp
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-1.06
0.08
-0.84
-1.4
-26.69
 | string 19.6943 23.8157 20.3924 17.4117 26.8895 6.323 17.1985 15.0086 15.4824 7.191 9.9435 14.3226 9.7213 19.2346 | Total
105
60
57
23
74
22
29
24
41
65
21
21
21
21
21
27
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33
-0.26
-0.4
-0.4

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.892
10.1864
15.5314
14.6253
14.6222
29.269 | Total
100
57
53
22
39
24
21
26
24
26
24
45
62
42
42
42
42
20
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
3.9%
3.9%
3.9%
3.3%
2.9%
3.3%
2.4%
1.1% | Mean Difference
IV, Random, 95% CI
-2.26 [+3.14, 3.62]
-2.40 [+10.41, 5.61]
-2.51 [+3.37, 8.95]
-2.379 [+3.78, 3.1020]
2.19 [+8.82, 13.20]
2.86 [+1.12, 8.84]
2.03 [+5.67, 9.73]
-2.45 [+10.71, 5.81]
-0.32 [+10.00, 4.34]
-0.94 [+4.64, 2.76]
0.85 [+3.71, 5.41]
0.41 [+7.13, 7.95]
0.55 [+6.65, 5.49]
-1.00 [+10.34, 8.34]
-1.00 [+10.34, 8.34] | Mean Difference
IV. Random, 95% Cl | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atkali et al. 2020
Akkari et al. 2020
Akkari et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Darand et al. 2019
Ebrahimi-Mameghani et al. 2016
Ferro y et al. 2020
Ferro y. et al. 2022
Ghaffari et al. 2018 (CHP)
Ghaffari et al. 2018 (CHP)
Ghaffari et al. 2018 (CHP)
Hormati et al. 2018 (TUR)
Hosselin et al. 2018
 | Exq
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-22
-1.06
0.08
-0.84
-1.4
-25.58
-9.22
 | SD 19.6943 23.8157 20.3924 17.4117 26.8895 6.323 17.1985 15.0086 15.4824 7.191 9.9435 14.3226 9.7213 19.2346 40.0347 15.419.4 | Total
105
60
57
23
74
25
22
29
24
41
65
21
21
21
21
37
24
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33
-0.26
-0.4
-27.13
-19.28

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4258
10.892
10.1864
15.5314
14.5138
14.6253
14.6223
38.2687
34.0361 | Total
100
57
53
22
39
24
21
26
24
45
62
42
42
42
42
42
39
9
23
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
3.9%
3.7%
2.8%
3.9%
3.3%
2.4%
1.1%
1.4% | Mean Difference
V, Random, 95% CI
-2.26 [-8.14, 3.62]
-2.30 [-10.41, 5.61]
-2.51 [-13.07, 8.96]
-2.379 [-37.38, -10.20]
2.19 [-8.82, 13.20]
2.86 [-1.12, 6.84]
-0.94 [-1.12, 6.84]
-0.94 [-1.12, 6.84]
-0.94 [-1.12, 7.95]
-0.56 [-6.65, 5.49]
-0.56 [-6.65, 5.49]
1.00 [-1.53, [-5.218]
-0.56 [-6.65, 2.84]
-0.56 [-6.65, 2.84]
-0.56 [-6.65, 2.84]
-0.56 [-6.65, 2.84]
-0.56 [-6.52, 28]
-0.56 [-6.528]
-0.56 [-6.588]
-0.56 [-6.588] | Mean Difference IV, Random, 95% CI | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzali et al. 2020
Akbari et al. 2020
Akbari et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Ebrahimi-Mameghani et al. 2016
Ferro et al. 2020
Ferro Y, et al. 2022
Ghaffari et al. 2018 (CHI)
Ghaffari et al. 2018 (CUR+CHI)
Horseni et al. 2017
Hosseini et al. 2017
 | Exq
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-1.06
0.08
0.08
-0.84
-1.4
-25.58
-9.22
-2.093
 | st 19.6943 23.8157 20.3924 17.4117 26.8895 6.323 17.1985 15.0086 15.4824 7.191 9.9435 14.3226 9.7213 19.2346 40.0347 15.4124 7.0646 | Total
105
60
57
23
74
25
22
29
24
41
65
21
21
21
37
24
37
24
35
 | Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33
-0.26
-0.4
-27.13
-19.28
-3.83

