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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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A R T I C L E I N F O

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Non-alcoholic fatty liver disease
Herbal
Polyherbal
Meta-analysis

A B S T R A C T

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 ≥18 years, published in English, and a Jadad score ≥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 % worldwide[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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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 evidence-based 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 (W*R* 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 ≥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 (W*R*) 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 (W*R* 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 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 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 I^2 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 high-quality Jadad score (n=14), full text-article not available in English (n=2), the full-text article being not available (n=8). By manually

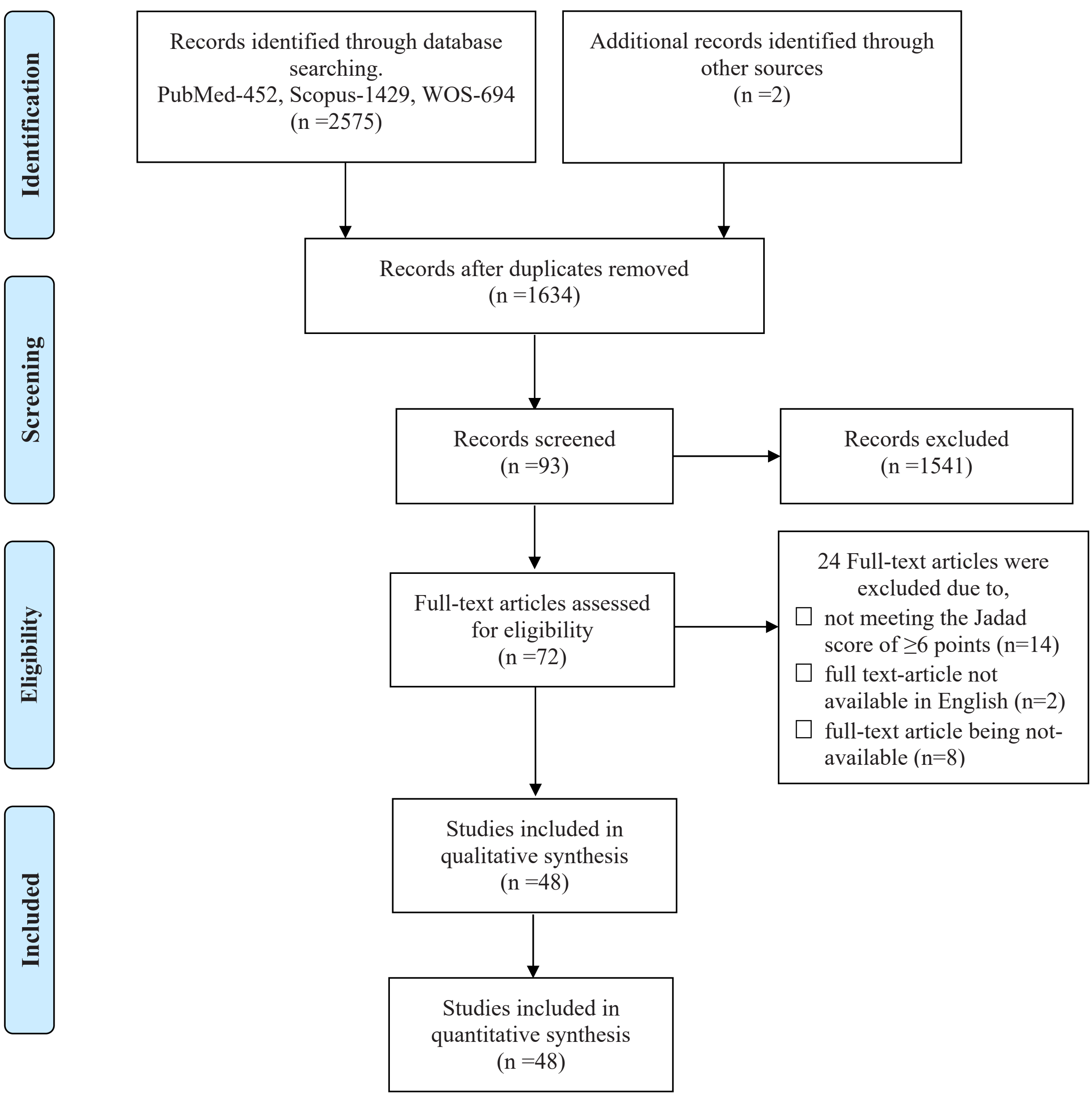

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for study selection.

