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SPECIALTY SECTION This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 08 August 2022 ACCEPTED 30 January 2023 PUBLISHED 14 February 2023

CITATION

Wang L-I, Zhang P-h and Yan H-h (2023) Functional foods and dietary supplements in the management of non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Front. Nutr.* 10:1014010. doi: 10.3389/fnut.2023.1014010

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Functional foods and dietary supplements in the management of non-alcoholic fatty liver disease: A systematic review and meta-analysis

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Objective: In this systematic review and meta-analysis, we aimed to clarify the overall effects of functional foods and dietary supplements in non-alcoholic fatty liver disease (NAFLD) patients.

Methods: Randomized controlled trials (RCTs) published in PubMed, ISI Web of Science, Cochrane library, and Embase from January 1, 2000 to January 31, 2022 were systematically searched to assess the effects of functional foods and dietary supplements in patients with NAFLD. The primary outcomes were liver-related measures, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic fibrosis and steatosis, while the secondary outcomes included body mass index (BMI), waist circumference (WC), triacylglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). These indexes were all continuous variables, so the mean difference (MD) was used for calculating the effect size. Random-effects or fixed-effects models were used to estimate the mean difference (MD). The risk of bias in all studies was assessed with guidance provided in the Cochrane Handbook for Systematic Reviews of Interventions.

Results: Twenty-nine articles investigating functional foods and dietary supplements [antioxidants (phytonutrients and coenzyme Q10) = 18, probiotics/symbiotic/prebiotic = 6, fatty acids = 3, vitamin D = 1, and whole grain = 1] met the eligibility criteria. Our results showed that antioxidants could significantly reduce WC (MD: -1.28 cm; 95% CI: -1.58, -0.99, P < 0.05), ALT (MD: -7.65 IU/L; 95% CI: -11.14, -4.16, P < 0.001), AST (MD: -4.26 IU/L; 95% CI: -5.76, -2.76, P < 0.001), and LDL-C (MD: -0.24 mg/dL; 95% CI: -0.46, -0.02, P < 0.05) increased in patients with NAFLD but had no effect on BMI, TG, and TC. Probiotic/symbiotic/prebiotic supplementation could decrease BMI (MD: -0.57 kg/m²; 95% CI: -0.72, -0.42, P < 0.05), ALT (MD: -3.96 IU/L; 95% CI: -5.24, -2.69, P < 0.001), and AST (MD: -2.76; 95% CI: -3.97, -1.56, P < 0.0001) levels but did not have beneficial effects on serum lipid levels compared to the control group. Moreover, the efficacy of fatty acids for treating NAFLD was full of discrepancies. Additionally, vitamin D had no significant effect on BMI, liver transaminase, and serum lipids, while whole grain could reduce ALT and AST but did not affect serum lipid levels.

Conclusion: The current study suggests that antioxidant and probiotic/symbiotic/prebiotic supplements may be a promising regimen for NAFLD

patients. However, the usage of fatty acids, vitamin D, and whole grain in clinical treatment is uncertain. Further exploration of the efficacy ranks of functional foods and dietary supplements is needed to provide a reliable basis for clinical application.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier: CRD42022351763.

KEYWORDS

non-alcoholic fatty liver disease, antioxidants, phytonutrients, probiotics, symbiotics, prebiotics

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), renamed metabolicassociated fatty liver disease (MAFLD) in 2020 (1), is a chronic and progressive metabolic disease characterized by excessive fat deposition in the hepatocytes in the absence of alcohol exposure or other identifiable causes. This may finally lead to cirrhosis, hepatocellular carcinoma (HCC), and other severe liver diseases (2, 3), adversely impacting people's quality of life. It is reported that the global prevalence of NAFLD is 24.1%, of which the highest are in the Middle East and South America and the lowest are in Africa (4, 5). The prevalence of NAFLD in China is about 30%, and this rate is expected to increase further as obesity and type 2 diabetes mellitus (T2DM) are gradually becoming the most common diseases in humans (6, 7).

The occurrence and development of NAFLD depend on multiple factors, including metabolic comorbidities, gut microbiome, and environmental and genetic factors (8). Except for the genetic factors that human beings cannot intervene, the other three conditions are closely related to our current lifestyle and affect each other. In particular, they are influenced by a sedentary lifestyle and the intake of high-energy foods, including fried foods, desserts, and soft drinks (9). The habits mentioned above account for obesity, T2DM, and hyperlipidemia, which are major risk factors for NAFLD (10). It is reported that the prevalence of NAFLD is as high as 60–90%, 27–92%, and 28–70% in patients with obesity, hyperlipidemia, and T2DM, respectively (6).

As no approved pharmacological options exist for NAFLD, lifestyle modifications, including increased physical activity and reduced energy intake, remain the first line of therapy (10, 11); however, consistent low-energy intake and exercise are difficult to achieve in both adults and children. Recently, researchers have found

that gut microbiota plays an important role in the pathophysiology of metabolic diseases, especially obesity-related disorders, including metabolic syndrome and NAFLD (12). The hypothesis underlying its mechanism is that decreased microbial gene richness leads to a decline in bacteria producing short-chain fatty acids and an increase in bacteria synthesizing lipopolysaccharide, which can induce the development of steatosis and trigger systemic inflammation (13, 14). Early probiotic, prebiotic, symbiotic, and fecal microbiota transfer interventions may prevent NAFLD exacerbation (15, 16). Meanwhile, some investigations have reported that the intake of dietary supplements (such as vitamin D, vitamin E, and fatty acid) (17, 18) and functional foods (such as garlic powder, Nigella sativa, sumac powder, and olive oil) (19-23) may ameliorate and/or reverse NAFLD, which may be due to their antioxidant properties. For example, organosulfur compounds in garlic powder and flavonoids in green tea extract belong to the category of functional foods, but in terms of properties, they exhibit antioxidant activities. Their protection is mainly achieved in NAFLD by decreasing oxidative stress and inflammatory responses (12, 20, 24). Although some functional foods may have other properties, such as anticancer and antimicrobial effects (12, 25), these effects on NAFLD are unclear and need to be further explored.

Some functional foods and dietary supplements may decrease liver damage, such as liver disease without cirrhosis, there are inconsistencies in the results obtained by different studies. Considering the inconsistencies of clinical randomized controlled trials (RCTs), we performed this systematic review and meta-analysis to provide clinicians, nutritionists, and other health professionals with relatively unified clinical evidence to help them make relevant clinical decisions, that is, whether functional foods and dietary supplements should be applied to NAFLD management.

2. Materials and methods

2.1. Eligibility criteria

This study was only limited to RCTs that reported the effects of functional foods and dietary supplements on liver-related indices in patients suffering from NAFLD, regardless of the method of diagnosis [fibroscan/ultrasonography/elastography technique/magnetic resonance spectroscopy/acoustic structure quantification (ASQ) liver scan/percutaneous liver biopsy/computed tomography (CT)], obesity status, and other metabolic syndrome statuses. Animal or *in vitro* studies, case reports, abstracts, guidelines, reviews, meta-analyses, and conference proceedings were excluded.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ASQ, acoustic structure quantification; AST, aspartate transaminase; BMI, body mass index; CI, Confidence interval; CRP, C-reactive protein; CT, computed tomography; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FBS, fasting blood sugar; GGT, glutamyltransferase; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; HOMA–IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic-associated fatty liver disease; MD, mean differences; NAFLD, Nonalcoholic Fatty Liver Disease; PUFA, polyunsaturated fatty acid; QUICKI, quantitative insulin sensitivity check index; RCTs, Randomized controlled trials; RoB2, Risk of Bias Tool; SPB-201, powdered-water extract of Artemisia annua; TC, total cholesterol; T2DM, type 2 diabetes mellitus; TNF- α , tumor necrosis factor- α ; TG, triacylglyceride; WC, waist circumference; WHR, waist to height ratio.

Two reviewers determined the inclusion and exclusion criteria jointly and retrieved articles separately.

2.1.1. Inclusion criteria

(1) Patients were adults (\geq 18-year-old) with NAFLD; (2) interventions in studies included: dietary supplementation (synbiotic, symbiotic, prebiotic, probiotic, vitamin, and omega-3 supplementation) and functional foods only (exhibiting effects, including antioxidant, anti-inflammatory, immunomodulatory, antimicrobial action); (3) the placebo in the control group was identical in color, shape, size, and packaging to that of the intervention group; (4) the main outcomes were the changes in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), hepatic fibrosis, and hepatic steatosis; (5) there were no restrictions on the duration of intervention; (6) only publications written in English were chosen, but the country was not a limiting factor.

2.1.2. Exclusion criteria

(1) Patients with advanced liver disease or/and gastrointestinal dysfunction; (2) interventions in studies combined with exercise

or/and active lifestyle modification, medicine, weight loss surgery, and enteral and/or parenteral nutrition treatment; (3) studies that did not report transaminase values (AST and/or ALT).

2.2. Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA). Its protocol was registered on PROSPERO (CRD42022351763). One of the researchers was responsible for keyword searches across four major electronic databases: PubMed, ISI Web of Science, Cochrane library, and Embase, from January 1, 2000 to January 31, 2022. The search strategy and results were finalized through group discussions.

The search method was as follows: ("non-alcoholic fatty liver disease" OR "NAFLD" OR "nonalcoholic fatty liver disease" OR "fatty liver, nonalcoholic" OR "fatty livers, nonalcoholic" OR "liver, nonalcoholic fatty" OR "livers, nonalcoholic fatty" OR "nonalcoholic fatty liver" OR "nonalcoholic fatty livers" OR "nonalcoholic steatohepatitis" OR "nonalcoholic steatohepatitides" OR "steatohepatitides, nonalcoholic" OR "steatohepatitis,



Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram detailing the study selection process for systematic literature review.

TABLE 1 Characteristics of included trials.

