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Review

Effects of Resveratrol Supplementation on Metabolic and Anthropometric Outcomes in Non-Alcoholic Fatty Liver Disease: An Umbrella Review and Updated Meta-Analysis

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is strongly associated with dyslipidemia, insulin resistance, chronic inflammation, and abdominal obesity; therefore, NAFLD is considered a major public health concern. This highlights the need for effective early-stage interventions to halt disease progression. However, findings on the effects of resveratrol supplementation in patients with NAFLD have been inconsistent. This comprehensive meta-analysis aimed to synthesize existing evidence to determine the effects of resveratrol supplementation on metabolic and anthropometric outcomes in patients with NAFLD. **Method:** A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar using relevant keywords, with no date restrictions up to June 2025. Eligible studies were meta analyses published in English. The methodological quality of the included studies and the certainty of the evidence were assessed using the AMSTAR2 scale and the GRADE tool, respectively. Data analysis was performed using Stata version 17 (StataCorp LLC, College Station, Texas, USA). **Results:** A total of nine meta-analyses were involved in this study, comprising eight randomized controlled trials (RCTs),with a total of 266 patients with NAFLD. The administered resveratrol intervention dose and duration in the included studies ranged from 300 to 3000 mg/day for 8 to 26 weeks. Resveratrol supplementation significantly reduced serum alanine aminotransferase (ALT) levels (weighted mean difference (WMD) = –4.791 IU/L, 95% confidence interval (CI) (–8.823 to –0.759); $p = 0.020$) and body weight (WMD = –0.666 kg, 95% CI (–1.127 to –0.205); $p = 0.005$) of patients compared with the control group. In contrast, resveratrol intervention had no significant effects on serum aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) concentrations, glycemic indices, including fasting blood glucose, and insulin resistance assessed by the homeostasis model; lipid profile parameters, including serum low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG), and total cholesterol (TC) levels; or inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor α (TNF-α) levels. Moreover, body mass index (BMI) and central obesity (waist circumference (WC) and waist-to-hip ratio (WHR)) were not significantly altered following resveratrol supplementation. **Conclusion:** This meta-analysis suggests that resveratrol supplementation may modestly reduce body weight and ALT levels in adults with NAFLD, while exerting no significant effects on glycemic indices, inflammatory, markers, or lipid profiles. Therefore, further high-quality RCTs administration supplementationwith larger sample sizes and standardized dosing regimens are warranted to clarify the clinical benefits of resveratrol intervention in individuals with NAFLD. The PROSPERO Registration: ID number: CRD420251060258 (https://www.crd.york.ac.uk/prospero/).

Keywords: non-alcoholic fatty liver; resveratrol; supplementation; umbrella; meta-analysis

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of liver disorders, ranging from asymptomatic fatty liver to more severe conditions like cirrhosis [1]. NAFLD occurs when triglyceride (TG) accumulate in liver cells, constituting approximately 5%–10% of the liver's weight, without the presence of other causes, such as viral infections, alcohol use, or certain medications. This accumulation may lead to cirrhosis and affects around 30% of the population in both Western countries and Asia [1]. The condition is notably common among subjects with obesity, type 2 diabetes mellitus (T2DM), and even the broader population, positioning NAFLD as an important public health concern with the potential to progress to liver cancer if left untreated [2]. NAFLD is also closely linked to conditions including abdominal obesity, dyslipidemia, insulin resistance, chronic inflammation, hypertension, and kidney disease, further emphasizing the need for effective early-stage interventions to halt disease progression [2,3].

The use of complementary medicine for treating various human ailments has a rich history [4]. Recent studies have highlighted the antioxidant benefits of certain

plant-based compounds, such as resveratrol, on liver health [5]. Resveratrol (3,5,4′-trihydroxystilbene) is a type of stilbenoid and phytoalexin that, in response to damage or pathogen attacks, is produced by several plants, such as those from bacteria or fungi. It is mainly found in red grapes, Japanese knotweed, and a few other plants, though in relatively low levels [6]. Resveratrol activates silent information regulator 2 homolog 1 (sirtuin-1 (SIRT1)) and adenosine monophosphate-activated kinase (AMPK), two proteins essential for breaking down and removing fat from the liver, processes crucial for preventing liver diseases like fibrosis and cirrhosis [7]. Activating AMPK and SIRT1 can lead to suppression of acetyl-CoA carboxylase (ACC) and sterol regulatory element-binding protein-1c (SREBP-1c), key drivers of hepatic de novo lipogenesis. Activating AMPK also enhances fatty acid β-oxidation via upregulating of peroxisome proliferator-activated receptor-α (PPAR-α). By activating AMPK and SIRT1, enhancing the antioxidant enzymes activity such as superoxide dismutase (SOD) and glutathione peroxidase, and suppressing NF–κB–mediated inflammatory signaling, resveratrol may protect the liver and slow the progression of NAFLD [8,9]. Furthermore, resveratrol has been connected with several benefits, including improving insulin sensitivity, attenuating mitochondrial dysfunction, both of which contribute to decreased hepatic triglyceride accumulation, and effects like calorie-restriction [10]. These characteristics make it a promising candidate for managing NAFLD by inhibiting fat accumulation in the liver [11].

Despite its numerous health benefits, the specific impact of resveratrol on NAFLD is a debated topic. Moreover, based on our knowledge, there is no umbrella review in this regard. Therefore, this umbrella meta-analysis was planned to evaluate whether resveratrol supplementation provides significant benefits to patients with NAFLD. Given the mixed findings from previous research, this comprehensive umbrella review aims to clarify the influences of resveratrol on anthropometric measures and key metabolic factors related to NAFLD.

2. Methods

2.1 The Strategy of Search

The Cochrane Handbook for Systematic Reviews of Interventions [12] and the PRISMA criteria [13] were taken into consideration when conducting the umbrella review procedures (**Supplementary Table 1**). Additionally, the protocol for this review was entered into PROSPERO, an international database for systematic reviews (ID number: CRD420251060258).

Scopus, Web of Science, PubMed, and Google Scholar were searched to detect the systematic reviews and meta-analyses (SRMAs) that evaluated the resveratrol supplementation effects in subjects with NAFLD, published up to June 2025. The search was done utilizing the MeSH terms and the following keywords: “Resveratrol” AND “non-alcoholic fatty liver” OR “NAFLD” OR “Nonalcoholic Steatohepatitis” . We also manually examined the “cited by” and “related articles” sections and the selected studies’ reference lists to ensure all relevant research was included. The study design was not restricted to the search to update and recognize the original randomized controlled trials (RCTs) that were not involved in the review studies. Two separate authors searched, and disagreements were settled via conversation. The specifics of the database search approach are shown in **Supplementary Table 2**.