 | Control
SD
23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.892
10.1864
15.5314
14.5138
14.6223
38.2687
38.2687
34.0361
6.3634 | Total
100
57
53
22
39
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62
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42
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39
23
35
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
3.8%
3.9%
3.9%
3.7%
2.8%
3.9%
3.3%
2.4%
1.1%
1.4%
4.0% | Mean Difference V, Random, 95% CI -2.26 [-8.14, 3.62] -2.30 [-10.41, 5.61] -2.51 [+13.97, 8.96] -2.37 [+73.9, -10.21] 2.88 [+1.12, 6.84] 2.08 [+1.12, 6.84] 2.03 [-6.7, 9.73] -2.45 [+10.71, 5.81] -0.34 [+4.64, 2.76] 0.85 [-3.71, 5.41] -0.84 [+6.42, 2.76] 0.85 [-3.71, 5.41] 0.41 [-7.13, 7.95] -0.58 [-6.65, 5.49] 1.00 [-10.34, 8.34] 1.55 [-16.08, 19.18] 10.06 [-5.16, 25.29] -17.10 [-0.25, -1.39] | Mean Difference
IV, Random, 95% C1 | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbai et al. 2020
Akbai et al. 2024
Cerletti et al. 2024
Cheraghpour et al. 2019
Darand et al.2019
Darand et al.2019
Ebrahim-Mameghani et al.2016
Fapohizadeh et al.2010
Ferro 41.2020
Ferro 41.2018 (TUR+CH)
Ghaffari et al. 2018 (TUR+CH)
Hormait et al.2018 (TUR+CH)
Hormait et al.2018
Hussain et al.2018
 | Exq
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-1.06
0.08
-0.84
-1.4
-25.58
-0.84
-1.4
-25.58
-2.2
-2.02
-3.2
-6.37
-12.8
 | SD 19.6943 23.8157 20.3924 17.4117 26.8825 15.0886 15.4824 7.191 9.9435 14.3226 9.7213 19.2346 40.0347 15.4194 7.6646 8.8721 19.07 | Total
105
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Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33
-0.26
-0.4
-27.13
-19.28
-3.83
-2.02
-1.34
-3.83
-2.02
-1.43
-1.74
-3.83
-2.56
-1.74
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 | 23.016
20.3066
37.767
27.6963
29.1629
7.7914
6.4956
16.1258
10.1864
15.5314
14.6253
14.6253
14.6253
14.6253
14.6253
14.6253
14.6254
38.2687
34.0361
13.7869 | Total
100
57
22
39
24
21
26
24
24
24
24
45
62
42
42
42
39
23
35
23
24
24
 | Weight
3.3%
2.7%
2.0%
1.6%
2.0%
3.8%
2.8%
3.9%
3.7%
2.8%
3.9%
3.7%
2.4%
1.1%
1.4%
4.0%
3.8%
2.4% | Mean Difference V, Random, 95% CI -2.26 [+8.14, 362] -2.26 [+8.14, 362] -2.40 [-10.41, 561] -2.51 [+3.37, 8.95] -23.79 [+3.73, -10.20] 2.19 [+8.27, 13.20] 2.86 [+1.12, 6.84] 2.03 [-56.7, 9.73] -2.45 [-10.71, 561] -0.94 [+4.64, 2.76] 0.85 [-3.71, 5.41] 0.45 [-13.71, 7.95] -0.56 [-6.65, 5.49] 1.00 [-10.34, 834] 1.55 [-16.00, 9.18] 10.06 [-5.16, 25.20] -4.36 [-6.52, -0.13] -4.36 [-6.52, -0.13] -4.36 [-6.52, -0.13] -4.36 [-6.52, -0.13] | Mean Difference
IV, Random, 95% C1 | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Aktail et al. 2020
Aktari et al. 2020
Aktari et al. 2024
Cerietti et al. 2014
Cerietti et al. 2014
Cerietti et al. 2019
Darand et al. 2019
Evanium-Mameghani et al. 2016
F aghihzadeh et al. 2019
Ferro Y. et al. 2020
Fhaffari et al. 2018
Chaffari et al. 2018
Chaffari et al. 2018
Chaffari et al. 2018
Hussain et al. 2018
Hussain et al. 2021
Kazemi et al. 2021
Kazemi et al. 2020
Khonche et al. 2019
 | Exp
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-0.84
-0.84
-0.84
-1.4
-25.58
-9.22
-20.93
-6.37
-12.8
-12.8
 | SD 19.6943 23.8157 20.3924 17.4117 26.8923 17.1985 15.0886 15.4824 7.191 9.9435 14.3226 9.7213 19.2346 40.0347 15.4194 7.6646 8.8721 19.07 14.7937 | Total
105
60
57
23
74
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29
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41
65
21
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24
35
42
20
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60
 |
Mean
-2.69
-11.43
-2.56
-1.74
-6.11
-2.02
-1.08
-4.68
-7.57
-1.06
-1.91
-0.33
-0.26
-0.4
-27.13
-19.28
-3.83
-2.02
-1.34
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-2.02
-1.34
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 | Control
SD
23.016
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atzail et al. 2020
Akbari et al. 2020
Akbari et al. 2020
Cheraghpour et al. 2014
Cerietti et al. 2019
Darand et al. 2019
Darand et al. 2019
Darand et al. 2019
Faror X, et al. 2020
Ferror y, et al. 2020
Chaffari et al. 2018
Chaffari et al. 2018
Chaffari et al. 2018
(TUR+CHI)
Horsaini et al. 2018
Hussain et al. 2018
Hussain et al. 2021
Kazemi et al. 2021
 | Ext
Mean
-4.95
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-7.13
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 | SD 19.6943 23.8157 23.8157 26.8295 6.323 17.1985 15.0086 15.4824 7.191 9.9435 14.3226 9.7213 19.2346 40.0347 7.0646 8.8721 19.07 14.7937 20.8625 | Total
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-0.33
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IV. Random, 95% Cl | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Atkali et al. 2020
Akkari et al. 2020
Akkari et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Darand et al. 2019
Ebrahimi-Mameghani et al. 2016
Ferro et al. 2020
Ferro et al. 2020
Chaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Horsni et al. 2018
Hussain et al. 2017
Jazayen et al. 2021
Khonche et al. 2019
Li et al. 2019
Musszadeh et al. 2025
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 | Mean Difference V, Random, 95% CI -2.26 [-8.14, 3.62] -2.30 [-10.41, 5.61] -2.37 [-37.8, -10.20] 2.19 [-8.82, 13.20] 2.86 [-1.12, 6.84] 2.03 [-6.67, 9.73] -2.45 [-10.71, 5.81] -2.35 [-5.67, 9.73] -2.45 [-10.71, 5.81] -0.94 [-4.64, 2.76] 0.85 [-3.71, 5.41] 0.45 [-10.71, 5.81] 0.94 [-4.64, 2.76] 0.95 [-6.65, 5.49] 1.00 [-15.6, 52.20] -1.14 [-10.75, -4.17] -11.31 [-16.34, -6.22] -11.46 [-18.75, -4.17] -11.31 [-16.34, -6.22] 0.05 [-3.17, 8.07] -11.25 [-22, 2.28] 0.10 [-6.03, 6.23] | Mean Difference IV, Random, 95% CI | | | | | | | | | |
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| B | Study or Subgroup Abu Hassan et al. 2023 Azali et al. 2020 Akbari et al. 2024 Askari et al. 2014 Cerletti et al. 2014 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al. 2016 Ferro et al.2010 Ferro et al.2018 Chaffari et al. 2018 (TUR) Ghaffari et al.2018 (TUR-CHI) Hormait et al.2018 Hussain et al.2017 Jazayen et al.2017 Jazayen et al.2017 Jazayen et al.2010 Khonche et al.2010 Musazadeh et al.2010 Musazadeh et al.2020 Pour et al.2020
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| B | Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbai et al. 2020
Akbai et al. 2021
Cheraghpour et al. 2014
Cerletti et al. 2020
Cheraghpour et al. 2019
Darand et al.2019
Ebrahim-Mameghani et al.2016
Faghihzadeh et al. 2015
Ferro Y. et al.2020
Ghaffari et al. 2018
Ghaffari et al. 2018 (TUR+)
Ghaffari et al. 2018 (TUR+)
Ghaffari et al. 2018
Horseini et al. 2020
Kajerni et al. 2020
Kajerni et al. 2020
Kussach et al. 2020
Fuesach et al. 2020
Raiendra et al. 2020
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-2.26 [+3.14, 3.62]
-2.20 [+10.41, 5.61]
-2.51 [+13.97, 8.95]
-23.79 [+37.83, -10.20]
-28 [+11.2, 6.84]
-2.03 [+5.67, 9.73]
-2.45 [+10.71, 5.61]
-3.23 [+10.08, 4.34]
-0.94 [+6.45, 2.76]
-0.58 [+6.65, 5.49]
-1.00 [+10.34, 8.34]
-1.00 [+10.34, 8.34]
-1.00 [+5.14, 6.22]
-1.71 [+5.22]
-1.13 [+16.34, -6.28]
-0.55 [+3.71, 8.41]
-1.13 [+16.34, -6.28]
-0.55 [+3.71, 8.41]
-1.13 [+16.34, -6.28]
-0.55 [+3.71, 8.41]
-1.14 [+18.75, 4.11]
-1.13 [+16.34, -6.28]
-0.55 [+3.71, 8.408]
-1.14 [+18.75, 4.11]
-1.12 [+2.22, 2.98]
0.10 [+6.03, 6.23]
-1.34 [+7.36, 4.68]
-5.68 [+11.60, -178]
-5.68 [+11.60, -178]
-5.68 [+11.60, -178]
-5.68 [+11.60, -178]
-5.68 [+2.72, 0.468]
-5.68 [+11.60, -178]
-5.68 [+11.60, -178]
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-5.68 [+11.60, -178]
-5.68 [+2.72, 0.468]
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-5.68 [-2.72, 0.468]
-5.68 [-2.72, 0.468] | Mean Difference
N, Random, 95% Cl | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Aktail et al. 2020
Aktari et al. 2020
Aktari et al. 2021
Cheraghpour et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Ebrahimi-Mameghani et al. 2016
Faghihzadeh et al. 2019
Ferro Y. et al. 2020
Chaffari et al. 2018
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Chaffari et al. 2018 (TUR+)
Chaffari et al. 2018 (TUR+)
Chaffari et al. 2018
Hussein et al. 2019
Hussein et al. 2021
Kazemi et al. 2021
Kazemi et al. 2021
Furo et al. 2020
Rafie et al. 2020
Rafie et al. 2020
Ragiendra et al. 2022
(Shifmarin)
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| B | Study or Subgroup Abu Hassan et al. 2023 Atkait et al. 2020 Akbari et al. 2020 Akbari et al. 2020 Cheraghpour et al. 2014 Cerietti et al. 2014 Cerietti et al. 2015 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Cheraghpour et al. 2019 Cheraghinzade et al. 2016 Ferro Y. et al. 2022 Chaffari et al. 2018 (CHR) Chaffari et al. 2018 CHR) CHR) Chaffari et al. 2018 CHR) CHR) CHR CHR CHR CHR) CHR
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3.8 | Mean Difference V, Random, 95% C1 -2.26 [-8.14, 3.62] -2.40 [-10.41, 5.61] -2.37 [-7.38, 9.10.20] 2.19 [-8.82, 13.20] 2.28 [-1.12, 6.84] 2.03 [-10.20] 2.86 [-1.12, 6.84] 2.03 [-6.78, 9.73] -2.45 [-10.71, 5.81] -3.23 [-10.30, 4.34] -0.94 [-4.64, 2.76] -0.85 [-6.55, 49] -0.05 [-6.55, 5.49] -1.00 [-10.34, 8.34] 1.55 [-6.10, 9.11] 1.65 [-6.52, 20.11] -11.46 [-18, 75, -417] -11.31 [-6.34, 6.22] 0.05 [-9.17, 8.07] -1.12 [-5.22, 2.91] -1.34 [-7.36, 4.68] 0.10 [-6.01, 6.23] -1.34 [-7.36, 4.61] 0.11 [-6.01, 7.8] -1.34 [-7.36, 4.62] 0.12 [-6.01, 7.8] -1.34 [-7.36, 4.62] 0.10 [-6.01, 7.8] -3.34 [-7.36], 4.62] 0.10 [-6.01, 7.8] -4.36 [-9.22, 0.48] -0.13 [-6.36, 4.52] -0.13 [-6.36, 4.52] -0.13 [-6.36, 4.52] -0.14 [-5.40, 1.78] <td>Mean Difference
IV. Random, 95% CI</td> | Mean Difference
IV. Random, 95% CI | | | | | |
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| B | Study or Subgroup Abu Hassan et al. 2023 Abu at 2020 Akbari et al. 2020 Akbari et al. 2020 Cheraghpour et al. 2019 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Ebrahimi-Mameghani et al. 2015 Ferro et al. 2020 Chaffari et al. 2018 (TUR>) Chaffari et al. 2018 Hussain et al. 2017 Jazayen et al. 2011 Kazemi et al. 2019 Li et al. 2010 Musazadeh et al. 2020 Raffe et al. 2020 Chaffari et al. 2020 Chaffari et al. 2020 Chaffari et al. 2020 Shafezadeh et al. 2022 Shavakhi et al. 2020 Shavakhi et al. 2020
 | Exq
Mean
-4.955
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-25.53
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-0.84
-1.4
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 | Mean -2.69 -11.43 -2.56 -1.74 -2.57 -1.64 -2.713 -0.26 -0.27 -0.28 -0.26 -3.06 -3.08 -4.48 -4.61 -0.27 -0.28 -0.26 -3.08 -3.08 -4.47 -0.38 -1.08 -4.47 -0.38 -3.06 -3.06 -4.32 -4.32 -4.32 -4.32 -4.32 -4.32