References	Country	Sample size	Target population	Age (years)	Duration	Intervention group	Control group	Outcomes measures	Changes to outcome measures post intervention
Aller et al. (42)	Spain	30	NAFLD	≥18	3 months	Lactobacillus bulgaricus and Streptococcus thermophilus	Starch	BMI/weight/FM/WHR/TC/TG/LDL/HDL/insulin/ HOMA/TNF-α/ALT/AST/GGT	↓ALT/AST/GGT
Sangouni et al. (23)	Iran	90	NAFLD	≥18	12 weeks	Garlic powder	Starch	Hepatic steatosis/weight/BMI/WC/ALT/ASL/GGT/ALP/ TC/TAG/HDL/LDL	↓Hepatic steatosis/ALT/ASL/GGT/TC/HDL/LDL
Pezeshki et al. (30)	Iran	80	NAFLD with obesity	20-50	12 weeks	Green tea extract	Placebo	Weight/BMI/ALT/AST/ALP	↓ALT/AST/ALP
Asgharian et al. (43)	Iran	80	NAFLD	18-60	8 weeks	Probiotic	Starch	Steatosis grade/ALT/AST/CRP/weight/BMI	↓Steatosis grade
Han et al. (31)	Korea	96	NAFLD	≥18	8 weeks	SPB-201	Crystallin cellulose	ALT/AST/blood RT/ALP/glucose/BUN/Cr/UA	↓ALT/AST
Soleimani et al. (garlic) (20)	Iran	110	NAFLD	20-70	15 weeks	Garlic powder	Placebo	Weight/TC/TG/LDL/HDL/FBS/HbA1c/ALT/AST/ hepatic steatosis	↓Hepatic steatosis/weight/TC/TG/LDL/FBS/HbA1c/ ALT/AST
Soleimani et al. (Propolis) (32)	Iran	54	NAFLD	18-60	4 months	Poplar propolis	Placebo	Weight/fat mass/fat free mass/FBS/insulin/HOMA- IR/QUICKI/TC/TG/LDI/HDL/Hs- CRP/albumin/ALP/ALT/AST/GGT/T-Bil/D- Bil/hepatic steatosis	↓Hs-CRP//hepatic steatosis
Scorletti et al. (DHA) (53)	UK	103	NAFLD	≥18	15 months	DHA/EPA	Olive oil	BMI/WC/FBS/MRI subcutaneous fat/MRI visceral fat/HbA1c/TG/TC/LDL/HDL/AST/ALT/liver fat/liver fibrosis score/NAFLD fibrosis score	↑HDL
Scorletti et al. (synbiotics) (44)	UK	104	NAFLD	≥18	10 months	Polymerization	Maltodextrin	Weight/BMI/fat/FBS/HbA1c/TG/TC/LDL/HDL/ AST/ALT/GGT/MRS-measured liver/ELF score	↓NAFLD fibrosis score
Jafarvand et al. (48)	Iran	44	NAFLD	20-65	4 weeks	CoQ10	Placebo	BMI/WC/TG/TC/LDL/HDL/AST/ALT	↓WC/AST
Askari et al. (33)	Iran	50	NAFLD	20-66	12 weeks	Cinnamon	Wheat flour	FBS/QUICKI/HOMA/TC/TG/LDL/HDL/ASL/ALT/ GGT/hs-CRP	↓FBS/HOMA/T/LDL/TG/ASL/ALT/GGT/hs- CRP
Farsi et al. (49)	Iran	42	NAFLD	19–54	12 weeks	CoQ10	Starch	Weight/WC/HC/WHR/BMI/NAFLD/grade/ TNF-α/adiponection/ leptin/hs-CRP/AST/ALT/GGT/AST to ALT ratio	↓hs-CRP/AST/GGT/NAFLD grade/TNF-α/leptin; ↑adiponection
Izadi et al. (34)	Iran	70	NAFLD	20-55	8 weeks	Sour tea powder	Placebo	Weight/BMI/WC/TC/TG/LDL/HDL/AST/ALT	↓TG/ALT/AST/

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TABLE 1 (Continued)

References	Country	Sample size	Target population	Age (years)	Duration	Intervention group	Control group	Outcomes measures	Changes to outcome measures post intervention
Barchetta et al. (54)	Italy	65	NAFLD with DM	25-70	24 weeks	Cholecalciferol	Placebo	Hepatic fat fraction/BMI/WC/ TC/TG/LDL/HDL/FBG/ HbA1c/AST/ALT/r-GT/AST to ALT/FHOMA-IR/QUICKI/adiponectin	No difference
Bae et al. (35)	Korea	78	NAFLD with DM	20-70	12 weeks	Carnitine-orotate complex	Placebo	Weight/BMI/WC/FBS/HbA1c/ HOMA-IR/HOMA-B/AST/ALT/γ- GT/TG/HDL/LDL/CT attenuation	↓ALT/HbA1c/liver attenuation values
Cansanção et al. (52)	Brazil	44	NAFLD	≥18	6 months	n-3 PUFA	Olive oil	ALT/AST/ALP/GGT/FBS/HbA1c/ TG/TC/LDL/HDL/BMI/BMI/WC/WHR/liver fibrosis	↓ALP/liver fibrosis
Hosseinikia et al. (36)	Iran	90	NAFLD	18-65	12 weeks	Quercetin	Placebo	BMI/WHR/ALT/AST/GGT/TNF-α/hs- CRP/TC/TG/HDL/LDL	↓BMI/WHR/TNF-α
Farhangi et al. (50)	Iran	44	NAFLD	20-65	4 weeks	CoQ10	Placebo	FSG/insulin/HOMA-IR/QUICKI/AST/ ALT/vaspin/chemerin/pentraxin	↓AST
Masoumeh et al. (55)	Iran	112	NAFLD	≥18	12 weeks	Whole grain foods	Usual cereals	Grade of fatty liver/ALT/AST/GGT/TG/TC/LDL/ HDL/FBS/HOMA-IR/QUICKI/insulin	↓Grade of fatty/liver/ALT/AST/GGT
Darand et al. (21)	Iran	50	NAFLD	≥18	12 weeks	<i>Nigella sativa</i> seed powder	Starch	Weight/BMI/WC/HC/WHR/ALT/AST/ GGT/hs-CRP/TNF-α/NF-κB/fibrosis grade/steatosis/percentage of steatosis	↓hs-CRP/TNF-α/NF- κb/percentage of steatosis
Mohamad Nor et al. (45)	Malaysia	46	NAFLD	≥18	6 months	Multi-strain probiotics	Placebo	Liver stiffness/AST/ALT/GGT/steatosis score/fibrosis score/BMI/TG/TC/fasting glucose	No difference
Mohammad Shahi et al. (37)	Iran	42	NAFLD	≥18	8 weeks	Phytosterol	Starch	AST/ALT/GGT/AST to ALT ratio/TC/TG/LDL/HDL/LDL to HDL ratio/VLDL/TC to HDL ratio/TNF-α/hs-CRP/adiponectin/leptin	↓AST/ALT/LDL
Rashidmayvan et al. (51)	Iran	44	NAFLD	20-60	8 weeks	NS oil	Paraffin oil	Weight/BMI/WC/WHR/FBS/TG/TC/ HDL/LDL/VLDL/insulin/AST/ALT/GGT/TNF- α/hs-CRP	↓TG/TC/HDL/LDL/VLDL/FBS/AST/ALT/TNF α/hs-CRP; ↑HDL
Zhang et al. (38)	China	74	NAFLD	25-65	12 weeks	Anthocyanin	Maltodextrin	Weight/BMI/WC/HC/WHR/AST/ALTNAFLD fibrosis score/TC/TG/LDL/DL/FBG/insulin/HOMA- IR/OGTT	↓ALT/HOMA-IR/2-h glucose
Chong et al. (47)	UK	42	NAFLD	25-70	10 weeks	VSL#3 [®] probiotic	Placebo	TC/TG/LDL/HDL/HbA1c//HOMA-IR/TAC/hs- CRP/ALT/AST/mode ASQ/NAFLD fibrosis risk score	No difference
Navekar et al. (39)	Iran	46	NAFLD with overweight/obesity	20-60	12 weeks	Turmeric powder	Placebo	FBS/insulin/HOMA-IR/leptin/AST/ALT	↓FBS/insulin/HOMA-IR/leptin

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Changes to outcome measures post

Outcomes measures

Control group

Duration Intervention group

Target population

Ahn et al. (46)	Korea	68	NAFLD with overweight or obesity	19-75	12 weeks	Six bacterial species	Placebo	W eight/BMI/visceral fat/total fat mass/total body fat/visceral fat grade/WHR/CAP/liver stiffness/intra-hepatic fat fraction/TG/TC/glucose/ insulin/AST/ALT/HOMA-I/total muscle mass/skeletal muscle/HDL/LPS/TNF-α	↓Intra-hepatic fat fraction/TG/weight
Cicero et al. (40)	Iran	65	NAFLD	>18	8 weeks	Phospholipidated curcumin	Placebo	W eight/BMI/leptin/adiponectin/ leptin:adiponectin/FBS/TG/TC/LDL/ HDL/AST/ALT	↓leptin/leptin: adiponectin; ↑adiponectin/HDL
Namkhah et al. [1ran (41)	Iran	44	NAFLD with overweight/obesity	20–65 4 weeks	4 weeks	Naringenin	Placebo	NAFLD grades/NFS levels/weight/BMI/WC/AST/ \$\$\UNFLD grades/TG/TC/LDL; \$\$\UNFLD grades/TG/TC/LDL; \$\$\UNFLD from the temperature of the temperature of tempera	↓NAFLD grades/TG/TC/LDL; ↑HDL
NAFLD, non-alcohol waist to height ratio; cholesterol: TG. triac	lic fatty liver dise FBS, fasting blov vlølvceride: ALT	ase; DHA, docc od sugar; HOM. . alanine amino	osahexaenoic acid; EPA, e 1A-IR, homeostasis mod ptransferase: AST, aspart;	eicosapentaer lel assessmen ate aminotra	noic acid; PUFA, <u>F</u> the for insulin resis naferase: GGT, v-	oolyunsaturated fatty acid; stance; QUICKI, quantitati olutamvltransferase: ALP.	SPB-201, powdered-v ive insulin sensitivity alkaline phosphatase	NAFLD, non-alcoholic fatty liver disease; DHA, docosaberatenoic acid; FDA, polyunsaturated fatty acid; SPB-201, powdered-water extract of Artemisia annua; DM, diabetes mellitus; BMI, body mass index; WC, weight circumference; WHR, waist to height ratio; FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; QUICKI, quantitative insulin sensitivity check index; HDL-C, high-density lipoprotein cholesterol; TLD-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triacoblyceride; AIT, alanine aminotrancferase; AST, assartate aminotransferase; AST, schutzmyltransferase; ALP, allaline phosshatase; CRP, C-reactive protein; TNF-a, tumor necrosis factor-a: UK, the United Kindom, I., indicated a decrease in	, body mass index; WC, weight circumference; WHR, LDL-C, low-density lipoprotein cholesterol; TC, total UK, the United Kinedom indicated a decrease in

outcome measures. \uparrow , indicated an increase in outcome measures 3 cholest NAFL vaist

nonalcoholic") AND ("diet" OR "diets" OR "dietary supplements" OR "dietary supplement" OR "supplements, dietary" OR "dietary supplementations" OR "supplementations, dietary" OR "food supplementations" OR "food supplements" OR "food supplement" OR "supplement, food" OR "supplements, food" OR "nutraceuticals" OR "nutraceutical" OR "nutriceuticals" OR "nutriceutical" OR "neutraceuticals" OR "neutraceutical" OR "herbal supplements" OR "herbal supplement" OR "supplement, herbal" OR "supplements, herbal" OR "nutrients" OR "nutrient" OR "macronutrients" OR "macronutrient" OR "micronutrient" OR "micronutrients" OR "functional food" OR "food, functional" OR "foods, functional" OR "functional foods") AND ("randomized controlled trial" [publication type] OR "randomized controlled trial" OR "randomized" OR "placebo").