2.2 Screening and Eligibility Criteria

For better management, the retrieved articles from databases were transferred to EndNote software version 21 (Clarivate, Philadelphia, PA, USA). In the first step, after removing the duplicate studies, the articles’ titles and abstracts were checked by two separate reviewers (RMG and SS). In the second step, the remaining articles’ full texts were critically screened based on the eligibility criteria. This umbrella review covered all peer-reviewed English-language meta-analyses that studied the effects of resveratrol supplementation in individuals with NAFLD. The PICOS criteria for this review included Population: adult subjects with NAFLD, Intervention: resveratrol supplements, Comparison: placebo, Outcomes: Changes in liver enzymes and glycemic indices were the major outcomes, whereas changes in lipid profiles and other biochemical parameters like anthropometric indices and inflammatory variables were the secondary outcomes, and Study design involved meta-analyses of RCTs. The eligibility criteria for the current review were defined based on the PICOS items. The cases that were not included in this study were original articles, conference papers, letters, editorials, and theses. Meta-analyses of resveratrol effects combined with other interventions were excluded. In addition, articles without full text were eliminated.

2.3 Data Extraction

Two separate authors (RMG and SS) extracted the required data. The information that was extracted from the RCTs involved in the chosen SRMAs included: the name of the first authors, year of publication, participants’ number in both the intervention and control or placebo groups, participant age and gender, supplement dose and duration, the quality assessment scales, the results, and the mean (standard deviation (SD)) for the study’s outcomes.

2.4 Quality Assessment and Certainty of the Evidence

The AMSTAR2 was used to evaluate the quality of the eligible reviews, a widely recognized tool for evaluating the rigor of SRMAs [14]. These assessments were separately performed by two authors (RMG and SS), and any differences were resolved through mutual agreement. Additionally, the GRADE scale was applied to evaluate the degree of certainty of the acquired data [15]. This tool has five do-

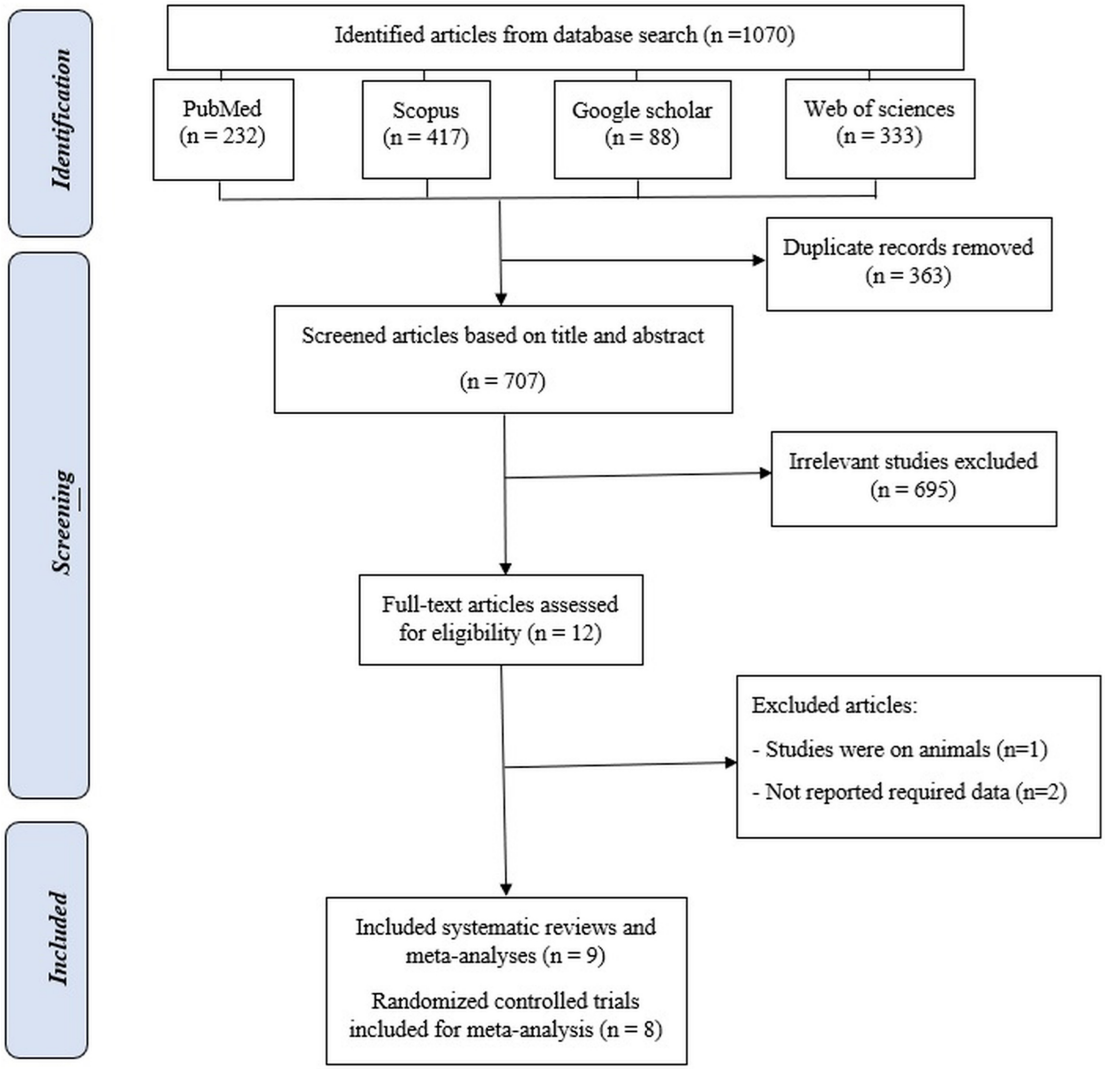

Fig. 1. PRISMA diagram: the study search and selection process.

mains, including the risk of bias of the studies, directness, publication bias, consistency of the findings, and accuracy. The quality of the evidence will decline when each of these criteria is not satisfied, and finally will be regarded as very low, low, moderate, or high quality.