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3.3 | Mean Difference V, Random, 95% CI -2.26 [-8.14, 3.62] -2.30 [-10.41, 5.61] -2.375 [-9.73, 8, -10.20] 2.19 [-8.82, 13.20] 2.86 [-11.2, 6.84] 2.03 [-6.77, 73] -2.45 [-10.71, 5.81] -2.376 [-6.78, 73] -2.45 [-10.71, 5.81] -0.94 [-4.64, 2.76] -0.94 [-4.64, 2.76] -0.85 [-6.65, 5.49] -0.05 [-0.43, 8.34] -1.06 [-10.27, -13.96] -0.55 [-16.07, 8.70] -1.13 [-16.34, -6.22] -1.146 [-16.75, -4.17] -1.13 [-16.34, -6.22] -0.10 [-0.36, 6.23] -1.13 [-16.34, -6.22] -1.13 [-16.34, -6.22] -1.13 [-16.34, -6.22] -1.13 [-16.34, -6.22] -1.13 [-16.34, -6.22] -1.13 [-16.34, -6.22] -1.13 [-17.24, 2.22] -1.13 [-16.34, -6.24] -1.13 [-17.24, 2.22] -2.64 [-14.6] -2.74 [-2.42] -2.74 [-2.42] -2.74 [-2.42] -2.74 [-1.44] -1.09 [-2.22] -2.76 [-1.44] | Mean Difference IV, Random, 95% CI | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbai et al. 2020
Akbai et al. 2021
Cerietti et al. 2024
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al.2019
Evranium-Mameghani et al.2016
Faphihzadeh et al. 2015
Ferro 9, et al.2022
Ghaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Ghaffari et al. 2018 (TUR)
Horsseini et al. 2018
Hosseini et al. 2019
Hussain et al. 2010
Khonche et al. 2020
Khonche et al. 2020
Raijendra et al. 2022
Pour et al. 2020
Raijendra et al. 2022
Raijendra et al. 2022
Raijendra et al. 2020
Shanfazadeh et al. 2020
Shanfazade
 | Exq
Mean
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3 | $\begin{array}{r} \label{eq:heat} \textbf{Wean Difference} \\ \hline \textbf{W, Random, 95% Cl} \\ \hline 2.226 [+3.14, 3.62] \\ -2.240 [+10.41, 561] \\ -2.51 [+13.97, 8.96] \\ -2.3.79 [+37.8, -10.20] \\ 2.19 [+8.2, 13.20] \\ 2.88 [+1.12, 6.84] \\ 2.03 [+567, 9.73] \\ -2.45 [+10.71, 5.81] \\ -0.34 [+4.64, 2.76] \\ 0.88 [+3.71, 5.41] \\ -0.34 [+4.64, 2.76] \\ 0.88 [+3.71, 5.41] \\ -0.34 [+6.6, 5.54] \\ -0.56 [+6.65, 5.49] \\ -1.76 [+6.22, 2.98] \\ -1.76 [+6.22, 2.98] \\ -1.75 [+6.22, 2.98] \\ -1.34 [+7.36, 4.68] \\ -1.34 [+7.36, 4.68] \\ -1.34 [+7.36, 4.68] \\ -2.76 [+1.26, 7.14] \\ -2.76 [+1.26, 7.14] \\ -1.76 [+2.22, 2.98] \\ -1.34 [+7.36, 4.68] \\ -2.76 [+1.49, -1.21] \\ -2.76 [+2.47, 7.14] \\ -1.14 [+1.39, 4.68] \\ -7.70 [+1.49, -1.21] \\ -2.24 [+6.88, 1.132] \\ \end{array}$ | Mean Difference
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| B | Study or Subgroup
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Cheraghpour et al. 2014
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Darand et al. 2019
Eshahim-Mameghani et al. 2016
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Chaffari et al. 2018
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Hussain et al. 2018
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Kazemi et al. 2021
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Faffe et al. 2020
Pour et al. 2020
Raigendra et al. 2020
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N. Random, 95% CI</td></td_<></td></tr<></tr> <tr><th>B</th><td>Study or Subgroup
Abu Hassan et al. 2023
Aktail et al. 2020
Aktari et al. 2020
Aktari et al. 2020
Cheraghpour et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al. 2019
Darand et al. 2019
Ferro Y. et al. 2020
Chaffari et al. 2018
CHP)
Chaffari et al. 2018 (CHP)
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Chaffari et al. 2018
CHR-CHP)
Hormabi et al. 2018
Hussain et al. 2019
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Hussain et al. 2021
Kazemi et al. 2020
Rafie et al. 2020
Shavakin et al. 2022
Pour et al. 2020
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Shavakin et al. 2020
Shavakin et al. 2020
Solhi et al. 2021
Yan et al. 2021 (Hesseflay)
Yan et al. 2021
(Hesseflay)</td><td>Exq
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N. Random, 95% Cl</td></td></tr> <tr><th>B</th><td>Study or Subgroup Abu Hassan et al. 2023 Abu at 2020 Abbari et al. 2020 Abbari et al. 2020 Cheraghpour et al. 2014 Cerietti et al. 2014 Cerietti et al. 2015 Darand et al. 2019 Cheraghinzade et al. 2016 Ferro Y, et al. 2020 Chaffari et al. 2018 (CHR) Chaffari et al. 2018 (CHR) Chaffari et al. 2018 (CHR) Chaffari et al. 2018 CHR) Chaffari et al. 2020 Chaffari et al. 2021 Chaffari et al. 2020 Chaffari</td><td>Exq
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N, Random, 95% CI</td></td></tr> <tr><th>B</th><th>Study or Subgroup Abu Hassan et al. 2023 Aztail et al. 2020 Akbari et al. 2021 Akbari et al. 2021 Cerletti et al. 2021 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Farro et al.2020 Ferro et al.2020 Ghaffari et al. 2018 (TUR+CH) Hormati et al.2018 (TUR+CH) Hormati et al.2018 (TUR+CH) Hosseini et al.2017 Jazayen et al.2020 Kazemi et al.2018 Hussain et al.2018 Hussain et al.2017 Jazayen et al.2020 Kazemi et al.2018 Pour et al.2020 Raife et al.2018 Hussain et al.2018 Hussain et al.2017 Jazayen et al.2020 Raife et al.2020 Raife et al.2020 Raife et al.2020 Raiferdra et al.2022 Pour et al.2020 Shafezadeh et al.2020 <</th><th>Exq
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IV, Random, 95% CI
</th></th></tr> <tr><th>B</th><th>Study or Subgroup Abu Hassan et al. 2023 Akzail et al. 2020 Akbari et al. 2021 Akkari et al. 2024 Ackari et al. 2024 Cerletti et al. 2020 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Ferro Y. et al.2022 Chaffari et al. 2018 (CUR) Chaffari et al. 2017 (CUR) Chaffari et al. 2017 (CUR) Musazadeh et al. 2020 Pour et al. 2020 Raiendra et al. 2020 Raiendra et al. 2021 (CL16049F Soleimani et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2021 (HessPerlax) Yari et al. 2014 Yari et al. 2014
(HessPerlax)</th><th>Exq
Mean
-4.95
-13.83
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- 2.69
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- 11.43
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- 1.143
- 2.02
- 1.74
- 0.18
- 0.4
- 2.02
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IV, Random, 95% C1
-2.26 [+3.14, 3.62]
-2.20 [+3.14, 3.61]
-2.51 [+13.97, 8.95]
-2.37 [+73.87, 8.95]
-2.37 [+73.87, 10.20]
2.86 [+11.2, 6.84]
2.03 [-5.67, 9.73]
-2.45 [+10.71, 5.81]
-0.85 [+3.71, 5.41]
0.45 [+6.65, 5.49]
-1.00 [+10.34, 8.34]
-0.56 [+6.65, 5.49]
-1.00 [+0.34, 8.34]
1.55 [+16.06, 19.18]
10.06 [+5.16, 25.20]
-1.71.0 [+20.25, -13.96]
-4.35 [+5.52, -0.18]
-1.13 [+16.34, 4.628]
-0.55 [+9.77, 8.17]
-1.13 [+16.34, 4.628]
-0.56 [+11.00, -17.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-2.25 [+9.64, 1.14]
-2.27 [+2.86, 4.648]
-7.70 [+1.19, -1.21]
-3.33 [+7.77, 1.11]
-1.72 [+2.89, 3.45]
2.60 [+1.38, 6.58]
-3.08 [-5.23, -0.92]</th><th>Mean Difference
M. Random, 95% CI</th></tr> <tr><th>B</th><th>Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbar et al. 2020
Akbar et al. 2021
Cheraghpour et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al.2019
Darand et al.2019
Ebrahim-Mameghani et al.2016
F aghihzadeh et al. 2010
Chaffari et al. 2012
Chaffari et al. 2018
ChuShari et al. 2018
ChuShari et al. 2018
ChuShari et al. 2018
Hosseini et al. 2018
Hosseini et al. 2010
Kazemi et al. 2020
Kalenda et al. 2021
Kazemi et al. 2020
Raiendra et al. 2020
Sharakhi et al. 2021
Solimi et al. 2014
Yari et al. 2014
Hestergeneity: Tau² = 27.85; Chi²