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 co-interventions; dietary modifications, physical activity [38], or both [39]. The most measured outcomes were related to response measures of 1iver 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 (I^2 = 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 (I^2 = 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

Table 1
Study characteristics of single herbal preparations.

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; ≥ 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 *Beta vulgaris* 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 (*Rosmarinus officinalis* 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-β.
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 significantly.
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-IR, TC, TG, LDL-C, HDL-C, Weight, BMI, WHR, Energy, MET, TNF-α, NF-κB steatosis, fibrosis	Hesperidin supplementation accompanied with lifestyle modification is superior to lifestyle modification alone in management of NAFLD at least partially through inhibiting NF-κB 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, lipid profile, and blood

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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
							pressure between the two groups.
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 kg/m^2; 43/44; M=54, F=33; 30–60 years	Two 500 mg capsules 3 times/day with meals. Ingredient - *Elettaria cardamomum (L.) Maton*	Placebo	-	FBS, FBI, HOMA-IR, QUICKI TC, TG, LDL, HDL, Liver steatosis grade, BMI, Serum irisin	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 differences in FBS, TC, and BMI
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) *Nigella sativa* seed	Placebo - 2 g/day starch	-	AST, ALT, GGT, TNF-α, hs-CRP, NF-κB, Weight, BMI, WC, HC, WHR, Fibro scan exam - CAP score, steatosis, fibrosis	TNF-α decreased significantly in both, hs-CRP and NF-κB 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 two groups.
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 *Chlorella vulgaris* - 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	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 differed significantly between groups.
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 - *Rhus coriaria Linn,*	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	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 IG compared to CG
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- *Curcuma longa* 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	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

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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 IL−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 groups.
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 fatigue.
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 *Nigella sativa* and dry leaf of *Melissa officinalis*) (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 compared to CG.
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 ≥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 (p=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 *Plantago major* 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

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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
		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 *Berberis vulgaris* 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, LDL, HDL
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} *Camelina 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- *Rhus coriaria* 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

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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
		(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 no significant effect.
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 - *Capparis spinosa*	Placebo	lifestyle changes	Weight, WC, AST, ALT, FBS, insulin, HOMA-IR, LDL/HDL, TG/HDL, TC/HDL, non-HDL.C, hs-CRP	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) decreased more significantly in the IG than the CG.
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 *Nigella sativa* seed oil every 12 hourly	placebo	-	AST, ALT, LDL, HDL, TG ultrasound grade- 0, 1, 2, 3 hepatic steatosis, blood urea nitrogen, creatinine, BMI	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 placebo.
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 -*Vitis vinifera*	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

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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
							enzymes in the IG compared with the CG.
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 - *Silybum marianum*	Placebo three times daily	Dietary restriction of saturated and total fats, maintain a target weight/BMI of </= +/- 10 % change of body weight.	Histological improvement in NAS ALT and AST, ALP, FBG, HOMAr, TG, TC, BMI	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 significantly different from other groups.
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 - *Crocus sativus* extract	Placebo capsules once a day	-	AST, ALT, TG, HDL, LDL, BMI, WC	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 groups.
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 (*Crocus sativus*)	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	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 indexes (p >.05)
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 ≥ 25 kg/m^2; 28/24; M=0, F=60; 18–65 years	1000 mg/day powder of licorice root extract (*Glycyrrhiza glabra*) 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 (*Allium sativum* 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

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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
							in skeletal muscle mass, serum concentration of SOD, and TAC.
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 (*Allium sativum* 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	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 serum ALP.
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 - *Carum copticum* (or *Trachyspermum ammi*) 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 (*Cuminum cyminum*) 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 (*Allium sativum* L.) per day	Placebo	-	ALT, AST, FBS, Hb A1C, TC, TG, LDL, HDL, USS - hepatic steatosis, Weight, BMI, Body fat mass	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.

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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
		I=43.6±8.3 y, C=39.4±10 y					
Wah Kheong, C. et al. [33], 2017; Malaysia	R, DB, PC; 48 weeks; 8 points	Biopsy-proven NASH and a NAFLD activity score (NAS) of 4 or more and ALT and AST levels ≥ 40 IU/L 49/50; M=46, F=53 > 18 years	Silymarin (*Silybum marianum*) 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, not seen in the CG.
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	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 patients.
Yari et al. [73], 2021; Iran	R, PG, OL; 12 weeks; 6 points	patients with more than 37 % hepatic fat (CAP ≥ 260, grade ≥ 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-κB 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-IR
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 other outcomes.