2.5 Data Analysis

We identified primary RCTs from the included SR-MAs, incorporating additional RCTs not included in these studies. We pooled the primary RCTs' results that were involved in the eligible meta-analyses and were obtained from database searches to prevent the overlapping of the original RCTs' results that were included multiple times in the meta-analyses. The mean difference (MD) and 95% confidence interval (CI) were recalculated using the DerSimonian and Laird random-effect model [16]. To evaluate heterogeneity across studies, we used the I^2 statistic [17]. According to the Cochrane Handbook, I^2 values were evaluated as follows: minor heterogeneity (I^2 = 0%–40%), moderate heterogeneity (I^2 = 30%–60%), substantial heterogeneity (I^2 = 50%–90%), and considerable heterogeneity (I^2 = 75%–100%) [18]. Publication bias was assessed using the Begg test [19] and the funnel plots' visual inspection. A trim-and-fill test was carried out, if asymmetry was detected in the funnel plot [20]. The Stata software, version 17.0 (StataCorp LLC, College Station, Texas, USA), was applied for statistical analyses, considering a $p < 0.05$ as a significance threshold.

3. Results

3.1 Study Selection

Fig. 1 presents the study search and selection procedure for this review (PRISMA diagram). Following the search of databases, 1070 articles were retrieved from PubMed (n = 232), Web of Science (n = 333), Scopus (n = 417), and Google Scholar (n = 88). By deleting duplicate articles (n = 363), 707 studies remained and were further screened. During the first screening phase, 695 papers were eliminated because they were judged irrelevant by the title

Table 1. The meta-analyses' characteristics that assessed the effects of resveratrol on NAFLD patients.

First Author, year of publication/ country	Gender of patients	No. of studies in meta-analysis	No. of patients in meta-analysis	Age range (mean age)	Supplement dose (mg/day)	Duration (week)	Studied outcomes and Findings	Quality assessment scale and outcome
Zhang et al. [33] (2016)/China	m/f	4	156	18–65	300–3000	8 to 25	BMI, body weight, AST, ALT, GGT, HDL-C, insulin, glucose, DBP, SBP ↔ LDL-C, TC ↑	Cochrane, Good
Elgebaly et al. [27] (2017)/Egypt	m/f	4	158	18–65	300–3000	8 to 24	BMI, body weight, WC, FBS, insulin, AST, ALT, glucose, TG, LDL-C ↔	Cochrane, Good
Rafiee et al. [31] (2021)/Iran	m/f	6	266	39–48	300–3000	8 to 24	BMI, body weight, WC, WHR, ALT, AST, GGT, ALP, SBP, DBP, bilirubin, TC, HDL-C, TG, LDL-C, LDL to HDL ratio, apo-B, apo-A1, glucose, insulin, HOMA-IR, creatinine, and IL-6 ↔ TNF-α, hs-CRP ↓	Cochrane, Good
Jakubczyk et al. [29] (2020)/Poland	m/f	7	302	39.25–48.15	500–3000	8 to 25	Body weight, BMI, WC, glucose, insulin, TC, LDL-C, HDL-C, SBP, DBP, AST ↔ ALT ↑	Cochrane, Good
Wei and Yu [32] (2021)/China	m/f	5	216	39–48	300–3000	8 to 25	ALT, AST ↔	Cochrane, Good
Nemati et al. [30] (2023)/Iran	m/f	6	232	18–70	500–3000	8 to 24	BMI, body weight, WC, WHR, glucose, insulin, HOMA-IR, adiponectin, LDL-C, HDL-C, TC, ALT, AST, DBP ↔ IL-6, TNF-α, TG, SBP ↓	Cochrane, Good
He et al. [28] (2023)/China	m/f	5	216	39–48	300–3000	8 to 25	BMI, body weight, WC, WHR, glucose, insulin, ALT, AST, LDL-C, TC, TG, HDL-C ↔ TNF-α ↓	Cochrane, Good
Ebrahimpour et al. [25] (2024)/Iran	m/f	6	256	NR	300–3000	8 to 26	↔ALT, AST	JADAD scale, High
Ranneh et al. [26] (2024)/UAE	m/f	6	305	39.5–46.8	300–3000	8–26	Controversial results as a systematic review	Cochrane, Good

ALT, Alanine aminotransferase; Apo, Apolipoprotein; AST, Aspartate aminotransferase; BMI, Body mass index; DBP, Diastolic blood pressure; FBS, Fasting blood sugar; TC, Total cholesterol; TG, Triglyceride; UAE, United Arab Emirates; NR, Not reported; LDL-C, Low-density lipoprotein-cholesterol; HDL-C, High-density lipoprotein-cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; SBP, Systolic blood pressure; TNF-α, Tumor necrosis factor α; hs-CRP, High-sensitivity C-reactive protein; GGT, Gamma-glutamyl transferase; IL-6, Interleukin-6; WHR, Waist-to-hip ratio; WC, Waist circumference; m, Male; f, Female; NAFLD, non-alcoholic fatty liver disease.

↔ No change, ↓ Decrease, ↑ Increase.

and abstract. In the second step, 12 articles were critically screened, and 3 studies were excluded due to being narrative review [21] and not reporting the required data [22,23]. Additionally, one RCT [24] was detected during screening of the original studies that were not involved in the included SRMAs. Finally, nine SRMAs [25,26,27,28,29,30,31,32,33] of eight RCTs [24,34,35,36,37,38,39,40] were involved in the current umbrella review.

3.2 The Included Studies' Characteristics

The general attributes of the eligible SRMAs are displayed in Table 1 [25,26,27,28,29,30,31,32,33]. As presented in Table 1, the publication years of the SRMAs were from 2016 to 2024. The meta-analyses comprised a range of four to seven RCTs. Both sexes of participants aged 18 to 70 years were encompassed in the meta-analyses. However, Ebrahimpour et al. [25] did not report the age range of the included participants. Moreover, the quality of the RCTs involved in the meta-analyses was evaluated by the Cochrane Collaboration's criteria and the JADAD scale, which showed that all the RCTs were of high quality. After removing the overlapped studies, 8 RCTs of 266 adults with NAFLD were included in the meta-analyses. It should be mentioned that the participants of the Farzin et al. [24,39] and Faghihzadeh et al. [37,38] studies were only considered once in the total number of patients involved in this review. The publication years of RCTs were 2014 to 2025. The intervention dosage and duration used by the RCTs were 300 to 3000 mg/day and 8 to 26 weeks, respectively.

3.3 The Included Studies' Quality Assessment and Grading of the Evidence

The results of the included SRMAs' risk of bias assessment are shown in **Supplementary Table 3**. Based on the AMSTAR2 criterion, seven of the included SRMAs had a low risk of bias, whereas two had a moderate risk. Most of the SRMAs did not have an established protocol for their review. In addition, using the GRADE scale, the evidence for body weight and body mass index (BMI) had a high quality, and for other outcomes, a moderate quality (Table 2).