Literature was managed using a software program (EndNote X8.1, Thomson Reuters, New York, USA), in which the "find duplicates" function was used to eliminate duplicate papers. The studies inconsistent with our eligibility criteria were screened out using the title and abstract. The remaining articles were fully read, and the qualified studies were chosen according to the inclusion and exclusion criteria (Figure 1). All stages of the selection process were repeated by another author, and the differences were solved through group discussion.

2.3. Data extraction and risk of bias assessment

The data from each trial were extracted independently by two authors using a standardized, pre-designed data-extraction form. The data included: (1) study characteristics (first author's name, year of publication, country, and sample size); (2) baseline patient characteristics (targeted population and age); (3) intervention characteristics (type and dose in the intervention and control groups and duration of follow-up); (4) main outcomes (outcome measures and the changes to outcome measures post-intervention). The risk of bias in all studies was assessed using the Cochrane Risk of Bias Tool (RoB2) provided in the Cochrane Handbook for Systematic Reviews of Interventions (26). The tool contains seven domains, including method of sequence generation, concealment, blinding, blinded outcome, incomplete outcome data, selective outcome reporting, and other biases. All these domains were respectively classified as low risk, high risk, and unclear risk of bias according to the guideline in the Cochrane Handbook. The trial was considered to have "good" quality if it was low-risk for at least three items, "fair" if it was low-risk for two items, and "weak" if it was low-risk for less than two items (27, 28). The quality assessment was separately done by two authors. There was little disagreement between them.

2.4. Outcome measures

The primary outcomes were liver-related measures, such as transaminase values (AST and/or ALT), and hepatic fibrosis and steatosis. Secondary outcomes included anthropometric measurements [such as body mass index (BMI) and waist circumference (WC)] and lipid analyses [triacylglyceride (TG),

[TABLE 1 (Continued)

<u>Ref</u>erences

total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)].

2.5. Statistical analysis

The mean differences (MD) and 95% confidence interval (CI) between intervention and placebo groups at baseline and postintervention were used for each parameter in this review and metaanalysis. I^2 value was used to evaluate heterogeneity. When the I^2 value was <50%, the fixed-effects model was used; otherwise, the random-effects model was adopted. We used a narrative synthesis when the data were too heterogeneous to be aggregated or when there were only a few articles on intervention measures (29). The publication bias was evaluated using Begg's rank correlation test and Egger's regression asymmetry test. Sensitivity analysis was carried out to define whether the overall effect depended on any particular study. The statistical significance was assessed at $\alpha = 0.05$. All statistical analyses were carried out using Review Manager 5.4 and Stata 12.0.

3. Results

3.1. Study selection

The study selection process is summarized in Figure 1. We selected 2,120 articles through keywords and six articles through references, from which 617 duplicate and 37 ongoing studies were removed. Next, we excluded 1,350 studies after screening the title and abstract. A total of 122 studies were considered eligible and needed a full-text review. Finally, 93 articles were excluded after reading the full text because of the following reasons: non-RCTs; full text not in English; did not measure pre-set outcomes (AST/ALT/hepatic fibrosis and steatosis); abstracts and conference proceedings; and combined with lifestyle interventions (physical exercise and/or weight loss diet). Finally, 29 articles were included in this review and meta-analysis.

3.2. Study characteristics

The characteristics of included studies are summarized in Table 1. Fifteen trials (20, 21, 23, 30-41) evaluated phytonutrients; six trials (42-47) evaluated probiotic/symbiotic/prebiotic; three trials (48-50) evaluated coenzyme Q10; three trials (51-53) evaluated fatty acids; and one trial (54, 55) evaluated vitamin D and whole grain separately in the management of NAFLD. The duration of the intervention varied from 4 weeks to 18 months. The patients were all adults, and the studies were from different countries, including Iran, Korea, Brazil, North America, the United Kingdom, Italy, Malaysia, and China. Among the 29 included studies, 23 (79.31%) articles studied patients with NAFLD only, 2 (6.90%) articles studied NAFLD patients with diabetes, and 4 (13.79%) articles were on overweight/obese patients with NAFLD. The study design of all included RCTs was parallel (Table 1).

3.3. Risk of bias in studies

Out of all the studies, 21 trials (20, 21, 23, 30, 32-36, 38-41, 43, 45-47, 50, 52, 54, 55) had "good" quality, while five trials (42, 44, 48, 51, 53) were "fair". Additionally, the remaining three trials (31, 37, 49) were "weak". Figures 2, 3 show the results of each source of bias.

3.4. Effect of functional foods and dietary supplements on anthropometric parameters

The effect of functional foods and dietary supplements on BMI was examined in 22 clinical trials. It was seen that 13 out of 22 trials (21, 23, 30, 33-36, 38-41, 48, 50) were about antioxidants (phytonutrients and coenzyme Q10), five (42-46)on probiotic/symbiotic/prebiotic, three (51-53) on fatty acids, and one (54) on vitamin D. The meta-analysis showed no significant effect of antioxidants on BMI compared to the placebo (MD: 0.01 kg/m²; 95% CI: -0.07, 0.08, P > 0.05) (Figure 4A). There was no heterogeneity in these included studies ($I^2 = 29.0\%$, P = 0.16). As shown in Figure 4B, BMI significantly decreased (MD: -0.57 kg/m²; 95%



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



CI: -0.72, -0.42, P < 0.05) after taking probiotic, symbiotic, and prebiotic in NAFLD patients, with no heterogeneity across studies ($I^2 = 0\%$, P = 0.82). Sensitivity analysis showed that the overall

effect did not depend on any single study (Appendix S1 in the Supplementary material 1).

The proportion and type of fatty acids varied between the three studies; oil composition contained docosahexaenoic acid (DHA)/eicosapentaenoic acid (EPA)/linoleic acid/oleic acid and linolenic acid. Three studies used different oils as a placebo. All three studies showed that BMI did not change significantly in NAFLD patients after using fatty acids (51–53). Barchetta et al. (54) reported that BMI did not change after taking vitamin D and placebo.

Nine studies (21, 23, 33–35, 38, 41, 48, 50) reported the effect of supplements on WC. Our meta-analysis reported that WC declined significantly in nine antioxidant trials compared to the control group (MD: -1.28 cm; 95% CI: -1.58, -0.99, P < 0.05). The effect was homogeneous across the included trials ($I^2 = 37\%$, P = 0.12) (Figure 4C). The effects of probiotic/symbiotic/prebiotic on WC have not been reported. Sensitivity analysis showed that the exclusion of any trials did not affect the results (Appendix S2 in the Supplementary material 1). Four studies (51–54) noted no changes in the WC after taking fatty acid (three trials) and vitamin D (one trial).

No publication bias was found for BMI (Begg's test P = 0.82; Egger's test P = 0.600) and WC (Begg's test P = 0.348; Egger's test P = 0.829).

3.5. Effect of functional foods and dietary supplements on the liver function

Twenty-nine datasets evaluated the effect of functional foods and dietary supplements on ALT. Eighteen out of 29 trials were about antioxidants (phytonutrients and coenzyme Q10), six (42–47) on probiotic/symbiotic/prebiotic, three (51–53) on fatty acids, one (55) on whole grain, and one (54) on vitamin D.

There was a statistical significance in the mean difference of ALT levels in the antioxidant-supplemented group compared to the control group (MD: -7.65 IU/L; 95% CI: -11.14, -4.16, *P* < 0.0001). There was high heterogeneity across studies ($I^2 = 91\%$, P < 0.00001). Subgroup analysis based on the type of antioxidants (phytonutrients or coenzyme Q10) was performed using data from 18 studies. There was statistically significant difference in ALT reductions between phytonutrients group and control group (MD: -9.5 IU/L; 95% CI: -14.12, -4.89, P < 0.0001), but high heterogeneity of these studies still existed ($I^2 = 92\%$, P < 0.00001). Heterogeneity was attenuated among those studies taking coenzyme Q10 ($I^2 = 54\%$, P = 0.11) (Figure 5A), but the ALT reductions had no difference. The intake of probiotic, symbiotic, and prebiotic supplements led to a more significant decrease in ALT compared with control (MD: -3.96 IU/L; 95% CI: -5.24, -2.69, P < 0.001), with no heterogeneity across studies ($I^2 = 0\%$, P = 0.65) (Figure 5B). Sensitivity analysis indicated that no trial changed the pooled effect size (Appendix S3 in the Supplementary material 1). Publication bias were seen for ALT (Begg's test P = 0.722; Egger's test P = 0.016).

The effect of functional foods and dietary supplements on AST levels was examined in 29 clinical trials. The literature distribution on AST was consistent with that on ALT. Our meta-analysis revealed a significant reduction in AST levels after taking antioxidant supplements (MD: -4.26 IU/L; 95% CI: -5.76, -2.76, P < 0.00001), with substantial heterogeneity ($I^2 = 92\%$, P < 0.00001). Studies of phytonutrients or coenzyme Q10 were subgroup analyzed. The AST



reductions were significantly different between the phytonutrients group and control group (MD: -4.79 IU/L; 95% CI: -6.49, -3.08, P < 0.00001), with high heterogeneity among those studies ($I^2 = 93\%$, P < 0.00001). Meanwhile, the AST reductions had significant difference in studies taking coenzyme Q10 (MD: -1.82 IU/L; 95% CI: -3.15, -0.48, P = 0.008), with no heterogeneity ($I^2 = 0\%$, P = 0.57) (Figure 5C). The AST levels after taking probiotic, symbiotic, and prebiotic showed a decrease in the antioxidant-supplemented group compared to the control group (MD: -2.76; 95% CI, -3.97, -1.56, P < 0.0001), with no heterogeneity across

studies ($I^2 = 0\%$, P = 0.46) (Figure 5D). Sensitivity analysis revealed that no specific study affected pooled effects (Appendix S4 in the Supplementary material 1). publication bias was seen for AST levels (Begg's test P = 0.985; Egger's test P = 0.000).