Test for overall effect: Z = 2.80
(P</th><th>Exq
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-4.95
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M. Random, 95% CI
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Yan et al. 2021 (Hesseflay)
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IV, Random, 95% CI
 | B | Study or Subgroup Abu Hassan et al. 2023 Akzail et al. 2020 Akbari et al. 2021 Akkari et al. 2024 Ackari et al. 2024 Cerletti et al. 2020 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Ferro Y. et al.2022 Chaffari et al. 2018 (CUR) Chaffari et al. 2017 (CUR) Chaffari et al. 2017 (CUR) Musazadeh et al. 2020 Pour et al. 2020 Raiendra et al. 2020 Raiendra et al. 2021 (CL16049F Soleimani et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2021 (HessPerlax) Yari et al. 2014 Yari et al. 2014 (HessPerlax) |
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5 | Mean Difference
IV, Random, 95% C1
-2.26 [+3.14, 3.62]
-2.20 [+3.14, 3.61]
-2.51 [+13.97, 8.95]
-2.37 [+73.87, 8.95]
-2.37 [+73.87, 10.20]
2.86 [+11.2, 6.84]
2.03 [-5.67, 9.73]
-2.45 [+10.71, 5.81]
-0.85 [+3.71, 5.41]
0.45 [+6.65, 5.49]
-1.00 [+10.34, 8.34]
-0.56 [+6.65, 5.49]
-1.00 [+0.34, 8.34]
1.55 [+16.06, 19.18]
10.06 [+5.16, 25.20]
-1.71.0 [+20.25, -13.96]
-4.35 [+5.52, -0.18]
-1.13 [+16.34, 4.628]
-0.55 [+9.77, 8.17]
-1.13 [+16.34, 4.628]
-0.56 [+11.00, -17.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-2.25 [+9.64, 1.14]
-2.27 [+2.86, 4.648]
-7.70 [+1.19, -1.21]
-3.33 [+7.77, 1.11]
-1.72 [+2.89, 3.45]
2.60 [+1.38, 6.58]
-3.08 [-5.23, -0.92] | Mean Difference
M. Random, 95% CI | B | Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbar et al. 2020
Akbar et al. 2021
Cheraghpour et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al.2019
Darand et al.2019
Ebrahim-Mameghani et al.2016
F aghihzadeh et al. 2010
Chaffari et al. 2012
Chaffari et al. 2018
ChuShari et al. 2018
ChuShari et al. 2018
ChuShari et al. 2018
Hosseini et al. 2018
Hosseini et al. 2010
Kazemi et al. 2020
Kalenda et al. 2021
Kazemi et al. 2020
Raiendra et al. 2020
Sharakhi et al. 2021
Solimi et al. 2014
Yari et al. 2014
Hestergeneity: Tau ² = 27.85; Chi ²
Test for overall effect: Z = 2.80 (P | Exq
Mean
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19.0714 19.0714 9.9264 8.8721 13.9144 25.868 9.9268 13.2265 7.823 10.47 5.81 10.47 5.81 10.47 5.81 10.47 5.81 10.47 5.81 10.47 5.81 10.47 5.81 14.53 45.81 10.47 5.81 5.81 5.81 5.81 < | Total 105 60 57 23 74 25 22 29 24 41 21 21 21 21 21 21 21 22 24 60 32 40 60 32 40 51 32 40 51 33 24 40 51 33 24 40 51 33 24 400 51 33 24 0.00000 | Mean
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3 | Mean Difference V, Random, 95% C1 -2.26 [-8.14, 3.62] -2.40 [-10.41, 5.61] -2.51 [-13.97, 8.95] -2.37 [-57.38, 10.20] -2.19 [-8.82, 13.20] -2.86 [-11.2, 6.84] -2.37 [-57.38, 10.20] -2.86 [-11.2, 6.84] -3.23 [-10.08, 4.34] -0.94 [-4.64, 2.76] -0.85 [-6.65, 5.49] -1.00 [-10.24, 8.34] 1.006 [-5.16, 25.20] -1.13 [-15.22, 2.98] -0.16 [-6.36, 25.2] -1.13 [-15.34, 4.62] -0.56 [-9.17, 8.07] -1.38 [-5.22, 2.98] 0.10 [-6.03, 6.23] -1.34 [-7.36], 4.62] -0.55 [-9.17, 8.07] -1.34 [-5.34], 4.62] -0.56 [-1.38], 4.62] -0.56 [-1.38], 4.62] -1.2 [-2.22, 2.98] 0.10 [-6.38, 4.64] -1.34 [-5.34], 4.62] -0.55 [-9.17, 8.07] -1.34 [-7.36], 4.68] -6.69 [+11.60, -1.70] -4.38 [-9.22, 0.48] -4.25 [+0.84, 1.14] -2.27 [-8.84, 1.14] -2.27 [-8.84, 4.64] | Mean Difference
M. Random, 95% CI
 | B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akkar et al. 2021 Akkar et al. 2014 Cerietti et al. 2015 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Derand et al. 2019 Cerietti et al. 2010 Ferro V. et al. 2020 Chaffari et al. 2018 Choffari et al. 2018 Hosseini et al. 2018 Hosseini et al. 2017 Jazayeri et al. 2021 Kazerni et al. 2020 Fornor et al. 2020 Romer et al. 2021 Kazerni et al. 2021 Musazadeh et al. 2020 Raigendra et al. 2020 Raigendra et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2021 Yari et al. 2021 (HessetS) Yari et al. 2021 (HessetG) Yari et al. 2021 (HessetG) Yari et al. 2021 (HessetG) |
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N. Random, 95% CI |
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Cheraghpour et al. 2014
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Hormabi et al. 2018
Hussain et al. 2019
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Kazemi et al. 2020
Rafie et al. 2020
Shavakin et al. 2022
Pour et al. 2020
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| B | Study or Subgroup Abu Hassan et al. 2023 Abu at 2020 Abbari et al. 2020 Abbari et al. 2020 Cheraghpour et al. 2014 Cerietti et al. 2014 Cerietti et al. 2015 Darand et al. 2019 Cheraghinzade et al. 2016 Ferro Y, et al. 2020 Chaffari et al. 2018 (CHR) Chaffari et al. 2018 (CHR) Chaffari et al. 2018 (CHR) Chaffari et al. 2018 CHR) Chaffari et al. 2020 Chaffari et al. 2021 Chaffari et al. 2020 Chaffari
 | Exq
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 | Total 105 60 57 23 4 25 224 4 66 211 214 41 65 211 211 24 40 60 60 22 23 300 322 40 61 323 300 321 322 40 51 332 44 251 323 300 322 4 252 222 233 324 252 2284
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| B | Study or Subgroup Abu Hassan et al. 2023 Aztail et al. 2020 Akbari et al. 2021 Akbari et al. 2021 Cerletti et al. 2021 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Farro et al.2020 Ferro et al.2020 Ghaffari et al. 2018 (TUR+CH) Hormati et al.2018 (TUR+CH) Hormati et al.2018 (TUR+CH) Hosseini et al.2017 Jazayen et al.2020 Kazemi et al.2018 Hussain et al.2018 Hussain et al.2017 Jazayen et al.2020 Kazemi et al.2018 Pour et al.2020 Raife et al.2018 Hussain et al.2018 Hussain et al.2017 Jazayen et al.2020 Raife et al.2020 Raife et al.2020 Raife et al.2020 Raiferdra et al.2022 Pour et al.2020 Shafezadeh et al.2020 <
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzail et al. 2020 Akbari et al. 2021 Akkari et al. 2024 Ackari et al. 2024 Cerletti et al. 2020 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Ferro Y. et al.2022 Chaffari et al. 2018 (CUR) Chaffari et al. 2017 (CUR) Chaffari et al. 2017 (CUR) Musazadeh et al. 2020 Pour et al. 2020 Raiendra et al. 2020 Raiendra et al. 2021 (CL16049F Soleimani et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2021 (HessPerlax) Yari et al. 2014 Yari et al. 2014 (HessPerlax)
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- 1.74
- 0.18
- 0.4
- 2.02
- 1.74
- 0.33
- 0.26
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5 | Mean Difference
IV, Random, 95% C1
-2.26 [+3.14, 3.62]
-2.20 [+3.14, 3.61]
-2.51 [+13.97, 8.95]
-2.37 [+73.87, 8.95]
-2.37 [+73.87, 10.20]
2.86 [+11.2, 6.84]
2.03 [-5.67, 9.73]
-2.45 [+10.71, 5.81]
-0.85 [+3.71, 5.41]
0.45 [+6.65, 5.49]
-1.00 [+10.34, 8.34]
-0.56 [+6.65, 5.49]
-1.00 [+0.34, 8.34]
1.55 [+16.06, 19.18]
10.06 [+5.16, 25.20]
-1.71.0 [+20.25, -13.96]
-4.35 [+5.52, -0.18]
-1.13 [+16.34, 4.628]
-0.55 [+9.77, 8.17]
-1.13 [+16.34, 4.628]
-0.56 [+11.00, -17.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-1.32 [+20.24, -13.8]
-2.25 [+9.64, 1.14]
-2.27 [+2.86, 4.648]
-7.70 [+1.19, -1.21]
-3.33 [+7.77, 1.11]
-1.72 [+2.89, 3.45]
2.60 [+1.38, 6.58]