3.4 Outcomes

3.4.1 Effects of Resveratrol Supplementation on Liver Enzymes

Nine SRMAs of six RCTs of 266 patients with NAFLD assessed the impacts of resveratrol supplementation on serum alanine aminotransferase (ALT) levels. Pooling their results by the random-effect model indicated that resveratrol administration decreased ALT levels compared to the placebo (WMD = –4.79 IU/L, 95% CI (–8.82, –0.76), $p = 0.020$) (Fig. 2A). There was a minor variation between the RCTs ($I^2 = 4.3\%$, $P_{heterogeneity} = 0.389$). Subgroup tests demonstrated that the effects of resveratrol intake in reducing ALT levels were considerable in RCTs with a sample size ≥50 and an intervention dose <1000 (WMD = –4.705 IU/L, 95% CI (–8.644, –0.767)) (Table 3). Thus, the heterogeneity sources could be the intervention dose and sample size. Following the leaving out the study by Chen et al. [36] (WMD = –4.092, 95% CI: –10.601, 2.416) and Asghari et al. [34] (WMD = –5.566, 95% CI: –11.185, 0.052) by the sensitivity analysis, the effects of resveratrol intervention on reducing ALT levels became non-significant (**Supplementary Fig. 1A**). The Begg test revealed no significant small study influence ($p = 0.573$), despite a partial asymmetry in the right part of the funnel plot. So, the trim-and-fill method was used, but as no study was imputed, the results remained unchanged (**Supplementary Fig. 1B**).

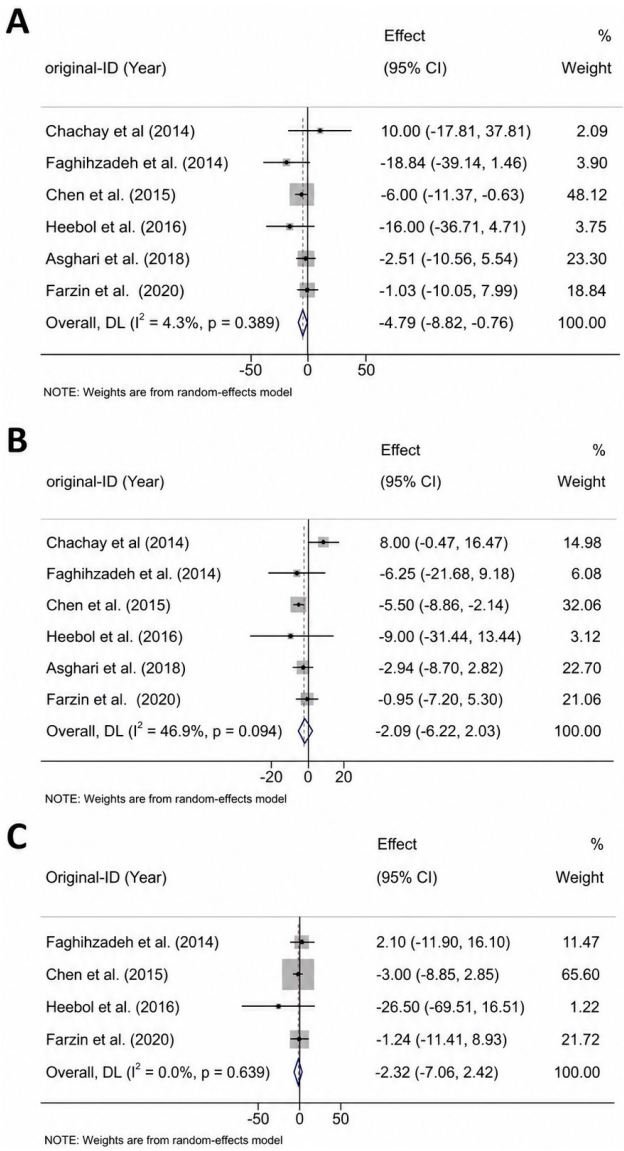

Fig. 2. Forest plot of the impact of resveratrol supplementation on alanine aminotransferase (A), aspartate aminotransferase (B), and gamma-glutamyl transferase (C).

Table 2. Results summary and evaluation of the quality of the evidence using the GRADE method.

Outcome measures	Summary of findings		Quality of evidence assessment (GRADE)					
	No. of patients/RCTs	Effect size (95% CI)	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence[f]
Liver enzymes								
ALT	266/6	–4.791 IU/L (–8.823, –0.759)	Not serious	Serious	Not serious	Not serious	Not serious	Moderate
AST	266/6	–2.094 IU/L (–6.218, 2.030)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
GGT	186/4	–2.319 IU/L (–7.060, 2.423)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
Glycemic indices								
FBS	266/6	–0.275 mg/dL (–0.640, 0.090)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
HOMA-IR	216/5	–0.138 (–0.765, 0.489)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
Insulin	266/6	–0.84 μIU/mL (–3.32, 1.64)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
Lipid profiles								
LDL-C	216/5	–0.004 mg/dL (–0.807, 0.799)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
TC	190/4	–0.151 mg/dL (–0.879, 0.577)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
HDL-C	216/5	0.061 mg/dL (–0.029, 0.151)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate
TG	266/6	0.115 mg/dL (–0.401, 0.631)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
Inflammatory factors								
TNF-α	156/4	–0.312 mg/L (–0.869, 0.246)	Not serious	Serious	Not serious	Not serious	Not serious	Moderate
hs-CRP	124/3	–0.731 mg/L (–3.266, 1.805)	Not serious	Serious	Not serious	Serious	Not serious	Moderate
Anthropometric measures								
Body weight	266/6	–0.666 kg (–1.127, –0.205)	Not serious	Not serious	Not serious	Not serious	Not serious	High
BMI	266/6	–0.173 kg/m^2 (–0.486, 0.140)	Not serious	Not serious	Not serious	Not serious	Not serious	High
WC	195/4	–1.86 cm (–5.86, 2.14)	Not serious	Not serious	Not serious	Not serious	Serious	Moderate
WHR	246/5	–0.00 (–0.02, 0.02)	Not serious	Serious	Not serious	Not serious	Serious	Moderate

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; BMI, Body mass index; FBS, Fasting blood sugar; RCTs, Randomized controlled trials; TC, Total cholesterol; TG, Triglyceride; TNF, Tumor necrosis factor; LDL-C, Low-density lipoprotein-cholesterol; HDL-C, High-density lipoprotein-cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; hs-CRP, High-sensitivity C-reactive protein; IU, International Unit; GGT, Gamma-glutamyl transferase; WHR, Waist-to-hip ratio; WC, Waist circumference; CI, confidence interval.

[a] Risk of bias based on the AMSTAR2 results.

[b] Downgraded if meta-regression or subgroup analyses failed to explain a significant amount of unexplained heterogeneity (I^2 >50%, $p < 0.10$).