In three trials (51–53) on fatty acids, Rashidmayvan et al. (51) reported that *Nigella sativa* oil containing linoleic acid, oleic acid, and linolenic acid reduced ALT and AST levels, whereas Cansanção et al. (52) and Scorletti et al. (53) found that supplements containing DHA and EPA did not affect ALT and AST levels. Barchetta et al. (54) did not observe any discrepancy in AST and ALT levels between

A		ntion gro			rol grou			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% Cl
1.1.1 phytonutrients	10	11.01	45	0.0	10.01	40	5.004	0.501.45.05 4.051	
Abbas Ali Sangouni 2020	-4.9	14.61	45	3.6	16.61	43	5.9%	-8.50 [-15.05, -1.95]	
Ali Pezeshki2016	-13.21 -15.97	21.04 18.82	35 38	-5.74 -7.41	23.4 15.9	36 41	4.5% 5.5%	-7.47 [-17.81, 2.87]	
Byoungduck Han2020 Davood Soleimani(Garlic)2020	-10.5	13.5	47	0.25	15.9	51	5.5% 6.3%	-8.56 [-16.27, -0.85]	
Davood Soleimani(Ganic)2020 Davood Soleimani(propolis)2020	-3.57	9.2	24	-3.67	9.2	25	6.4%	-10.75 [-16.43, -5.07] 0.10 [-5.05, 5.25]	+
Faezeh Askari2014	-26.6	9.91	23	-1.5	11.35	22		-25.10 [-31.34, -18.86]	-
Fatemeh Izadi2020	-4.63	16.55	30		21.72	31	4.8%	-5.83 [-15.50, 3.84]	
Ji Cheol Bae2015	-73.7	38.7	39	-5.38	37.1	39		-68.32 [-85.15, -51.49]	
Mahboobe Hosseinikia 2020	-3	18.87	39	-0.00	20.85	39	5.1%	-4.00 [-12.83, 4.83]	
Mina Darand2019	-1.68	14.13	22	-1.4	8.28	21	5.8%	-0.28 [-7.17, 6.61]	+
Mohammad Ali Javanmardi2018	-18.63	9.62		-14.58	10.64	19	6.0%	-4.05 [-10.50, 2.40]	
Pei-Wen Zhang2015	-8	6.74	34	-1	6.31	29	7.0%	-7.00 [-10.23, -3.77]	+
Rova Navekar2017	-16.6	22.45		-16.66	24.97	21	3.3%	0.06 [-14.30, 14.42]	
Seyed Reza Mirhafez2019	-16.26	9.56	32	-0.95	12.86	29	6.2%	-15.31 [-21.04, -9.58]	-
Zahra Namkhah2021	-1	1.75	22	-0.5	1.25	22	7.5%	-0.50 [-1.40, 0.40]	
Subtotal (95% CI)			470			468	83.1%	-9.50 [-14.12, -4.89]	♦
Heterogeneity: $Tau^2 = 67.32$; $Chi^2 = 17$ Test for overall effect: $Z = 4.03$ (P < 0.0		14 (P < 0	.00001	; ² = 92	2%				
1.1.2 Coenzyme Q10									
Elnaz Jafarvand 2015	0	23.4	20	-37	10.54	21	4.2%	3.70 [-7.50, 14.90]	+
Farnaz Farsi2015	-6.95	11.98	20		14.43	21	4.2%	-6.80 [-14.90, 1.30]	
Mahdieh Abbasalizad Farhangi2014	-4.25	3.08	20	-6.14	2.63	21	7.4%	1.89 [0.13, 3.65]	-
Subtotal (95% CI)	-4.25	0.00	60	-0.14	2.03	63	16.9%	-0.10 [-5.73, 5.53]	•
Heterogeneity: Tau ² = 13.99; Chi ² = 4.3 Test for overall effect: Z = 0.03 (P = 0.9		(P = 0.11)		1%					
									A
Total (95% CI)			530			531	100.0%	-7.65 [-11.14, -4.16]	r
Heterogeneity: Tau ² = 42.25; Chi ² = 19 Test for overall effect: Z = 4.30 (P < 0.0 Test for subaroup differences: Chi ² = 6	0001)				1%				-100 -50 0 50 100 intervention group control group
В									
5	interv	ention gr	roup	con	trol gro	up		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total				Weight	IV. Fixed, 95% CI	IV, Fixed, 95% CI
ALLER, D.A2011	-7.3	28.13	14		33.93	14	-	-11.40 [-34.49, 11.69]	
Atefe Asgharian2016	3.13	3.29	38	7.17		36	96.8%	-4.04 [-5.34, -2.74]	
Eleonora Scorletti2020	-2		45	-6.32		44	0.8%	4.32 [-9.89, 18.53]	
Mohamad Hizami Mohamad Nor2021	14		17	1.13		22	0.2%	12.87 [-13.35, 39.09]	
Pui Lin Chong2021	-5	31.51	19	-2		16	0.5%	-3.00 [-21.20, 15.20]	
Sang BongAhn2019	-2.3	24.73	30	2.8	19.17	35	1.4%	-5.10 [-15.99, 5.79]	
-									
Total (95% CI)			163			167	100.0%	-3.96 [-5.24, -2.69]	•
Heterogeneity: Chi ² = 3.35, df = 5 (P = Test for overall effect: Z = 6.08 (P < 0.0		0%							-50 -25 0 25 50 intervention group control group
						10			
c	interve	ntion are	aur	cont					Mean Difference
		ention gro SD			rol grou SD		Weight	Mean Difference IV. Random, 95% CI	Mean Difference IV. Random, 95% Cl
Study or Subgroup	interve Mean		oup Total				Weight	Mean Difference IV. Random. 95% CI	
Study or Subgroup 1.2.1 phytonutrients	Mean	SD	Total	Mean	SD	Total		IV. Random. 95% CI	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020	Mean -2.2	SD 10.09	Total 45	Mean 1.9	SD 8.55	Total 43	6.5%	IV. Random, 95% CI -4.10 [-8.00, -0.20]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016	Mean -2.2 -7.25	SD 10.09 11.76	<u>Total</u> 45 35	Mean 1.9 -3.07	8.55 13.07	Total 43 36	6.5% 4.3%	IV, Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020	Mean -2.2 -7.25 -0.21	SD 10.09 11.76 0.22	Total 45 35 38	1.9 -3.07 -0.13	8.55 13.07 0.26	Total 43 36 41	6.5% 4.3% 11.7%	IV. Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020	Mean -2.2 -7.25 -0.21 -5.59	SD 10.09 11.76 0.22 10.7	Total 45 35 38 47	1.9 -3.07 -0.13 1.4	8.55 13.07 0.26 8.6	Total 43 36 41 51	6.5% 4.3% 11.7% 6.6%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Gartic)2020 Davood Soleimani(propolis)2020	Mean -2.2 -7.25 -0.21 -5.59 -2.77	SD 10.09 11.76 0.22 10.7 6.97	Total 45 35 38 47 24	1.9 -3.07 -0.13 1.4 -2.39	8.55 13.07 0.26 8.6 6.97	Total 43 36 41 51 25	6.5% 4.3% 11.7% 6.6% 6.5%	-4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Faezeh Askari2014	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5	SD 10.09 11.76 0.22 10.7 6.97 16.58	Total 45 35 38 47 24 23	1.9 -3.07 -0.13 1.4 -2.39 -2.1	SD 8.55 13.07 0.26 8.6 6.97 19.83	Total 43 36 41 51 25 22	6.5% 4.3% 11.7% 6.6% 6.5% 1.7%	V, Random, 95% Cl -4,10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Gropolis)2020 Faezeh Askari2014 Fatemeh Izadi2020	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06	Total 45 35 38 47 24 23 30	1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3	SD 8.55 13.07 0.26 8.6 6.97 19.83 7.39	43 36 41 51 25 22 31	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7%	IV, Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9	Total 45 35 38 47 24 23 30 39	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72	SD 8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1	Total 43 36 41 51 25 22 31 39	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4%	V, Random, 95% Cl -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68	Total 45 35 38 47 24 23 30 39 39	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47	Total 43 36 41 51 25 22 31 39 39	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Grafic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49	Total 45 35 38 47 24 23 30 39 39 22	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05	SD 8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65	Total 43 36 41 51 25 22 31 39 39 21	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5%	IV, Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Grafic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93	Total 45 35 38 47 24 23 30 39 39 22 19	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03	Total 43 36 41 51 25 22 31 39 39 21 19	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1%	V, Random, 95% Cl -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88	Total 45 35 38 47 24 23 30 39 39 22 19 34	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82	Total 43 36 41 51 25 22 31 39 21 19 29	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1% 10.6%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Grapolis)2020 Faezh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51	Total 45 35 38 47 24 23 30 39 39 22 19 34 21	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0 -0.29	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94	Total 43 36 41 51 25 22 31 39 39 21 19 29 21	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1% 10.6% 3.4%	V, Random, 95% Cl -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Grafic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14 -12.68	SD 10.09 11.76 0.22 10.7 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0 -0.29 -0.42	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76	Total 43 36 41 51 25 22 31 39 39 21 19 29 21 29	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 4.5% 3.1% 10.6% 3.4% 4.2%	IV, Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32 22	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0 -0.29	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94	Total 43 36 41 51 25 22 31 39 39 21 19 29 21 29 22	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1% 10.6%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39] 0.25 [-0.27, 0.77]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 196	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14 -12.68 -1.25 3.30, df =	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34 0.75	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32 22 470	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0 -0.29 -0.42 -1.5	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1	Total 43 36 41 51 25 22 31 39 39 21 19 29 21 29	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 4.5% 3.1% 10.6% 3.4% 4.2%	IV, Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Grafic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14 -12.68 -1.25 3.30, df =	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34 0.75	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32 22 470	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0 -0.29 -0.42 -1.5	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1	Total 43 36 41 51 25 22 31 39 39 21 19 29 21 29 22	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1% 10.6%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39] 0.25 [-0.27, 0.77]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 196	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14 -12.68 -1.25 3.30, df =	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34 0.75	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32 22 470	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 0 -0.29 -0.42 -1.5	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1	Total 43 36 41 51 25 22 31 39 39 21 19 29 21 29 22	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1% 10.6%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39] 0.25 [-0.27, 0.77]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Garlic)2020 Faezh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (65% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 198 Test for overall effect: Z = 5.50 (P < 0.	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14 -12.68 -1.25 3.30, df =	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34 0.75	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32 22 470	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 -1.5 ² = 93	8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1	Total 43 36 41 51 25 22 31 39 39 21 19 29 21 29 22	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.4% 1.3% 4.5% 3.1% 10.6%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -6.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39] 0.25 [-0.27, 0.77]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 1987 Test for overall effect: Z = 5.50 (P < 0.12)	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.77 -31.5 -5.7 -0.8 -44.0.8 -1.55 0.14 -12.68 -1.25 3.30, df = 000001)	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34 0.75 14 (P < 0.	Total 45 35 38 47 24 23 30 39 39 22 19 34 21 32 22 470 000001)	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 -1.5 ² = 93	SD 8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1 %	Total 43 36 41 51 25 22 31 39 21 29 21 29 22 468	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 1.4% 1.3% 4.7% 3.1% 3.1% 3.4% 4.2% 10.6% 3.4% 82.1%	IV, Random, 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39] 0.25 [-0.27, 0.77] -4.79 [-6.49, -3.08]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 1987 Test for overall effect: Z = 5.50 (P < 0.12) 1.2.2 Coenzyme Q10 Einaz Jafarvand 2015 Farnaz Farsi2015 Mahdieh Abbasalizad Farhangi2014	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -4.8.15 -1.5 0.14 -12.68 -1.25 3.30, df = - 00001)	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 11.93 2.88 10.51 10.34 0.75 14 (P < 0. 11.53	Total 45 35 38 47 24 23 30 39 39 22 19 34 470 000001)	Mean 1.9 -3.07 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2.7 -1.05 -9.42 0 -0.29 -0.42 -1.5 ² = 93 -2.7	SD 8.55 13.07 0.26 8.6 6.97 19.83 7.39 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1 %	Total 43 36 41 51 25 31 39 39 21 29 22 468 21 21 21 21 21 21 21 21 21 21 21 21 21 21	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.3% 3.1% 10.6% 82.1% 2.9% 4.3% 10.6%	IV, Random, 95% Cl -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] -1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -2.26 [-18.13, -6.39] 0.25 [-0.27, 0.77] -4.79 [-6.49, -3.08] -1.70 [-9.35, 5.95] -4.85 [-10.59, 0.89] -1.64 [-3.04, -0.24]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 198 Test for overall effect: Z = 5.50 (P < 0. 1.2.2 Coenzyme Q10 Einaz Jafarvand 2015 Famaz Farsi2015 Mahdieh Abbasalizad Farhangi2014 Subtotal (95% CI)	Mean -2.2 -7.25 -0.21 -5.59 -31.5 -5.7 -26.1 -4 0.8 -48.15 -1.5 0.14 -12.68 -1.25 3.30, df = 1 000001) -4.4 -5.47 -4.4	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 27.68 10.34 0.75 14 (P < 0.	Total 45 35 38 47 24 23 30 39 39 39 39 39 32 19 34 21 32 470 000001) 20 20 20 20 60	Mean 1.9 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 -1.5 ² = 933 -2.7 -0.62 -2.76	SD 8.55 13.07 0.26 8.6 6.97 19.83 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1 %	Total 43 36 41 51 25 22 31 39 92 21 29 21 29 21 29 2468	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 1.4% 1.3% 4.7% 1.4% 3.1% 10.6% 3.4% 11.6% 82.1%	IV. Random. 95% CI -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] 1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -12.26 [-18.13, -6.39] 0.25 [-0.27, 0.77] -4.79 [-6.49, -3.08] -1.70 [-9.35, 5.95] -4.85 [-10.59, 0.89]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 198 Test for overall effect: Z = 5.50 (P < 0. 1.2.2 Coenzyme Q10 Einaz Jafarvand 2015 Famaz Farsi2015 Mahdieh Abbasalizad Farhangi2014 Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Chi ² = 1.1	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 0.14 -12.68 -1.25 3.30, df = - 000001) -4.4 -5.47 -4.4 3, df = 2 (I	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 27.68 10.34 0.75 14 (P < 0.	Total 45 35 38 47 24 23 30 39 39 39 39 39 32 19 34 21 32 470 000001) 20 20 20 20 60	Mean 1.9 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 -1.5 ² = 933 -2.7 -0.62 -2.76	SD 8.55 13.07 0.26 8.6 6.97 19.83 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1 %	Total 43 36 41 51 25 31 39 39 21 29 22 468 21 21 21 21 21 21 21 21 21 21 21 21 21 21	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.3% 3.1% 10.6% 82.1% 2.9% 4.3% 10.6%	IV, Random, 95% Cl -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] -1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -2.26 [-18.13, -6.39] 0.25 [-0.27, 0.77] -4.79 [-6.49, -3.08] -1.70 [-9.35, 5.95] -4.85 [-10.59, 0.89] -1.64 [-3.04, -0.24]	
Study or Subgroup 1.2.1 phytonutrients Abbas Ali Sangouni 2020 Ali Pezeshki2016 Byoungduck Han2020 Davood Soleimani(Garlic)2020 Faezeh Askari2014 Fatemeh Izadi2020 Ji Cheol Bae2015 Mahboobe Hosseinikia 2020 Mina Darand2019 Mohammad Ali Javanmardi2018 Pei-Wen Zhang2015 Roya Navekar2017 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Subtotal (95% CI) Heterogeneity: Tau ² = 5.49; Chi ² = 198 Test for overall effect: Z = 5.50 (P < 0.12) 1.2.2 Coenzyme Q10 Elnaz Jafarvand 2015 Farmaz Farsi2015 Mahdieh Abbasalizad Farhangi2014 Subtotal (95% CI)	Mean -2.2 -7.25 -0.21 -5.59 -2.77 -31.5 -5.7 -26.1 -4 0.8 -48.15 0.14 -12.68 -1.25 3.30, df = - 000001) -4.4 -5.47 -4.4 3, df = 2 (I	SD 10.09 11.76 0.22 10.7 6.97 16.58 13.06 22.9 27.68 12.49 27.68 10.34 0.75 14 (P < 0.	Total 45 35 38 47 24 23 30 39 39 39 39 39 32 19 34 21 32 470 000001) 20 20 20 20 60	Mean 1.9 -0.13 1.4 -2.39 -2.1 -0.3 -0.72 -2 -1.05 -9.42 -1.5 ² = 933 -2.7 -0.62 -2.76	SD 8.55 13.07 0.26 8.6 6.97 19.83 30.1 29.47 4.65 11.03 2.82 11.94 12.76 1 %	Total 43 36 41 51 25 31 39 39 21 29 22 468 21 21 21 21 21 21 21 21 21 21 21 21 21 21	6.5% 4.3% 11.7% 6.6% 6.5% 1.7% 4.7% 1.3% 3.1% 10.6% 82.1% 2.9% 4.3% 10.6%	IV, Random, 95% Cl -4.10 [-8.00, -0.20] -4.18 [-9.96, 1.60] -0.08 [-0.19, 0.03] -0.99 [-10.85, -3.13] -0.38 [-4.28, 3.52] -29.40 [-40.10, -18.70] -5.40 [-10.75, -0.05] -25.38 [-37.25, -13.51] -2.00 [-14.69, 10.69] -1.85 [-3.74, 7.44] -38.73 [-46.04, -31.42] -1.50 [-2.91, -0.09] 0.43 [-6.37, 7.23] -2.26 [-18.13, -6.39] 0.25 [-0.27, 0.77] -4.79 [-6.49, -3.08] -1.70 [-9.35, 5.95] -4.85 [-10.59, 0.89] -1.64 [-3.04, -0.24]	