(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

Table 2
Study characteristics of polyherbal preparations.

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 (*Cardo marianum*), choline bitartrate, curcumin and D-α-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 *Cynara cardunculus* 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 *Cynara cardunculus* 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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Table 2 (*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
							individuals over 50 years old.
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	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 men
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	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 = 0.001).
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 miltiorrhizae, 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	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)

Table 2 (*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
		(diagnosed by USS and echo) Bergamot Polyphenolic Fraction (BPF)=20, *Cynara cardunculus* (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 *Terminalia chebula* fruit and *Sphaeranthus indicus* 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 Silymarin 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 kg/m^2; 23/23; M=20, F=26; 20–70 years	3 capsules daily, each containing 500 mg of ginger (*Zingiber officinale*). Active ingredients- polyphenolic compounds as *gingerol* 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 [1]ratio; 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).

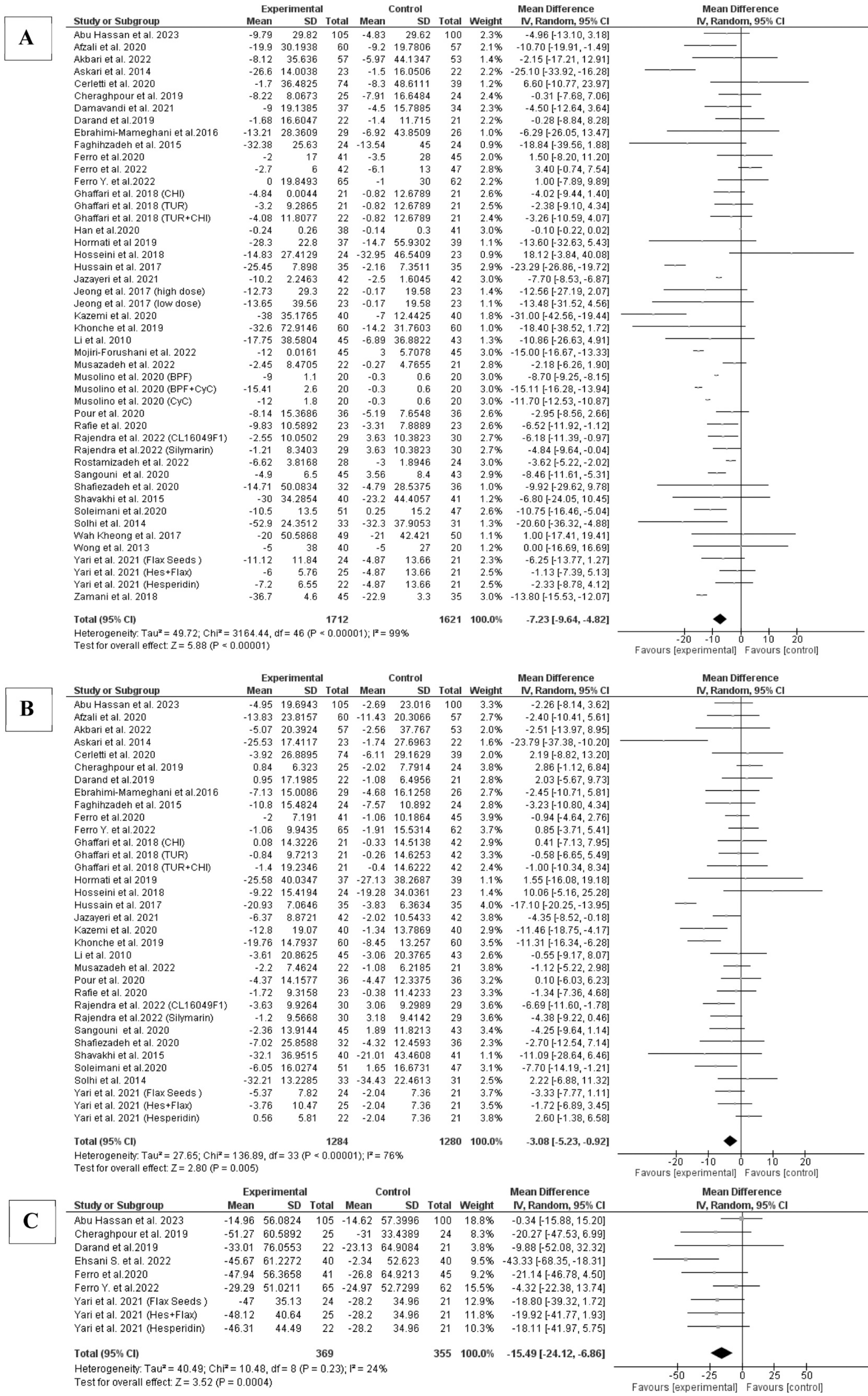

Fig. 2. Forest plot analysis of pre- and post-treatment changes in (A) ALT level, (B) AST level and (C) liver stiffness in treatment and control groups.