[c] Downgraded if the results' generalizability was restricted due to participant, intervention, or outcome-related issues.

[d] Downgraded if the optimal information size was not achieved or if the 95% confidence interval included the null value (0 for WMD outcomes).

[e] Downgraded if evidence of publication bias is detected based on the funnel plot.

[f] Since all included studies were meta-analyses of randomized clinical trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria. Quality was graded as high, moderate, low, or very low.

Pooling the findings of nine SRMAs of six RCTs comprising 266 patients by a random-effect model demonstrated no significant decrease in aspartate aminotransferase (AST) after resveratrol intake (WMD = –2.09 IU/L, 95% CI (–6.22, 2.03), $p = 0.320$) (Fig. 2B). Moderate heterogeneity ($I^2 = 46.9\%$, $P_{heterogeneity} = 0.094$) was seen among the studies. The subgroup analysis revealed that administration of resveratrol led to a considerable decline in AST levels in the trials with sample size ≥50 (WMD = –4.216 IU/L, 95% CI: –6.812, –1.620) and intervention dose <600 (WMD = –4.541, 95% CI: –7.449, –1.633) (Table 3). Furthermore, upon the sensitivity analysis, the impact of resveratrol treatment on lowering AST levels became significant (WMD = –4.278 IU/L, 95% CI (–6.857, –1.700)) after removing the Chachay et al. [35] study (**Supplementary Fig. 2A**). The Begg test result indicated that publication bias was not significant ($p = 0.851$), but because of the existing partial asymmetry on the funnel plots' left part, a trim-and-fill technique was employed. After imputing one study, the results remained unchanged (WMD = –1.813, 95% CI: –6.011, 2.385) (**Supplementary Fig. 2B**).

Four RCTs assessed the effects of resveratrol intervention on gamma-glutamyl transferase (GGT) levels reported by three SRMAs. Pooling their results indicated a non-significant reduction in serum GGT concentration in the resveratrol group in comparison with the placebo (WMD = –2.32 IU/L, 95% CI (–7.06, 2.42), $p = 0.338$), with a low heterogeneity ($I^2 = 0.0\%$, $P_{heterogeneity} = 0.639$) (Fig. 2C).

3.4.2 Effects of Resveratrol Supplementation on Glycemic Parameters

Seven SRMAs of six RCTs on 266 subjects with NAFLD investigated the effect of resveratrol intervention on fasting blood sugar (FBS) levels. Pooling the results of the RCTs demonstrated that intervention with resveratrol was not effective in significantly reducing the concentration of FBS levels compared to the placebo (WMD = –0.27 mg/dL, 95% CI (–0.64, 0.09), $p = 0.140$). Among the studies, there was a rather high variety ($I^2 = 62.9\%$, $P_{heterogeneity} = 0.019$) (Fig. 3A). However, subgroup analysis indicated that in the studies published after 2016, resveratrol significantly decreased FBS levels (WMD = –0.306, 95% CI: –0.566, –0.046) (Table 3). Upon sensitivity analysis, excluding the Chachay et al. [35] study, the effects of resveratrol on decreasing serum FBS levels became statistically significant (WMD = –0.425 mg/dL, 95% CI: –0.709, –0.141) (**Supplementary Fig. 3A**). There was no small-study impact, according to the Begg test ($p = 0.573$). The trim and fill method was used because of a partial asymmetry on the funnel plot, which did not change the findings (**Supplementary Fig. 3B**).

The findings of six RCTs, including 266 individuals with NAFLD, that assessed the resveratrol impact on serum insulin levels demonstrated that insulin levels did not alter significantly following the supplementation (WMD = –0.84, 95% CI (–3.32, 1.64), $p = 0.508$). The trials' heterogeneity was comparatively modest ($I^2 = 25.1\%$, $P_{heterogeneity} = 0.246$) (Fig. 3B). By the subgroup analyses, sample size, the year of publication, and intervention dose among the included studies did not influence the obtained effect (Table 3). Omitting each of the RCTs by the sensitivity analyses did not alter the results of resveratrol effects on insulin levels (**Supplementary Fig. 4A**). There was no discernible publication bias using the Begg test ($p = 0.091$). Due to observed asymmetry in the funnel plot, the trim-and-fill procedure by imputing three studies was applied, and the pooled effect of nine studies was not altered (**Supplementary Fig. 4B**). Therefore, no indication of publication bias was detected.

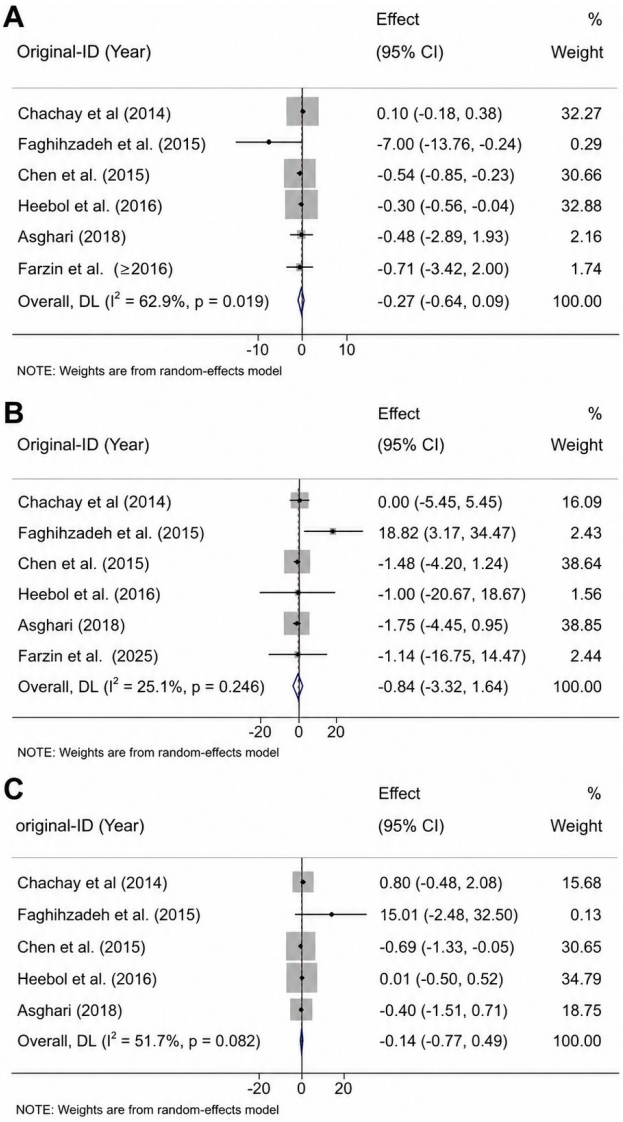

Fig. 3. Forest plot of resveratrol supplementation effects on fasting blood sugar (A), insulin (B), and HOMA-IR (C).