 Total (95% CI)
 530

 Heterogeneity: Tau² = 5.01; Chi² = 205.73, df = 17 (P < 0.00001); I² = 92%

 Test for overall effect: Z = 5.56 (P < 0.00001)</td>

 Test for subarouo differences: Chi² = 7.22, df = 1 (P = 0.007). I² = 86.2%

FIGURE 5 Continued 50

531 100.0%

-4.26 [-5.76, -2.76]

-50

٠

-25 0 25 intervention group control group

	interve	ention gr	oup	cont	trol gro	up		Mean Difference	Mean Difference
itudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
LLER, D.A2011	-5.7	13.68	14	4.7	13.46	14	1.4%	-10.40 [-20.45, -0.35]	
tefe Asgharian2016	-1.02	3.47	38	1.78	1.78	36	92.9%	-2.80 [-4.05, -1.55]	
leonora Scorletti2020	0	17.43	45	0.3	27.04	44	1.6%	-0.30 [-9.77, 9.17]	
Nohamad Hizami Mohamad Nor2021	2	17.31	17	-3.4	17.09	22	1.2%	5.40 [-5.50, 16.30]	
ui Lin Chong2021	-2	18.33	19	1	16.09	16	1.1%	-3.00 [-14.41, 8.41]	
ang BongAhn2019	-1.9	20.58	30	0.5	16.68	35	1.7%	-2.40 [-11.61, 6.81]	
otal (95% CI)			163			167	100.0%	-2.76 [-3.97, -1.56]	•
leterogeneity: $Chi^2 = 4.64$, df = 5 (P = fest for overall effect: Z = 4.51 (P < 0.1		0%							-50 -25 0 25 50 intervention group control group
RE 5									

the vitamin D and control groups. Masoumeh et al. (55) found that ALT and AST levels decreased significantly after taking whole grain compared to the control group. The outcome indicators of hepatic fibrosis and steatosis were too few to be described.

3.6. Effect of functional foods and dietary supplements on lipid profiles

Eighteen trials (20, 23, 32–36, 38, 40–42, 44–48, 51, 53–55) assessed the effect of functional foods and dietary supplements on TG. The quantitative analysis of TG values indicated no significant reduction in TG after antioxidant supplementation [11 trials (20, 23, 32–36, 38, 40, 44, 48)] (MD: -0.13 mg/dL; 95% CI: -0.32, 0.07, P > 0.05) with high heterogeneity ($I^2 = 75\%$, P < 0.05) (Figure 6A). We were not able to perform a subgroup analysis to assess the source of heterogeneity as the number of papers on coenzyme Q10 subgroup was small. Our meta-analysis of five trials (43–47) involving probiotic, symbiotic, and prebiotic intake illustrated that these supplements had an unnoticeable effect on TG reduction (MD: -0.14 mg/dL; 95% CI: -0.42, 0.13, P > 0.05), with no heterogeneity ($I^2 = 0\%$, P > 0.05) (Figure 6B). Sensitivity analysis showed that the results did not depend on any single study (Appendix S5 in the Supplementary material 1).