-3.08 [-5.23, -0.92] | Mean Difference
M. Random, 95% CI | | | | | | | |
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| B | Study or Subgroup
Abu Hassan et al. 2023
Akbai et al. 2020
Akbar et al. 2020
Akbar et al. 2021
Cheraghpour et al. 2014
Cerietti et al. 2020
Cheraghpour et al. 2019
Darand et al.2019
Darand et al.2019
Ebrahim-Mameghani et al.2016
F aghihzadeh et al. 2010
Chaffari et al. 2012
Chaffari et al. 2018
ChuShari et al. 2018
ChuShari et al. 2018
ChuShari et al. 2018
Hosseini et al. 2018
Hosseini et al. 2010
Kazemi et al. 2020
Kalenda et al. 2021
Kazemi et al. 2020
Raiendra et al. 2020
Sharakhi et al. 2021
Solimi et al. 2014
Yari et al. 2014
Hestergeneity: Tau ² = 27.85; Chi ²
Test for overall effect: Z = 2.80 (P
 | Exq
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akkar et al. 2021 Akkar et al. 2014 Cerietti et al. 2015 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Darand et al. 2019 Derand et al. 2019 Cerietti et al. 2010 Ferro V. et al. 2020 Chaffari et al. 2018 Choffari et al. 2018 Hosseini et al. 2018 Hosseini et al. 2017 Jazayeri et al. 2021 Kazerni et al. 2020 Fornor et al. 2020 Romer et al. 2021 Kazerni et al. 2021 Musazadeh et al. 2020 Raigendra et al. 2020 Raigendra et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2021 Yari et al. 2021 (HessetS) Yari et al. 2021 (HessetG) Yari et al. 2021 (HessetG) Yari et al. 2021 (HessetG)
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akbar et al. 2021 Ackai et al. 2021 Cerletti et al. 2021 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al. 2016 Ferro et al. 2020 Ferro et al. 2018 (TUR+CH) Ghaffari et al. 2018 (TUR+CH) Horsseini et al. 2019 Lit et al. 2011 Krazemi et al. 2012 Pour et al. 2020 Rainer et al. 2020 Rainer et al. 2020 Rainer et al. 2021 Rainer et al. 2022 Pour et al. 2020 Rainer et al. 2021 (CL16049F Rainer et al. 2022 Pour et al. 2020 Shafezadeh et al. 2020 Shafezadeh et al. 2020 Soleimani et al. 2021 Yari et al. 2021 (HespElax) Yari et al. 2021 (HespElax) Yari et al. 2021 (HespElax)
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akbar et al. 2022 Akbar et al. 2014 Cerletti et al. 2020 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Ferro Y. et al.2022 Chaffari et al. 2018 (CHR) Chaffari et al. 2018 (CUR-CHI) Horseini et al. 2018 Hussain et al. 2019 Khonche et al. 2020 Khonche et al. 2021 Kazemi et al. 2020 Raiendra et al. 2020 Raiendra et al. 2020 Robert et al. 2020 Raiendra et al. 2020 Raiendra et al. 2020 Raiendra et al. 2020 Raiendra et al. 2020 Shafezadeh et al. 2021 (HessFlax) Yari et al. 2021 (HessFlax) <
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| B | Study or Subgroup
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Certetti et al. 2020
Cheraghpour et al. 2019
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Chaffari et al. 2018
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Chaffari et al. 2019
Hosseini et al. 2021
Kazemi et al. 2020
Rajendra et al. 2020
Chaffari et al. 2020
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akbar et al. 2021 Akbar et al. 2021 Cerletti et al. 2021 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al. 2016 Ferro et al. 2020 Ferro et al. 2018 (TUR-CHI) Chaffari et al. 2018 (TUR-CHI) Horsseini et al. 2018 (TUR-CHI) Horsseini et al. 2017 Jazzeyn et al. 2018 (TUR-CHI) Hosseini et al. 2018 (TUR-CHI) Hosseini et al. 2017 Jazzeyn et al. 2020 Khonche et al. 2019 Lit et al. 2010 Musazadeh et al. 2022 Pour et al. 2020 Rainert al. 2021 (CL16049F Rainert al. 2022 (CL16049F Rainert al. 2022 (CL16049F Rainert al. 2020 Shafezadeh et al. 2020 <td>Exq
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IV. Random, 95% CI</td> | Exq
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akbar et al. 2021 Akbar et al. 2024 Cerietti et al. 2020 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Ferro Y, et al.2022 Chaffari et al. 2018 (CUR) Chaffari et al. 2017 (CUR) Chaffari et al. 2017 (CUR) Musszadeh et al. 2020 Pour et al. 2020 Raiendra et al. 2022 (CL16049F Soleimani et al. 2020 Shafezadeh et al. 2021 (Hessels) Yari et al. 2021 (Hesselis)
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IV, Random, 95% C1
-2.26 [+3.4, 3.62]
-2.26 [+3.4, 3.62]
-2.30 [+10.41, 5.61]
-2.51 [+3.37, 8.95]
-2.35 [+3.37, 10.20]
2.86 [+11.2, 6.84]
2.03 [-5.67, 9.73]
-2.45 [+10.71, 5.61]
-3.23 [+10.08, 4.34]
-0.94 [+6.45, 2.76]
0.85 [+3.71, 5.41]
0.45 [+6.65, 5.49]
-1.00 [+10.34, 8.34]
1.00 [+5.14, 2.75]
-1.710 [+20.25, -13.96]
-4.35 [+5.52, -0.18]
-1.131 [+15.34, 4.628]
-0.55 [+9.72, -13.96]
-4.35 [+5.52, -0.18]
-1.14 [+13.75, -4.17]
-1.13 [+15.34, 4.628]
-0.55 [+9.17, 8.07]
-1.12 [+5.22, 2.98]
0.10 [+6.03, 6.23]
-1.34 [+7.36, 4.68]
-6.68 [+11.60, -1.78]
-1.32 [+2.84, 6.46]
-7.70 [+2.49, 7.41]
-1.72 [+2.89, 1.45]
-3.38 [+5.23, -0.92]
Mean Difference
IV, Random, 95% C1
-0.34 [+15.48, 15.20]
-20.27 [+4.75, 3, 6.98]
-3.08 [+5.23, -0.92]
Mean Difference
IV, Random, 95% C1
-0.34 [+1.648, 15.20]
-20.27 [+4.75, 3, 6.31]
-21.14 [+6.7, 8, 45.71]
-21.4 [+6.78, 45.71]
-3.33 [+7.71, 13]
-1.88 [+2.23, 2.32]
-3.33 [+7.71, 13]
-3.34 [+2.33, 13.74]
-1.88 [+3.32, 1.72]
-1.81 [+4.17, 1.93]
-1.811 [+4.17, 5.75] | Mean Difference
M. Random, 95% CI | | | | | | | | |
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2021 Akkar et al. 2021 Akkar et al. 2021 Cerietti et al. 2020 Cheraghpour et al. 2019 Darand et al.2019 Ebrahim-Mameghani et al.2016 Ferro Y. et al.2020 Chaffari et al. 2018 Chaffari et al. 2018 Hosseini et al. 2018 Hosseini et al. 2018 Hosseini et al. 2017 Jazayeri et al. 2020 Khonche et al. 2017 Hosseini et al. 2018 Hussain et al. 2018 Hussain et al. 2019 Li et al. 2010 Raiendra et al. 2020 Raiendra et al. 2020 Raiendra et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2020 Shavakhi et al. 2021 (HessPeridin) Solini et al. 2012 (HessPeridin) Sangouni et al. 2021 (HessPeridin) Yari et al. 2021 (HessPeridin) Total (95% CL) Heterogenely: Tau* 27.85; Chi ^a Testro overall effect: Z = 2.80 (P Ehsanis, et al. 2021 (HessPeridin)
 | Exq
Mean
-4.95
-13.83
-5.07
-25.53
-3.92
0.84
0.95
-7.13
-10.8
-2
-1.06
0.08
-0.84
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-2.09
-3.21
-5.537
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N. Random, 95% CI | | | | | | | |
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| B | Study or Subgroup Abu Hassan et al. 2023 Akzai et al. 2020 Akbar et al. 2020 Akbar et al. 2021 Aksar et al. 2021 Ackar et al. 2014 Cerietti et al. 2019 Darand et al.2019 Darand et al.2019 Darand et al.2019 Derand et al.2019 Derand et al.2019 Cerietti et al. 2012 Charginpour et al. 2019 Darand et al.2018 Ferro Y. et al.2020 Chaffari et al. 2018 Chostari et al. 2018 Hosseini et al. 2018 Hussain et al. 2019 Li et al. 2010 Khonche et al. 2020 Raigendra et al.2022 Pour et al. 2020 Raigendra et al.2020 Shavakhi et al. 2020 Shavakhi et al.2020 Shavakhi et al.2020 Shavakhi et al.2021 Pari et al.2021 (HessFilax) Yari et al.2021 (Hessefilax) </td <td>Exq
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Fig. 2. Forest plot analysis of pre- and post-treatment changes in (A) ALT level, (B) AST level and (C) liver stiffness in treatment and control groups.