The combined results of five RCTs involving 216 participants with NAFLD revealed that resveratrol intake did not significantly decrease homeostasis model assessment of

Table 3. The results of subgroup analyses for the effects of resveratrol supplementation on NAFLD patients.

	Effect size (n)	ES (95% CI)[a]	P-within[b]	I^2 (%)[c]	P-heterogeneity[d]
Resveratrol on ALT					
Publication year					
<2016	3	–6.637 (–16.673, 3.398)	0.195	28.5	0.247
≥2016	3	–2.951 (–8.719, 2.817)	0.316	0.0	0.425
Sample size					
<50	2	–4.725 (–29.979, 20.530)	0.714	53.7	0.142
≥50	4	–4.705 (–8.644, –0.767)	0.019	0.3	0.390
Dosage (mg/day)					
<1000	4	–4.705 (–8.644, –0.767)	0.019	0.3	0.390
≥1000	2	–4.725 (–29.979, 20.530)	0.714	53.7	0.142
Resveratrol on AST					
Publication year					
<2016	3	–1.012 (–10.852, 8.829)	0.840	76.5	0.014
≥2016	3	–2.266 (–6.427, 1.896)	0.286	0.0	0.752
Sample size					
<50	2	–2.806 (–12.541, 18.154)	0.720	48.2	0.165
≥50	4	–4.216 (–6.812, –1.620)	0.001	0.0	0.601
Dosage (mg/day)					
<600	3	–4.541 (–7.449, –1.633)	0.002	0.0	0.443
≥600	3	0.569 (–8.497, 9.636)	0.902	60.3	0.080
Resveratrol on FBS					
Publication year					
<2016	3	–0.291 (–1.008, 0.425)	0.426	84.5	0.002
≥2016	3	–0.306 (–0.566, –0.046)	0.021	0.0	0.948
Sample size					
<50	2	–0.102 (–0.494, 0.289)	0.608	76.3	0.040
≥50	4	–0.647 (–1.491, 0.196)	0.133	14.7	0.319
Dosage (mg/day)					
<1000	4	–0.647 (–1.491, 0.196)	0.133	14.7	0.319
≥1000	2	–0.102 (–0.494, 0.289)	0.608	76.3	0.040
Resveratrol on insulin					
Publication year					
<2016	3	1.592 (–4.658, 7.842)	0.618	68.5	0.042
≥2016	3	–1.719 (–4.359, 0.921)	0.202	0.0	0.995
Sample size					
<50	3	–0.180 (–5.161, 4.800)	0.943	0.0	0.987
≥50	3	–0.273 (–4.533, 3.986)	0.900	69.1	0.039
Dosage (mg/day)					
<1000	4	–0.538 (–4.256, 3.179)	0.777	53.7	0.923
≥1000	2	–0.071 (–5.326, 5.184)	0.979	0.0	0.091
Resveratrol on TG					
Publication year					
<2016	3	0.273 (–0.546, 1.091)	0.514	84.6	0.002
≥2016	3	–0.202 (–0.647, 0.244)	0.375	0.0	0.930
Sample size					
<50	2	0.258 (–0.624, 1.140)	0.567	88.9	0.003
≥50	4	–0.159 (–0.442, 0.124)	0.270	0.0	0.909
Dosage (mg/day)					
<1000	4	–0.159 (–0.442, 0.124)	0.270	0.0	0.909
≥1000	2	0.258 (–0.624, 1.140)	0.567	88.9	0.003

Table 3. Continued.

	Effect size (n)	ES (95% CI)[a]	P-within[b]	I^2 (%)[c]	P-heterogeneity[d]
Resveratrol on body weight					
Publication year					
<2016	3	–0.165 (–0.905, 0.575)	0.662	0.0	0.721
≥2016	3	–0.984 (–1.574, –0.394)	0.001	0.0	0.989
Sample size					
<50	2	–1.366 (–7.433, 4.702)	0.659	0.0	0.929
≥50	4	–0.611 (–1.148, –0.073)	0.026	14.2	0.321
Dosage (mg/day)					
<1000	4	–0.611 (–1.148, –0.073)	0.026	14.2	0.321
≥1000	2	–1.366 (–7.433, 4.702)	0.659	0.0	0.929
Resveratrol on BMI					
Publication year					
<2016	3	–0.124 (–0.471, 0.223)	0.482	0.0	0.597
≥2016	3	–0.385 (–1.112, 0.342)	0.299	0.0	0.988
Sample size					
<50	2	–0.343 (–2.250, 1.564)	0.724	0.0	0.764
≥50	4	–0.168 (–0.485, 0.149)	0.300	0.0	0.720
Dosage (mg/day)					
<1000	4	–0.168 (–0.485, 0.149)	0.300	0.0	0.720
≥1000	2	–0.343 (–2.250, 1.564)	0.724	0.0	0.764

ES, Effect size; CI, Confidence interval; ALT, Alanine aminotransferase; BMI, Body mass index; TG, Triglyceride.

[a] Obtained from the Random-effect model.

[b] Refers to the mean (95% CI).

[c] Inconsistency, the percentage of variation across studies due to heterogeneity.

[d] Obtained from the Q-test.

insulin resistance (HOMA-IR) (WMD = –0.14, 95% CI (–0.77, 0.49), $p = 0.665$) with a modest variety ($I^2 = 51.7\%$, $P_{heterogeneity} = 0.082$) (Fig. 3C). By sensitivity analyses excluding each RCTs did not impact the results significantly (**Supplementary Fig. 5A**). The Begg test revealed no discernible small study effect ($p = 0.142$). A minor asymmetry was seen on the funnel plot where the trim-and-fill test was done and imputed one study, but the pooled effect did not alter significantly (**Supplementary Fig. 5B**).

3.4.3 Effects of Resveratrol Supplementation on Lipid Profile

The impacts of resveratrol intervention on serum low-density lipoprotein cholesterol (LDL-C) levels were examined in five trials involving 216 individuals with NAFLD that were included in seven meta-analyses. The combined results of these trials showed a non-significant change in blood levels of LDL-C (WMD = –0.00, 95% CI (–0.81, 0.80), $p = 0.992$) (Fig. 4A) with a substantial degree of variation among the RCTs ($I^2 = 81.7\%$, $P_{heterogeneity} < 0.001$). The Beggs test showed that there was no considerable publication bias ($p = 0.142$). Removing each trial did not significantly affect the obtained effects based on sensitivity analyses (**Supplementary Fig. 6A**). A minor asymmetry was seen on the funnel plot, and the trim-and-fill procedure was applied with seven studies (two imputed), but the results were not altered (**Supplementary Fig. 6B**).