Consistently, nine datasets (30, 32–35, 39, 41, 42, 49) indicated no significant reduction in TC levels after taking antioxidant supplements compared to the control group (MD: -0.27 mg/dL; 95% CI: -0.58, 0.04, P > 0.05) (Figure 6C), with no heterogeneity ($I^2 =$ 18%, P > 0.05). Five datasets (43–47) on probiotic, symbiotic, and prebiotic supplements reported no significant decrease in TC levels after intervention (MD: 0.12 mg/dL; 95% CI: -0.18, 0.42, P > 0.05) (Figure 6D), with no heterogeneity ($I^2 = 0\%$, P > 0.05). The results of the sensitivity analysis showed that excluding either study from the analysis did not change the overall effect (Appendix S6 in the Supplementary material 1).

The pooled effect size of 10 trials (30, 32–36, 39, 41, 42, 49) reported a significant impact of the antioxidant supplements on HDL-C (MD: 0.09 mg/dL; 95% CI: 0.01, 0.17, P < 0.05) and LDL-C (MD: -0.24 mg/dL; 95% CI: -0.46, -0.02, P < 0.05), with no heterogeneity ($I^2 = 0\%$, P > 0.05; $I^2 = 1\%$, P > 0.05, respectively) (Figures 6E, G). Three trials (43–45) reported no significant effect of probiotic, symbiotic, and prebiotic supplementation on HDL-C (MD: 0.01 mg/dL; 95% CI: -0.09, 0.11, P > 0.05) and LDL-C (MD:

-0.18 mg/dL; 95% CI: -0.5, 0.14, P > 0.05), with no heterogeneity ($I^2 = 0\%$, P > 0.05 for both) (Figures 6F, H). We performed a sensitivity analysis and found that excluding a particular study from the analysis did not change the overall effect on HDL-C and LDL-C (Appendices S7, S8 in the Supplementary material 1).

Four trials (52–55) reported no difference in TG, TC, HDL-C, and LDL-C levels of DHA/EPA, vitamin D, or whole grainarms of the trial. Rashidmayvan et al. (51) reported that *Nigella sativa* oil decreased TG, TC, HDL-C, and LDL-C levels with significant differences between the NS seed and placebo groups.

No evidence of publication bias was seen for TG (Begg's test P = 0.753; Egger's test P = 0.120), TC (Begg's test P = 0.488; Egger's test P = 0.424), LDL-C (Begg's test P = 0.913; Egger's test P = 0.0.138), and HDL-C (Begg's test P = 0.743; Egger's test P = 0.084).

4. Discussion

NAFLD is considered a metabolic disorder that is closely related to lifestyle. The number of studies about the relationship between diet, nutrition, food, and NAFLD has increased in recent years (56), but there have been no recommendations in the guidelines in terms of this relationship. This systematic review and meta-analysis summarized the adjuvant therapy effects of various nutritional interventions on NAFLD, including antioxidants, probiotic/symbiotic/prebiotic, fatty acid supplements, vitamin D, and whole grain, providing guidance for clinical application.

A total of 1,907 patients from 29 trials were included in this review. Eighteen trials assessed the impact of antioxidants on NAFLD. The mechanism may be related to their antioxidant activity and the ability to scavenge free radicals, such as inhibiting the early formation of lipid peroxides in the liver, blocking the transmission process of free radicals by interrupting the chain reaction, or indirectly scavenging free radicals by acting on enzymes related to free radicals (57, 58). For humans, it can reduce liver inflammation, decrease oxidative stress, inhibit lipid oxidation in serum, and finally reduce serum aminotransferase and improve serum lipids (24). This meta-analysis found that the antioxidants significantly reduced WC, ALT, AST, and LDL-C and increased HDL-C in NAFLD patients but did not change the BMI, TC, and TG levels. This meta-analysis found that the antioxidants significantly reduced WC, ALT, AST, and LDL-C and increased HDL-C in NAFLD patients but did not change the BMI, TC, and TG levels. The positive results were consistent