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Advances in Integrative Medicine xxx (xxxx) xxx

		Exp	erimenta	Control				Mean Difference	Mean Difference	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
A	Abu Hassan et al. 2023	-0.26	13.5935	105	-0.54	16.6055	100	9.4%	0.28 [-3.89, 4.45]	
	Akbari et al. 2022	-2.81	15.7688	57	-2.23	14.2581	53	5.2%	-0.58 [-6.19, 5.03]	
	Askari et al. 2014	-0.24	11.2115	23	-0.8	11.1129	22	3.8%	0.56 [-5.96, 7.08]	
	Cerletti et al. 2020	0.07	16.9103	74	0.05	18.2372	39	3.4%	0.02 [-6.88, 6.92]	
	Damavandi et al. 2021	-2.18	12.9402	37	-0.93	12.5733	34	4.6%	-1.25 [-7.19, 4.69]	
	Darand et al.2019	-2.08	13.2019	22	2.73	12.616	21	2.7%	-4.81 [-12.53, 2.91]	
	Ebrahimi-Mameghani et al.2016	-5.24	14.953	29	-3.6	11.6328	26	3.3%	-1.64 [-8.68, 5.40]	
	Faghihzadeh et al. 2015	-1.35	10.5751	24	-0.76	10.965	24	4.4%	-0.59 [-6.68, 5.50]	
	Ferro et al.2020	-3.94	13.4576	41	-4.05	11.2313	45	5.9%	0.11 [-5.16, 5.38]	
	Hormati et al 2019	-3.5	8.7662	37	-0.23	9.1256	39	10.1%	-3.27 [-7.29, 0.75]	
	Jazayeri et al. 2021	-5.83	8.397	42	-1.29	9.5708	42	11.0%	-4.54 [-8.39, -0.69]	
	Kazemi et al. 2020	-3.43	13.6286	40	-2.51	11.1013	40	5.5%	-0.92 [-6.37, 4.53]	
	Musazadeh et al. 2022	-10.17	9.4406	22	-2.97	10.3222	21	4.7%	-7.20 [-13.12, -1.28]	
	Pour et al. 2020	-2.67	15.1891	36	-3.09	11.0419	36	4.3%	0.42 [-5.71, 6.55]	
	Rafie et al. 2020	-1.28	10.1515	23	-0.7	11.2749	23	4.2%	-0.58 [-6.78, 5.62]	
	Sangouni et al. 2020	-1.62	13.6918	45	0.01	14.9904	43	4.5%	-1.63 [-7.64, 4.38]	
	Sangouni et al. 2021	-1.6	13.706	45	-0.03	14.867	43	4.6%	-1.57 [-7.55, 4.41]	
	Yari et al. 2021 (Flax Seeds)	-9.5	20.5895	24	-2.46	13.5762	21	1.6%	-7.04 [-17.12, 3.04]	
	Yari et al. 2021 (Hes+Flax)	-7.36	10.9591	25	-2.46	13.5762	21	3.1%	-4.90 [-12.12, 2.32]	
	Yari et al. 2021 (Hesperidin)	-5.56	8.5697	22	-2.46	13.5762	21	3.5%	-3.10 [-9.92, 3.72]	
	Total (95% CI)			773			714	100.0%	-1.99 [-3.27, -0.71]	◆
	Heterogeneity: Tau ² = 0.00; Chi ² =	0.91); P	²= 0%				-			
	Test for overall effect: Z = 3.05 (P =	0.002)		,,						-10 -5 0 5 10 Favours [experimental] Favours [control]