The effects of resveratrol intervention on serum high-density lipoprotein cholesterol (HDL-C) levels also were reported by five trials of 216 participants with NAFLD that pooling their reports indicated no significant change in HDL-C concentration after resveratrol administration (WMD = 0.06 mg/dL, 95% CI (–0.03, 0.15), $p = 0.184$) (Fig. 4B). A minor heterogeneity was seen among the trials ($I^2 = 0.0\%$, $P_{heterogeneity} = 0.627$). Sensitivity analysis by removing individual trials did not significantly influence the obtained ES (**Supplementary Fig. 7A**). Additionally, the Begg method revealed no statistically significant small-study influence ($p = 0.327$). Nevertheless, the trim-and-fill test was conducted by five observed and two imputed studies because of an irregularity in the funnel plot. However, five observed and two imputed studies performed the trim-and-fill test because of an imbalance in the funnel plot, and the findings did not significantly change (**Supplementary Fig. 7B**).

The results of six RCTs, including 240 adults with NAFLD, were presented by six included meta-analyses combined and showed no significant decrease in serum TG levels following resveratrol treatment (WMD = 0.11 mg/dL, 95% CI (–0.40, 0.63), $p = 0.663$) (Fig. 4C). A

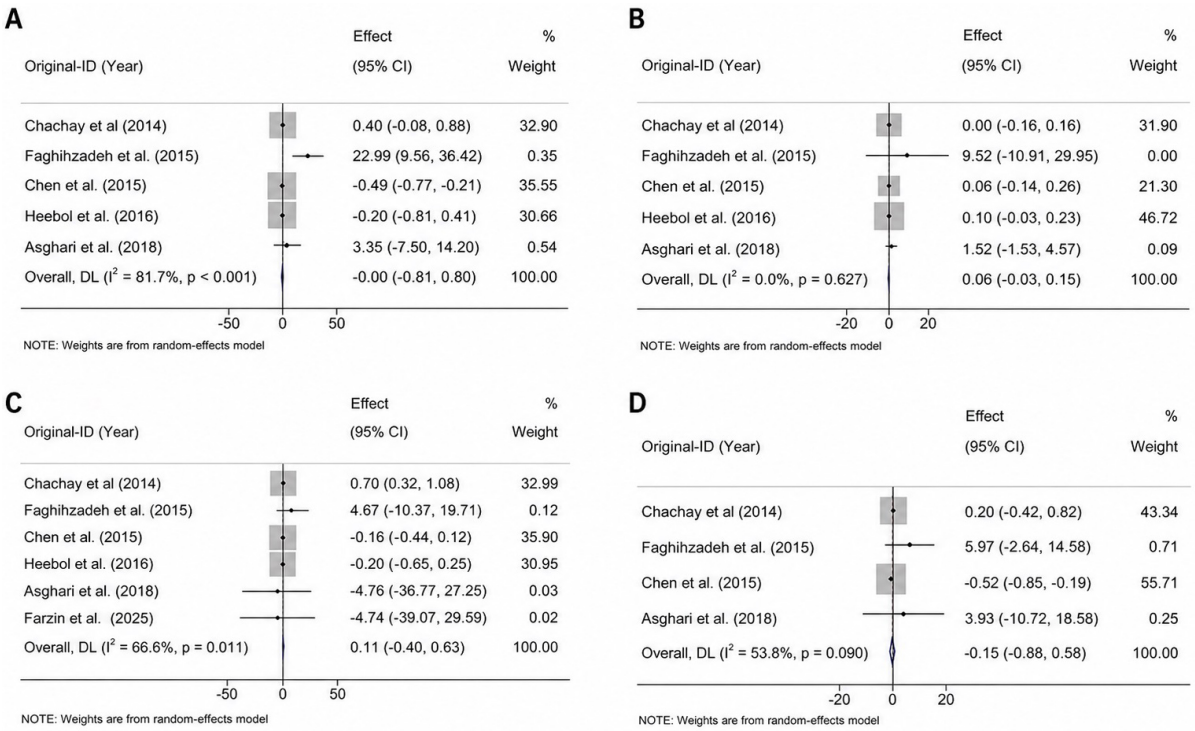

Fig. 4. Forest plot of the impact of resveratrol supplementation on LDL-C (A), HDL-C (B), TG (C), and TC (D).

comparatively high amount of heterogeneity was observed among the trials (I^2 = 66.6%, $P_{heterogeneity}$ = 0.011). Moreover, subgroup analyses showed that the year of publication, sample size, and resveratrol intake duration did not impact the obtained effect (Table 3). Sensitivity analyses were performed, and the estimated ES remained unchanged if each of the studies was excluded (**Supplementary Fig. 8A**). There was no small study effect upon the Begg test reports (p = 0.573). Nevertheless, due to an irregularity on the funnel plot, a trim and fill test was performed with seven trials (one imputed), which did not change the findings (**Supplementary Fig. 8B**).

The total cholesterol (TC) concentration of NAFLD patients did not substantially decrease following resveratrol administration, according to the meta-analysis of four trials (WMD = –0.15 mg/dL, 95% CI (–0.88, 0.58), p = 0.817), along a modest variety (I^2 = 53.8%, $P_{heterogeneity}$ = 0.090) (Fig. 4D). There was no discernible small study effect by the Begg test (p = 1.000).

3.4.4 Effects of Resveratrol Intake on Inflammatory Factors

The impact of resveratrol intervention on tumor necrosis factor α (TNF-α) as an inflammatory factor was reported by four RCTs comprising 156 participants with NAFLD. Combining their findings indicated that after the intervention, patients in the resveratrol group had lower TNF-α levels than those in the placebo group (WMD = –0.31, 95% CI (–0.87, 0.25), p = 0.274) (Fig. 5A), along with relatively low heterogeneity (I^2 = 46.6%, $P_{heterogeneity}$ = 0.132).