	interventio			trol group			Mean Difference	Mean Difference
tudy or Subgroup	Mean	SD Total	Mean	SD 1	Total V	Neight	IV, Fixed, 95% C	I IV. Fixed. 95% CI
6.1 phytonutrients						00 51		1
bbas Ali Sangouni 2020	-0.4 0.818		0.1	0.9		29.5%	-0.50 [-0.86, -0.14]	
avood Soleimani(Garlic)2020		36.1 47	-1.8	40.4	51	0.0%	-17.50 [-32.65, -2.35]	
avood Soleimani(propolis)2020		0.44 24	-22.24	50.44	25	0.0%	-7.10 [-35.35, 21.15]	
ezeh Askari2014	-0.5 77.72 -0.22 68.82			81.25202 57.08345	22 31	0.0% 0.0%	-0.47 [-46.96, 46.02]	
atemeh Izadi2020 Cheol Bae2015		20/1 30	0.05	84.3	39	0.0%	-0.17 [-31.95, 31.61] -0.03 [-74.06, 74.00]	
ahboobe Hosseinikia 2020	-0.38 37.65			38.42541	19	0.0%	-0.35 [-24.54, 23.84]	
ei-Wen Zhang2015	-0.17 0.452			0.484984		70.4%	0.04 [-0.19, 0.27]	_
eyed Reza Mirhafez2019		41.6 32	0.02	38.97	29	0.0%	-0.02 [-20.24, 20.20]	_ _ _
ahra Namkhah2021		59.7 22	39.8	55.9	22		92.50 [-126.68, -58.32]	
ubtotal (95% CI)		315				100.0%	-0.13 [-0.32, 0.07]	
eterogeneity: $Chi^2 = 39.45$, df = 9 (est for overall effect: Z = 1.26 (P =	Contraction of the second second	l² = 77%						
6.2 Coenzyme Q10								
Inaz Jafarvand 2015	-0.19 58.30	0926 20	-0.18	54.00444	21	0.0%	-0.01 [-34.46, 34.44]	
ubtotal (95% CI)		20			21	0.0%	-0.01 [-34.46, 34.44]	\bullet
eterogeneity: Not applicable est for overall effect: Z = 0.00 (P =	1.00)							
otal (95% CI)		335			331 1	100.0%	-0.13 [-0.32, 0.07]	
eterogeneity: Chi ² = 39.45, df = 10		l ² = 75%						-100 -50 0 50 100
est for overall effect: Z = 1.26 (P =	,							intervention group control group
est for subaroup differences: Chi ² =	= 0.00. df = 1 ((P = 0.99). I ² =	0%					
	8.0			5 8			100 100m	
Study or Subarous		vention group	tal M	control gro			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD T				al Weigh		
ALLER, D.A2011		83.69845		14 50.2764			6 -0.37 [-51.51, 50.77]	
Eleonora Scorletti2020 Mohamad Hizami Mohamad Nor202		1.153256 0.68	45 17 -0.	0 0.7211 07 0.7		4 48.9% 2 37.3%		
Pui Lin Chong2021	0.02	0.86885		28 1.30610		6 13.8%		
Sang BongAhn2019		99.78493	30 0.			13.87 15 0.0%	2. A set of the set	
Song Song in Eoro	-0.42	00.10400	. v.					
Total (95% CI)			125			1 100.0%		
Heterogeneity: Chi ² = 0.41, df = 4 (F			125					-50 -25 0 25 50
			125					
Heterogeneity: Chi ² = 0.41, df = 4 (F	: 0.31)			ntrol group	13			-50 -25 0 25 50
Heterogeneity: Chi ² = 0.41, df = 4 (F Fest for overall effect: Z = 1.02 (P =	: 0.31)	0% tion group			13		6 -0.14 [-0.42, 0.13]	-50 -25 0 25 50 intervention group control group
Heterogeneity: Chi ² = 0.41, df = 4 (F Fest for overall effect: Z = 1.02 (P =	0.31) intervent	0% tion group	co Mean		13	1 100.09	6 -0.14 [-0.42, 0.13] Mean Difference	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (F Test for overall effect: Z = 1.02 (P = <u>Study or Subgroup</u> Abbas Ali Sangouni 2020	intervent Mean	0% tion group <u>SD Tota</u> l	co <u>Mean</u> 0	SD	13 D Total	1 100.0%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed. 95% CI 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (F Fest for overall effect: Z = 1.02 (P = Study or Subgroup Nobas Ali Sangouni 2020 Davood Soleimani(Garlic)2020	intervent <u>Mean</u> -0.3 -12.95	0% tion group <u>SD Total</u> 0.9 45	co <u>Mean</u> 0 3.32	SD 0.953939	13 0 <u>Total</u> 43	1 100.0%	 6 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (F Fest for overall effect: Z = 1.02 (P = Study or Subgroup Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020	intervent <u>Mean</u> -0.3 -12.95	tion group SD Total 0.9 45 26.6 47 23.97 24	co <u>Mean</u> 0 3.32 -3.14	SD 0.953939 24.2	13 <u>Total</u> 43 51	1 100.0% Weight 64.0% 0.1%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Fest for overall effect: Z = 1.02 (P = hbbas Ali Sangouni 2020 Javood Soleimani(Garlic)2020 Javood Soleimani(propolis)2020 Einaz Jafarvand 2015	intervent <u>Mean</u> -0.3 -12.95 -4.24	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20	co <u>Mean</u> 0 3.32 -3.14 0.04	SD 0.953939 24.2 23.97	13 Total 43 51 25	Weight 64.0% 0.1% 0.1%	 6 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (F Fest for overall effect: Z = 1.02 (P = <u>Study or Subgroup</u> Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Javood Soleimani(Garlic)2020 Elnaz Jafarvand 2015 Faezeh Askari2014	intervent <u>Mean</u> -0.3 -12.95 -4.24 0.04 30.0	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446	13 Total 43 51 25 21	Weight 64.0% 0.1% 0.0%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Fest for overall effect: Z = 1.02 (P = Nobas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(gropolis)2020 Enaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015	intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.86 51.0 -0.22 45.2 -0.52 35.8	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23 25075 30 85034 19	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258	13 Total 43 51 25 21 22 31 19	Weight 64.0% 0.1% 0.0% 0.0% 0.0%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Fest for overall effect: Z = 1.02 (P = Multiple state of the state	intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.86 51.0 -0.22 45.2	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23 25075 30 85034 19	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06 0.43	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446	13 Total 43 51 25 21 22 31 19 29	Weight 64.0% 0.1% 0.0% 0.0% 0.0% 0.0% 35.7%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Study or Subgroup Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Enaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019	intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.22 45.2 0.52 35.8 0.25 0.8	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23 25075 30 85034 19	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06 0.43	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258	13 Total 43 51 25 21 22 31 19	Weight 64.0% 0.1% 0.0% 0.0% 0.0%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(gropolis)2020 Elnaz Jafarvand 2015 Faezeh Askarl2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019 Zahra Namkhah2021	intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.22 45.2 0.52 35.8 0.25 0.8	tion group SD Total 0.9 45 26.6 47 23.97 24 005312 20 09589 23 25075 30 85034 19 16149 34 27.79 32	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06 0.43	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436	13 Total 43 51 25 21 22 31 19 29 29	Weight 64.0% 0.1% 0.0% 0.0% 0.0% 0.0% 35.7% 0.1%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, -6.17] -0.09 [-25.89, 25.71] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] -0.34 [-14.01, 13.33] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Elnaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Fotal (95% CI)	intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.86 51.0 -0.22 45.2 -0.52 35.8 0.25 0.8 -0.23	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23 25075 30 85034 19 16149 34 27.79 32 274	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06 0.43	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436	13 Total 43 51 25 21 22 31 19 29 29	Weight 64.0% 0.1% 0.0% 0.0% 0.0% 0.0% 35.7%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] 	-50 -25 0 25 50 intervention group control group Mean Difference
Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Elnaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Total (95% CI) Heterogeneity: Chi ² = 9.80, df = 8 (intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.86 51.0 -0.22 45.2 -0.52 35.8 0.25 0.8° -0.23 P = 0.28); l ² =	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23 25075 30 85034 19 16149 34 27.79 32 274	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06 0.43	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436	13 Total 43 51 25 21 22 31 19 29 29	Weight 64.0% 0.1% 0.0% 0.0% 0.0% 0.0% 35.7% 0.1%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, -6.17] -0.09 [-25.89, 25.71] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] -0.34 [-14.01, 13.33] 	Mean Difference IV. Fixed, 95% CI
Heterogeneity: Chi ² = 0.41, df = 4 (F	intervent Mean -0.3 -12.95 -4.24 0.04 30.0 -0.86 51.0 -0.22 45.2 -0.52 35.8 0.25 0.8° -0.23 P = 0.28); l ² =	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 05312 20 09589 23 25075 30 85034 19 16149 34 27.79 32 274	co Mean 0 3.32 -3.14 0.04 -0.22 -0.13 0.06 0.43	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436	13 Total 43 51 25 21 22 31 19 29 29	Weight 64.0% 0.1% 0.0% 0.0% 0.0% 0.0% 35.7% 0.1%	 -0.14 [-0.42, 0.13] Mean Difference IV. Fixed, 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, -6.17] -0.09 [-25.89, 25.71] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] -0.34 [-14.01, 13.33] 	-50 -25 0 25 50 intervention group control group Mean Difference
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Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Elnaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Fotal (95% Cl) Heterogeneity: Chi ² = 9.80, df = 8 (Test for overall effect: Z = 1.72 (P = Study or Subgroup NLLER, D.A2011 Eleonora Scorletti2020 Johamad Hizami Mohamad Nor202 Pui Lin Chong2021 Sang BongAhn2019 Fotal (95% Cl) Heterogeneity: Chi ² = 1.26, df = 4 (P	intervent <u>Mean</u> -0.3 -12.95 -4.24 0.04 30.0 -0.22 45.2 -0.52 35.8 -0.23 P = 0.28); I ² = = 0.09) interve <u>Mean</u> 0.16 4 0.1 0 -1 0.23 -0.09 -0.56 11 -0.23 -0.99 -0.56 11 -0.24 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.99 -0.56 11 -0.56 11	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 005312 20 09589 23 25075 30 85034 19 16149 34 27.79 32 274 18% ention group <u>SD</u> To 43.37292 0.984886 0.93 1.32842 111.0956	co Mean 0 3.32 -3.14 0.04 0.22 -0.13 0.06 0.43 0.11 0.11 14 0.33 45 -0. 17 0.0 19 0.1 30 -0.3	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436 26.65 26.65 1 48.25464 1 0.8458855 5 1.01 1 1.825465 1 0.845855 5 1.01 9 0.972163	13 Total 43 51 22 21 22 31 19 29 29 29 270 270 444 7 444 7 422 3 16 3 35	Weight 64.0% 64.0% 0.1% 0.0% 0.0% 0.0% 0.1% 100.0% 35.7% 0.1% 0.0% 100.0% 61.8% 2.2.8% 15.4% 0.0% 0.0%	 Mean Difference IV. Fixed. 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] -0.34 [-14.01, 13.33] -0.27 [-0.58, 0.04] Mean Difference IV. Fixed. 95% CI -0.15 [-34.14, 33.84] 0.20 [-0.18, 0.58] 0.18 [-0.45, 0.81] -0.28 [-1.04, 0.48] -0.24 [-42.04, 41.56] 	Mean Difference IV. Fixed, 95% Cl -20 -10 0 10 20 intervention group control group Mean Difference IV. Fixed, 95% Cl
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Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Elnaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Fotal (95% Cl) Heterogeneity: Chi ² = 9.80, df = 8 (Test for overall effect: Z = 1.72 (P = Study or Subgroup NLLER, D.A2011 Eleonora Scorletti2020 Johamad Hizami Mohamad Nor202 Pui Lin Chong2021 Sang BongAhn2019 Fotal (95% Cl) Heterogeneity: Chi ² = 1.26, df = 4 (P	intervent <u>Mean</u> -0.3 -12.95 -4.24 0.04 30.0 -0.22 45.2 -0.52 35.8 -0.23 P = 0.28); I ² = = 0.09) interve <u>Mean</u> 0.16 4 0.1 0 -1 0.23 -0.09 -0.56 11 -0.23 -0.99 -0.56 11 -0.24 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.99 -0.56 11 -0.56 11	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 005312 20 09589 23 25075 30 85034 19 16149 34 27.79 32 274 18% ention group <u>SD</u> To 43.37292 0.984886 0.93 1.32842 111.0956	co Mean 0 3.32 -3.14 0.04 0.22 -0.13 0.06 0.43 0.11 0.11 14 0.33 45 -0. 17 0.0 19 0.1 30 -0.3	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436 26.65 26.65 1 48.25464 1 0.84588 5 1.01 1 1.825465 1 0.84588 5 1.01 9 0.972163	13 Total 43 51 22 21 22 31 19 29 29 29 270 270 444 7 444 7 422 3 16 3 35	Weight 64.0% 64.0% 0.1% 0.0% 0.0% 0.0% 0.1% 100.0% 35.7% 0.1% 0.0% 100.0% 61.8% 2.2.8% 15.4% 0.0% 0.0%	 Mean Difference IV. Fixed. 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] -0.34 [-14.01, 13.33] -0.27 [-0.58, 0.04] Mean Difference IV. Fixed. 95% CI -0.15 [-34.14, 33.84] 0.20 [-0.18, 0.58] 0.18 [-0.45, 0.81] -0.28 [-1.04, 0.48] -0.24 [-42.04, 41.56] 	Mean Difference IV. Fixed, 95% Cl -20 -10 0 10 20 intervention group control group Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Chi ² = 0.41, df = 4 (f Test for overall effect: Z = 1.02 (P = Abbas Ali Sangouni 2020 Davood Soleimani(Garlic)2020 Davood Soleimani(propolis)2020 Elnaz Jafarvand 2015 Faezeh Askari2014 Fatemeh Izadi2020 Pei-Wen Zhang2015 Seyed Reza Mirhafez2019 Zahra Namkhah2021 Fotal (95% Cl) Heterogeneity: Chi ² = 9.80, df = 8 (Fest for overall effect: Z = 1.72 (P = Mudy or Subgroup LLLER, D.A2011 Eleonora Scorletti2020 Aohamad Hizami Mohamad Nor202 Pui Lin Chong2021 Sang BongAhn2019 Fotal (95% Cl) Heterogeneity: Chi ² = 1.26, df = 4 (P	intervent <u>Mean</u> -0.3 -12.95 -4.24 0.04 30.0 -0.22 45.2 -0.52 35.8 -0.23 P = 0.28); I ² = = 0.09) interve <u>Mean</u> 0.16 4 0.1 0 -1 0.23 -0.09 -0.56 11 -0.23 -0.99 -0.56 11 -0.24 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.23 -0.99 -0.56 11 -0.99 -0.56 11 -0.56 11	tion group <u>SD</u> Total 0.9 45 26.6 47 23.97 24 005312 20 09589 23 25075 30 85034 19 16149 34 27.79 32 274 18% ention group <u>SD</u> To 43.37292 0.984886 0.93 1.32842 111.0956	co Mean 0 3.32 -3.14 0.04 0.22 -0.13 0.06 0.43 0.11 0.11 14 0.33 45 -0. 17 0.0 19 0.1 30 -0.3	SD 0.953939 24.2 23.97 37.21666 19.34658 57.04446 40.98258 1.212436 26.65 26.65 1 48.25464 1 0.84588 5 1.01 1 1.825465 1 0.84588 5 1.01 9 0.972163	13 Total 43 51 22 31 19 29 29 29 270 270 444 7 444 7 422 3 16 3 35	Weight 64.0% 64.0% 0.1% 0.0% 0.0% 0.0% 0.1% 100.0% 35.7% 0.1% 0.0% 100.0% 61.8% 2.2.8% 15.4% 0.0% 0.0%	 Mean Difference IV. Fixed. 95% CI -0.30 [-0.69, 0.09] -16.27 [-26.37, -6.17] -1.10 [-14.53, 12.33] 0.00 [-20.66, 20.66] -0.64 [-23.03, 21.75] -0.09 [-25.89, 25.71] -0.58 [-25.06, 23.90] -0.18 [-0.70, 0.34] -0.34 [-14.01, 13.33] -0.27 [-0.58, 0.04] Mean Difference IV. Fixed. 95% CI -0.15 [-34.14, 33.84] 0.20 [-0.18, 0.58] 0.18 [-0.45, 0.81] -0.28 [-1.04, 0.48] -0.24 [-42.04, 41.56] 	Mean Difference V. Fixed, 95% Cl -20 -10 0 10 20 intervention group control group Mean Difference IV. Fixed, 95% Cl -20 -10 0 10 20 intervention group control group