B

		Exp	perimental		Control				Mean Difference	Mean Difference
٦.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
	Akbari et al. 2022	-1.66	19.1174	57	-0.81	15.344	53	6.5%	-0.85 [-7.31, 5.61]	
	Cerletti et al. 2020	0	20.3963	74	0.05	23.2725	39	3.6%	-0.05 [-8.71, 8.61]	
	Damavandi et al. 2021	-1.98	18.4887	37	-1.24	20.2556	34	3.3%	-0.74 [-9.79, 8.31]	
	Darand et al.2019	-2.6	21.1061	22	-0.64	18.0901	21	2.0%	-1.96 [-13.69, 9.77]	
	Ebrahimi-Mameghani et al.2016	-3.7	15.5483	29	-2.03	19.0607	26	3.1%	-1.67 [-10.93, 7.59]	
	Ehsani S. et al. 2022	-2.72	14.5352	40	-2.02	21.1984	40	4.2%	-0.70 [-8.67, 7.27]	
	Ferro et al.2020	-4.04	16.7795	41	-2.94	15.3314	45	5.8%	-1.10 [-7.92, 5.72]	
	Ferro Y. et al.2022	-0.85	16.1944	65	-0.99	15.4497	62	8.9%	0.14 [-5.36, 5.64]	
	Hormati et al 2019	-2.82	21.6914	37	-2.13	95.9589	39	0.3%	-0.69 [-31.61, 30.23]	
	Hussain et al. 2017	-10.01	18.5543	35	-1.49	19.2375	35	3.4%	-8.52 [-17.37, 0.33]	
	Jazayeri et al. 2021	-2.75	15.0719	42	-2.51	15.4664	42	6.3%	-0.24 [-6.77, 6.29]	
	Kazemi et al. 2020	-2.81	14.4134	40	-2.16	12.2676	40	7.8%	-0.65 [-6.52, 5.22]	
	Musazadeh et al. 2022	-7.12	4.8162	22	-2.38	6.8721	21	21.2%	-4.74 [-8.30, -1.18]	
	Pour et al. 2020	-3.79	20.2818	36	-2.35	16.9268	36	3.6%	-1.44 [-10.07, 7.19]	
	Rafie et al. 2020	-2.27	15.7736	23	-2.2	8.7622	23	4.9%	-0.07 [-7.44, 7.30]	
	Sangouni et al. 2020	-0.58	16.6319	45	-0.13	18.8469	43	4.9%	-0.45 [-7.89, 6.99]	
	Sangouni et al. 2021	-0.44	16.7271	45	-0.14	19.0452	43	4.8%	-0.30 [-7.80, 7.20]	
	Soleimani et al.2020	-2.11	14.1212	51	-1	20.6834	47	5.4%	-1.11 [-8.18, 5.96]	
	Total (95% CI)			741			689	100.0%	-1.77 [-3.41, -0.13]	◆
	Heterogeneity: Tau ² = 0.00; Chi ² = 0	6.62, df =	-							
	Test for overall effect: Z = 2.11 (P =	0.03)								-20 -10 0 10 20 Favours (experimental) Favours (control)

	Ex	perimenta	d l	(Control			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
Abu Hassan et al. 2023	0.06	6.1085	105	-0.01	7.1886	100	3.3%	0.07 [-1.76, 1.90]			
Akbari et al. 2022	-0.6	5.5618	57	-0.17	5.3196	53	2.6%	-0.43 [-2.46, 1.60]			
Askari et al. 2014	-0.35	5.3468	23	-0.3	5.644	22	1.1%	-0.05 [-3.27, 3.17]			
Cerletti et al. 2020	-0.11	5.164	74	0.06	7.3811	39	1.6%	-0.17 [-2.77, 2.43]			
Damavandi et al. 2021	-0.71	5.1731	37	-0.37	5.68	34	1.7%	-0.34 [-2.87, 2.19]			
Darand et al.2019	-0.85	5.7636	22	-0.09	6.2389	21	0.8%	-0.76 [-4.35, 2.83]			
Ehsani S. et al. 2022	-0.95	2.073	40	-0.76	2.3735	40	11.4%	-0.19 [-1.17, 0.79]			
Faghihzadeh et al. 2015	-0.38	4.7987	24	-0.35	4.9758	24	1.4%	-0.03 [-2.80, 2.74]			
Ferro et al.2020	-1.63	4.214	41	-0.01	5.643	45	2.5%	-1.62 [-3.71, 0.47]			
Ferro Y. et al.2022	-0.37	5.6394	65	-0.42	4.9889	62	3.2%	0.05 [-1.80, 1.90]			
Ghaffari et al. 2018 (CHI)	-0.28	5.5086	21	-0.11	6.817	42	1.1%	-0.17 [-3.30, 2.96]			
Ghaffari et al. 2018 (TUR)	-0.84	6.5728	21	-0.11	6.8179	42	0.9%	-0.73 [-4.22, 2.76]			
Ghaffari et al. 2018 (TUR+CHI)	-0.69	6.2055	21	-0.08	6.8328	42	1.0%	-0.61 [-3.97, 2.75]			
Hosseini et al. 2018	-1.99	1.0284	24	-1.62	1.2076	23	26.4%	-0.37 [-1.01, 0.27]			
Hussain et al. 2017	-2.78	7.653	35	-0.48	5.6491	35	1.1%	-2.30 [-5.45, 0.85]			
Jazayeri et al. 2021	-0.9	2.9887	42	-0.79	3.4179	42	5.8%	-0.11 [-1.48, 1.26]			
Kazemi et al. 2020	-0.95	2.0735	40	-0.77	2.3904	40	11.3%	-0.18 [-1.16, 0.80]			
Khonche et al. 2019	-0.62	3.7307	60	-0.11	1.9665	60	9.6%	-0.51 [-1.58, 0.56]			
Musazadeh et al. 2022	-3.01	4.7292	22	-0.89	3.5119	21	1.8%	-2.12 [-4.60, 0.36]			
Rafie et al. 2020	-0.84	4.9807	23	-0.73	2.8227	23	2.0%	-0.11 [-2.45, 2.23]			
Sangouni et al. 2020	-0.19	4.3506	45	-0.16	5.3273	43	2.6%	-0.03 [-2.07, 2.01]			
Sangouni et al. 2021	-0.19	4.3478	45	-0.11	5.2982	43	2.6%	-0.08 [-2.11, 1.95]			
Shafiezadeh et al. 2020	-0.67	6.3041	32	-0.44	5.6364	36	1.3%	-0.23 [-3.09, 2.63]			
Shavakhi et al. 2015	-2.91	7.8387	40	-2.25	6.1003	41	1.2%	-0.66 [-3.72, 2.40]			
Yari et al. 2021 (Flax Seeds)	-2.32	5.7294	24	-0.95	7.9113	21	0.7%	-1.37 [-5.46, 2.72]			
Yari et al. 2021 (Hes+Flax)	-1.92	10.3728	25	-0.95	7.9113	21	0.4%	-0.97 [-6.26, 4.32]			
Yari et al. 2021 (Hesperidin)	-2.92	5.2718	22	-0.95	7.9113	21	0.7%	-1.97 [-6.01, 2.07]			
Total (95% CI)			1030			1036	100.0%	-0.38 [-0.71, -0.05]	•		
Heterogeneity: Tau ² = 0.00; Chi ²	= 7.02, d	f= 26 (P =	1.00);	l² = 0%							
Test for overall effect: 7 = 2.24 (P	= 0.03								-4 -2 U 2 4		