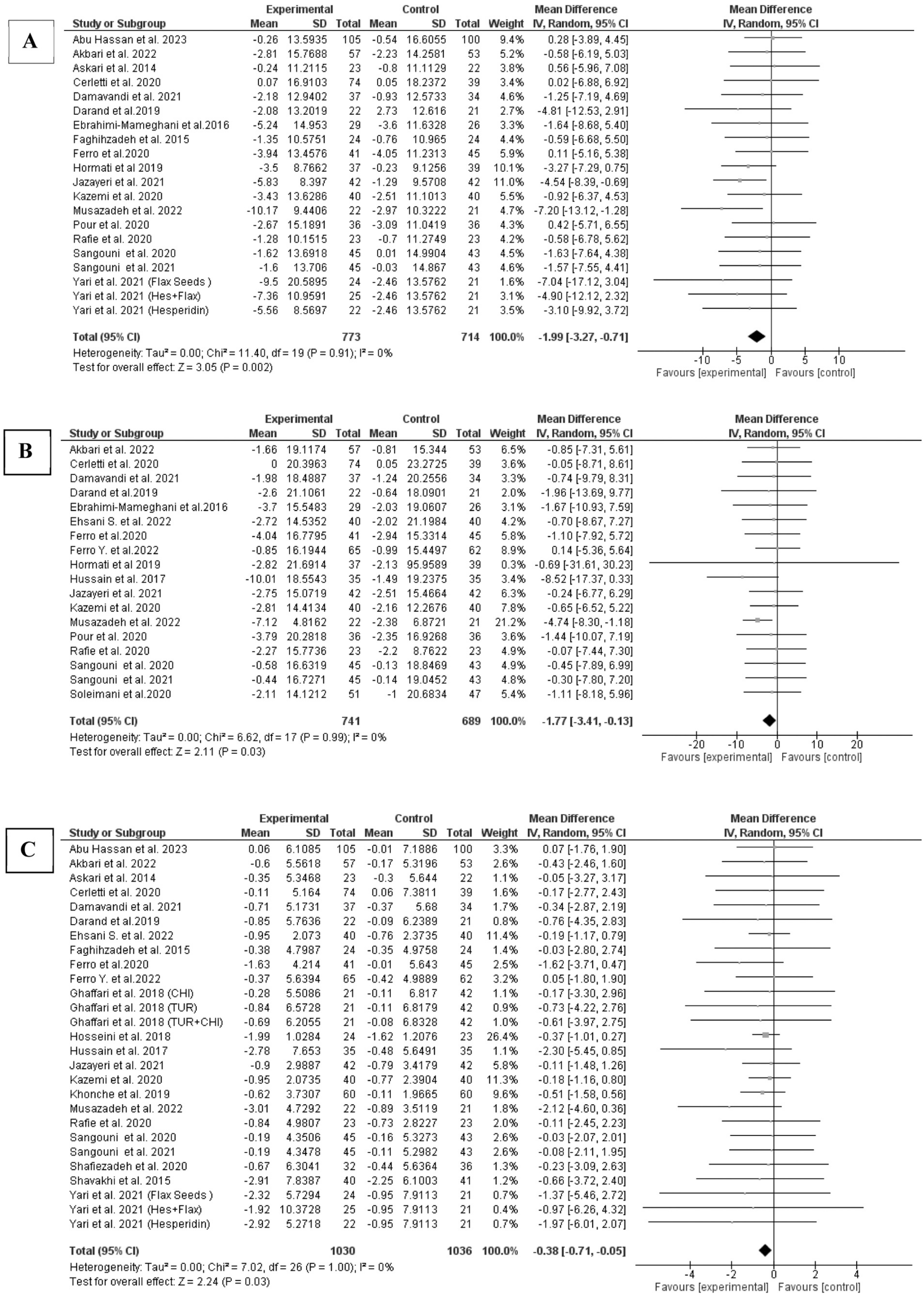

Fig. 3. Forest plot analysis of pre- and post-treatment changes in (A) waist circumference, (B) body weight, and (C) body mass index (BMI) in treatment and control groups.