		vention gro			ontrol grou			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total				Weigh			IV. Fixed. 95% CI	
Abbas Ali Sangouni 2020	0.1	0.2	45		0.264575						
Davood Soleimani(Garlic)2020	1.6	7.3	47	0.7	9.1	1000	0.1%				
Davood Soleimani(propolis)202		6.55	24	-1.73	6.55		0.0%				
Elnaz Jafarvand 2015		8.643495	20		12.15633		0.0%				
Faezeh Askari2014 Fatemeh Izadi2020		7.472617 8.983874	23 30		5.632051 11.29026	22 31	0.0%				
Ji Cheol Bae2015	0.04	5.6	39	0.03	5.3		0.09				
Pei-Wen Zhang2015		5.730236	19		11.63197		0.0%				
Seved Reza Mirhafez2019	0.02		34	0.1	0.32078					•	
Zahra Namkhah2021	0.01	7.93	32	-0.1	5.76		0.1%	and the second se			
Total (95% CI)			313			309	100.0%	6 0.09 [0.01, 0.17	71		
Heterogeneity: Chi ² = 0.86, df =	9 (P = 1.00)); l ² = 0%							+		+
Test for overall effect: Z = 2.20	(P = 0.03)								-10	intervention group control group	10
	interventio			ontrol				ean Difference		Mean Difference	
and the second	ner in the mentality		I Mear					V. Fixed, 95% CI		IV. Fixed. 95% Cl	
ALLER, D.A2011	0 11.752			8.02				0.08 [-7.54, 7.38]			
		0.2 45		0.36				0.01 [-0.11, 0.13]		-	
Pui Lin Chong2021 0	0.02 0.250	599 19	0.01	1 0.34	5109	16 26	6.3% (0.01 [-0.19, 0.21]		Ī	
otal (95% CI)		78	3		7	74 100	0.0% 0	.01 [-0.09, 0.11]			
Heterogeneity: Chi ² = 0.00, df	= 2 (P = 1.0	00); l ² = 0%							-50	-25 0 25	50
Fest for overall effect: Z = 0.19	9 (P = 0.85)									intervention group control group	
	interve	ention grou			trol group			Mean Difference		Mean Difference	
udy or Subgroup	intervo Mean	ention grou SD	Total N	lean	SD	Total V	A REAL PROPERTY.	IV, Fixed, 95%	CI		
tudy or Subgroup bbas Ali Sangouni 2020	intervo Mean -0.3 (ention grou SD	Total N 45	lean 0 (SD	43	63.2%	IV. Fixed, 95% -0.30 [-0.57, -0.0	<mark>6 CI</mark>)3]	Mean Difference	
tudy or Subgroup bbas Ali Sangouni 2020 avood Soleimani(Garlic)2020	intervo <u>Mean</u> -0.3 (-11.9	ention grou SD 0.655744 25.2	Total N 45 47	<u>lean</u> 0 (3.36	SD 0.655744 26.3	43 51	63.2% 0.0%	IV. Fixed. 95% -0.30 [-0.57, -0.0 -15.26 [-25.46, -5.0	<mark>5 CI</mark> 03] 06]	Mean Difference	
tudy or Subgroup obas Ali Sangouni 2020 avood Soleimani(Garlic)2020 avood Soleimani(propolis)2020	intervo Mean -0.3 (-11.9 0.92	ention grou SD 0.655744 25.2 23.41	Total M 45 47 24	<u>1ean</u> 0 (3.36 3.08	SD 0.655744 26.3 23.41	43 51 25	63.2% 0.0% 0.0%	IV. Fixed, 95% -0.30 [-0.57, -0.0 -15.26 [-25.46, -5.0 -2.16 [-15.27, 10.9	2 CI 03] 06] 95]	Mean Difference	
tudy or Subgroup obas Ali Sangouni 2020 avood Soleimani(Garlic)2020 avood Soleimani(propolis)2020 naz Jafarvand 2015	intervo Mean -0.3 (-11.9 0.92 0.09 2	ention grou SD 0.655744 25.2 23.41 29.12679	Total M 45 47 24 20	10 0 3.36 3.08 0.05 3	SD 0.655744 26.3 23.41 30.73125	43 51 25 21	63.2% 0.0% 0.0% 0.0%	IV. Fixed. 95% -0.30 [-0.57, -0.0 -15.26 [-25.46, -5.0 -2.16 [-15.27, 10.9 0.04 [-18.28, 18.3	2 CI 23] 26] 25] 36]	Mean Difference	
tudy or Subgroup obas Ali Sangouni 2020 avood Soleimani(Garlic)2020 avood Soleimani(propolis)2020 naz Jafarvand 2015 aezeh Askari2014	intervo Mean -0.3 (-11.9 0.92 0.09 2 -0.49 5	ention grou SD 0.655744 25.2 23.41 29.12679 57.21433	Total M 45 47 24 20 23	Mean 0 0 3.36 3.08 0.05 3 0.05 3 0.13 2	SD 655744 26.3 23.41 	43 51 25 21 22	63.2% 0.0% 0.0% 0.0% 0.0%	IV. Fixed. 95% -0.30 [-0.57, -0.0 -15.26 [-25.46, -5.0 -2.16 [-15.27, 10.9 0.04 [-18.28, 18.3 -0.36 [-25.31, 24.5	2 CI 03] 06] 95] 86] 59]	Mean Difference	
tudy or Subgroup obas Ali Sangouni 2020 avood Soleimani(Garlic)2020 avood Soleimani(propolis)2020 naz Jafarvand 2015 aczeh Askari2014 atemeh Izadi2020	interve Mean -0.3 (-11.9 0.92 0.09 2 -0.49 5 -0.25	ention grou SD 0.655744 25.2 23.41 29.12679 57.21433 19.86127	Total M 45 47 24 20 23 30	Mean 0 0 3.36 3.08 0.05 3 0.05 3 -0.13 2 -0.21 3 -0.21 3	SD 26.55744 26.3 23.41 20.73125 20.86121 35.61053	43 51 25 21 22 31	63.2% 0.0% 0.0% 0.0% 0.0%	V. Fixed. 95% -0.30 [-0.57, -0.0 -15.26 [-25.46, -5.0 -2.16 [-15.27, 10.9 0.04 [-18.28, 18.3 -0.36 [-25.31, 24.5 -0.04 [-14.45, 14.3	6 CI 03] 06] 05] 36] 59] 37]	Mean Difference	
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TG; **C**: antioxidants on TC; **D**: probiotic/symbiotic/prebiotic on TC; **E**: antioxidants on HDL-C; **F**: probiotic/symbiotic/prebiotic on HDL-C; **G**: antioxidants on LDL-C; and **H**: probiotic/symbiotic/prebiotic on LDL-C).

with the action mechanism of antioxidants, whose hypolipidemic properties were related to the reduction of liver adipogenesis (20). With the action of antioxidants, inflammation induced by hepatocyte steatosis was improved, and ALT/AST levels were significantly decreased. WC, which is closely related to visceral fat deposition (59), also decreased significantly. Moreover, the amount of cholesterol decreased, especially oxidized LDL, HDL increased (60), which was consistent with the results of this study. On the other hand, TC reflects the sum of all LDL-C, HDL-C and VLDL in serum. In this study, LDL-C decreased and HDL-C increased, so the resulting overall lack of change can be understood. The lack of significant changes in TG may be due to the fact that only a small part of TG is synthesized by the body itself, and most TG is obtained from diet, which is influenced by many factors (61). Finally, elevated BMI is not a prerequisite for the diagnosis of NAFLD, and many of the included studies included patients with normal BMI, so it is not difficult to understand the lack of changes in BMI levels caused by antioxidants. However, due to the different dosages and types of antioxidants used in each trial, its effect should be further investigated in clinical application.

Six randomized indicated that trials taking probiotic/symbiotic/prebiotic decreased BMI, ALT, and AST levels but did not have favorable effects on blood lipid levels compared to the control group. The results were inconsistent with the previous review (62). This difference might be related to the type of strains. Studies have shown that different strains have different effects on liver function and blood lipid levels (12, 15, 63). However, since few trials were included in the study, the respective effects of probiotic/symbiotic/prebiotic could not be compared through subgroup analysis. In general, their adjuvant therapeutic effect on NAFLD is clear. The potential mechanism may involve regulating human metabolism by decreasing inflammatory markers and altering lipid profile (3). However, the dose and duration of their clinical application are ill-defined; therefore, more multi-central clinical research is needed to provide detailed guidance in the future.

Three RCTs reported the role of fatty acid supplementation in the treatment of NAFLD, but the results showed significant heterogeneity, which might be related to the dosage and durations of the trials. The dosages ranged from 1,000 to 4,000 mg, and the durations were from 8 to 24 weeks (51–53), which was in agreement with the result of another review (64). Therefore, additional trials are needed to demonstrate the effectiveness of fatty acids in NAFLD patients.

The effect of vitamin D may be related to reduced inflammatory markers (65), while whole grain could change intestinal microbial metabolites (66, 67). There were only a few articles on vitamin D and whole grain in this study because several interventions combined physical exercise with other supplements had to be excluded. At present, vitamin D combined with other treatments has been proven as an adjunctive therapy to improve liver function for NAFLD patients (68, 69). However, the articles on whole grain were scarce; therefore, larger sample size studies will be needed to provide evidence for the use of the low-cost whole grain.

This review has several limitations. Although our study showed that functional food and dietary supplements improved AST and ALT in patients with NAFLD, the source of all heterogeneity could not be explained by the subgroup analysis, especially most of the studies did not identify the stage of NAFLD and the included subjects in some studies were from a single ethnicity- mainly from Asia. Moreover, functional foods and dietary supplements used in these articles were produced in different countries with various dosages, which might have an impact on the results. Multi-center clinical research from different countries should be carried out to explore effective doses using uniform sources of functional foods and dietary supplements in the clinic. In addition, we only searched studies published in English in databases such as PubMed, ISI Web of Science, Cochrane library, and Embase. Thus, additional relevant studies might exist, and additional reviews may be required.

5. Conclusion

The current study suggests that antioxidant and probiotic/symbiotic/prebiotic supplements alone or in combination

with other therapies may be a promising regimen for NAFLD patients. However, the usage of fatty acids, vitamin D, and whole grain in clinical treatment is uncertain. Further exploration of the efficacy ranks of functional foods and dietary supplements is needed to provide a reliable basis for clinical application.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

H-hY and L-lW conceived, designed the study, searched databases, screened articles, extracted data, and performed statistical analyses. P-hZ contributed to the revision of the manuscript. All authors contributed to the writing and revision of the manuscript.

Funding

The study was supported by Zhejiang Provincial Natural Science Foundation of China (LY22H160002).

Acknowledgments

We would like to thank TopEdit (www.topeditsci.com) for its linguistic assistance during the preparation of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023. 1014010/full#supplementary-material

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