Fig. 3. Forest plot analysis of pre- and post-treatment changes in (A) waist circumference, (B) body weight, and (C) body mass index (BMI) in treatment and control groups.

D.W. Rathnayake et al.





were 2.03 (95 % CI: -0.04; 4.10) mg/dL lower on average in the herb group than in the CG (Fig. 4.C). Among these studies, 14 used a single herb compound and four used polyherbal compounds. There was no difference in FBG levels between single herbal interventions over the controls (-2.0300 [95 % CI: -4.2946; 0.2346] vs -1.9996 [95 % CI: -6.2080; 2.2087], P = 0.9855).

3.6.2. HbA1c

There were four studies assessing HbA1c levels of 467 patients [32, 49,52,66]. Data showed low levels of heterogeneity ($I^2 = 0.0 \%$, P = 0.56). There was no difference in HbA1c levels between herbal interventions over the controls (-0.01 [95 % CI: -0.11; 0.12], P =0.90) (Fig. 4.D).

4. Discussion

The present systematic review and meta-analysis aimed to evaluate the efficacy of herbal medications in the management of NAFLD based on data from 48 articles. The meta-analysis revealed improvements in key parameters associated with NAFLD among patients who incorporated herbal medications into their treatment regimens. Results showed a noteworthy decline in liver enzymes, liver stifness, WC, body weight, BMI, TG and FBG.

Specifically, herbal interventions showed a higher ALT and AST reduction over the controls. It is known that herbal compounds possess hepatoprotective properties, mitigate liver inflammation and reduce oxidative stress, consequently leading to a decline in ALT and AST levels [75]. Moreover, single herb compounds showed a higher ALT reduction compared to polyherbal compounds. On the contrary, it is suggested that the active phytochemical components present in individual plants may not be adequate to attain the desired therapeutic effects [76]. By combining multiple herbs in specific ratios, a more potent therapeutic effect can be achieved [76], simultaneously minimizing toxicity. The use of herbal combinations is believed to address multiple targets simultaneously, offering comprehensive relief [77]. Due to synergism, polyherbal formulations offer some great benefits which lacks in single herbal formulation [78].

Herbal interventions also showed higher WC, weight, and BMI reduction over the controls. Single herb compounds showed a higher weight reduction compared to polyherbal compounds. Herbal interventions influence metabolic pathways associated with adipose tissue regulation, leading to decreased adiposity and improvements in weight-related parameters [79]. Herbal interventions also showed a higher TG reduction over the controls. Active compounds in herbal interventions could modulate lipid metabolism, promoting the breakdown of triglycerides and enhancing HDL function, contributing to a healthier lipid profile [80]. Herbal interventions showed a higher FBG reduction over the controls (P<0.02). Herbal compounds may impact insulin sensitivity and glucose metabolism, leading to improved blood glucose regulation and reduced fasting blood glucose levels [81].

Cynara cardunculus was identified as the predominant ingredient utilized in polyherbal preparations. Phytochemical analysis of *Cynara cardunculus* extract indicates a high concentration of antioxidants, including caffeic acid derivatives (e.g., cynarin and chlorogenic acid), flavonoids (luteolin glycosides), and sesquiterpenes like cynaropicrin [82]. Recent research suggests that one of its components, luteolin, exhibits a hypolipemic effect by inhibiting key enzymes involved in lipid metabolism. This inhibition leads to increased faecal excretion of sterols [83]. The presence of flavonoids may contribute antioxidant properties, sesquiterpene lactones could offer anti-inflammatory and hepatoprotective effects [84]. Additionally, *Cynara cardunculus* demonstrates synergistic effects with other nutraceuticals, making it a promising natural resource for addressing combined hyperlipidaemia and NAFLD.

In summary, the potential mechanism of action of the herbal compound on the improvement of NAFLD is multifactorial. Enhancing fatty acid metabolism proves to be an effective strategy in the treatment of NAFLD [85]. Numerous herbal remedies have been identified to suppress hepatic lipogenesis through diverse mechanisms, such as inhibiting lipogenesis by down-regulating sterol regulatory element-binding protein 1c (SREBP-1c); promoting β -fatty acid oxidation by up-regulating peroxisome proliferator-activated receptor α (PPAR α); elevating insulin sensitivity and mitigating oxidative stress by enhancing antioxidant levels through nuclear factor-erythroid 2-related factor 2 (Nrf2) and hindering the activation of inflammatory pathways [86].

Abundant polyphenols, flavonoids, terpenoids, and alkaloids identified in various plants have been extensively studied for their diverse pharmacological properties, showing significant promise in addressing NAFLD. The presence of *Cynara cardunculus* as a common ingredient in polyherbal formulations suggests a deliberate choice in polyherbal formulations, potentially harnessing the synergistic effects of its diverse bioactive compounds.

This systematic review has several limitations. Studies were searched across the three key databases but not the Ayurvedic database which may have included more studies exploring herbal treatments for NAFLD. Also, the meta-analysis encountered a higher degree of heterogeneity across the included studies in terms of study design, participant characteristics, duration, and intervention protocols. This variability may introduce limitations in the generalisability of the findings and should be considered when interpreting the results. Most studies did not include changes in histology with the incorporation of pre-and post-treatment liver biopsies. The limited number of studies that examined liver stiffness did not show a difference in liver stiffness readings between the groups.

However, this meta-analysis incorporated data from a substantial number of studies, providing a comprehensive overview of the current evidence regarding the potential efficacy of herbal medications in NAFLD management. In the absence of currently approved therapy for NAFLD, herbal therapies can be explored as alternatives to improving the outcomes of patients with NAFLD. Therefore, more high-quality RCTs with longer treatment and follow-up are required to determine whether the use of herbal therapies among patients with NAFLD, with resultant enhancements in metabolic parameters and liver biochemistries translates to improved clinical outcomes.

5. Conclusion

The results of the current meta-analysis demonstrated notably greater reductions in ALT, AST, liver stiffness, WC, weight, BMI, TG, and FBG in individuals with NAFLD who underwent herbal treatments compared to those who received a placebo. The reductions in ALT and weight were more pronounced in single herb compounds compared to polyherbal compounds. No significant differences were observed between the two groups regarding HbA1c levels. These findings highlight the potential effectiveness of herbal interventions, particularly single herb compounds, in ameliorating various health parameters associated with liver health.

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CRediT authorship contribution statement

Madunil Anuk Niriella: Writing – review & editing, Supervision, Methodology. Dileepa Ediriweera: Writing – review & editing, Methodology, Formal analysis. piumika piumika: Writing – original draft, Methodology, Data curation. Dulmini Wathsala Rathnayake: Writing – original draft, Methodology, Data curation. Jennifer Perera: Writing –

D.W. Rathnayake et al.

review & editing, Funding acquisition, Conceptualization.

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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aimed.2024.08.016.

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D.W. Rathnayake et al.

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