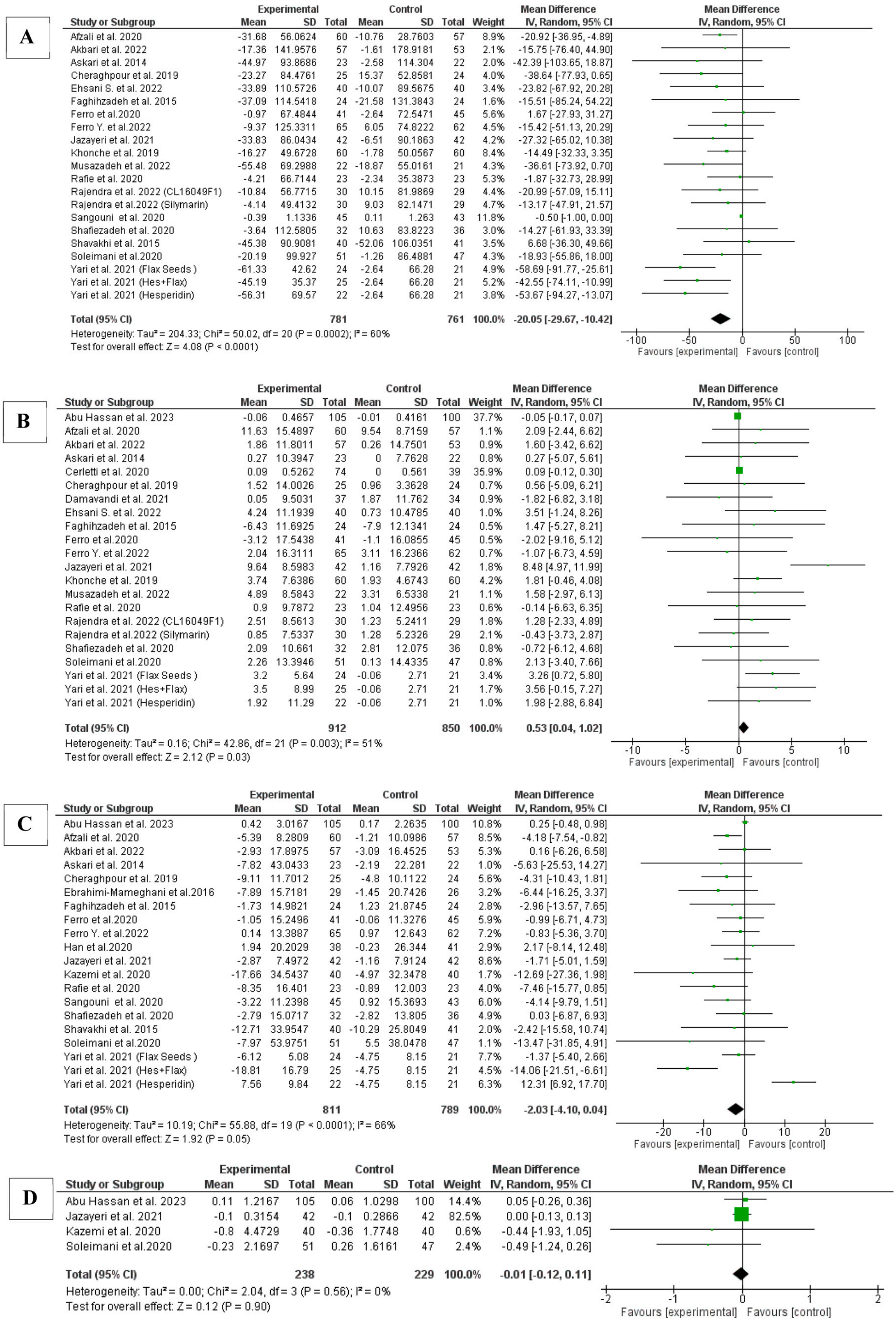

Fig. 4. Forest plot analysis of pre- and post-treatment changes in (A) TG level, (B) HDL level, (C) FBG level and (D) HbA1c level in treatment and control groups.

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 (PPARα); 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 –

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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