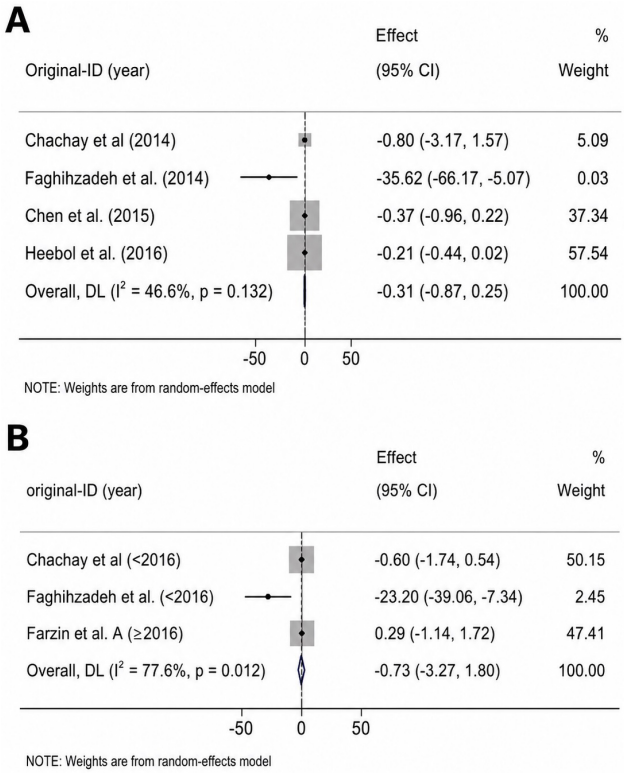

Fig. 5. Forest plot of the impact of resveratrol supplementation on TNF-α (A) and hs-CRP (B).

Pooling the results of three trials showed that resveratrol supplementation did not significantly decrease the lev-

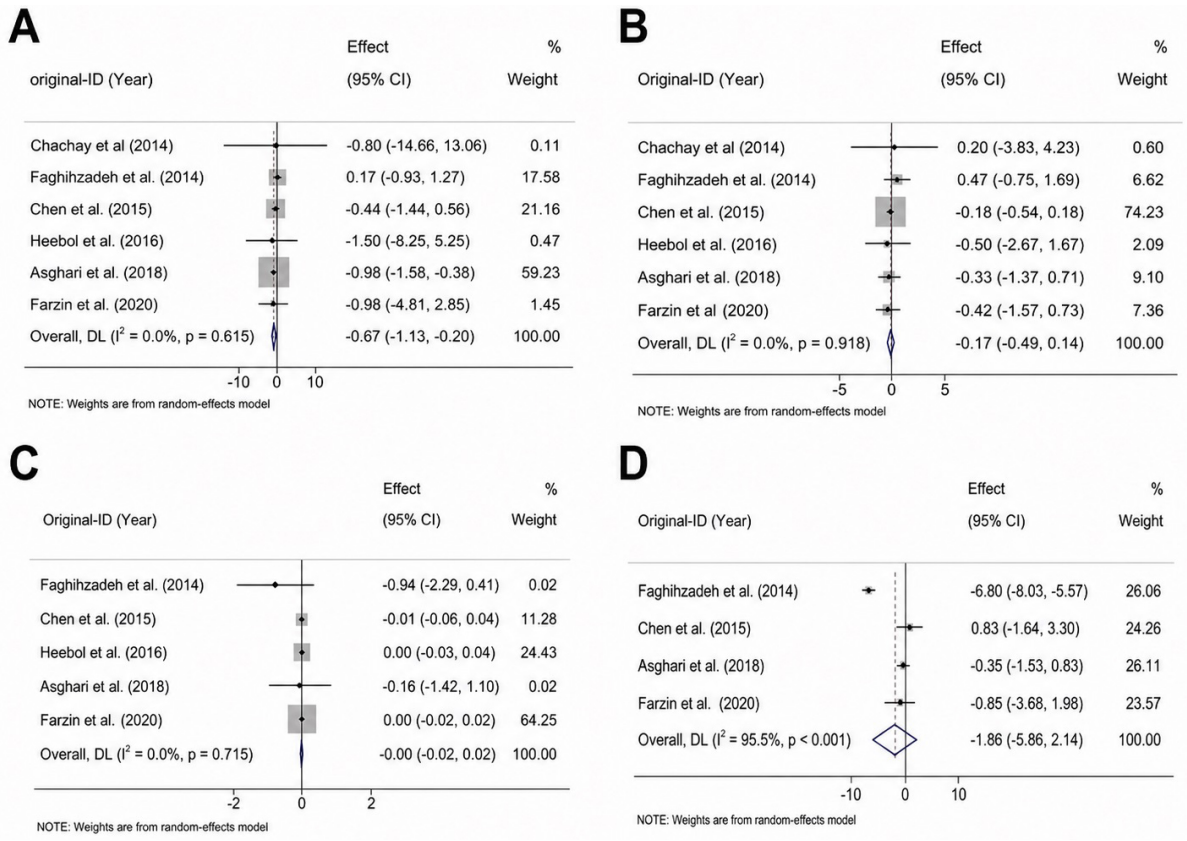

Fig. 6. Forest plot of the impact of resveratrol supplementation on body weight (A), BMI (B), WHR (C), and WC (D).

els of high-sensitivity C-reactive protein (hs-CRP) in subjects with NAFLD (WMD = –0.73, 95% CI (–3.27, 1.80), $p = 0.274$; $I^2 = 77.6\%$, $P_{heterogeneity} = 0.012$) (Fig. 5B).

3.4.5 Effects of Resveratrol on Anthropometric Indices

Seven SRMAs of six RCTs of 266 participants with NAFLD assessed the effect of resveratrol supplementation on body weight. Assembling their findings revealed that the body weight of participants significantly reduced by resveratrol intervention (WMD = –0.67, 95% CI (–1.13, –0.20), $p = 0.005$) (Fig. 6A) with a minor variation ($I^2 = 0.0\%$, $P_{heterogeneity} = 0.615$). Additionally, subgroup analysis showed that resveratrol impact was considerable in studies published after 2016 (WMD = –0.984, 95% CI: –1.574, –0.394), with sample sizes greater than 50 (WMD = –0.611, 95% CI: –1.148, –0.073), and with intervention doses less than 1000 mg/day (WMD = –0.611, 95% CI: –1.148, –0.073) (Table 3). Upon the sensitivity analysis, the obtained results became non-significant following the omission of the study by Asghari et al. [34] (WMD = –0.209, 95% CI: –0.931, 0.512) (**Supplementary Fig. 9A**). The Begg test findings showed that publication bias was insignificant ($p = 0.851$). Nevertheless, the trim-and-fill method was applied with eight trials (two imputed) because an asymmetry was observed in the funnel plot. Interestingly, the results became non-significant (WMD = –0.559, 95% CI: –1.165, 0.047) (**Supplementary Fig. 9B**).

Seven SRMAs of six RCTs, including 266 patients with NAFLD, reported resveratrol intervention effects on the BMI of participants. Pooling their results revealed that BMI of the patients did not decrease significantly following resveratrol intake (WMD = –0.17, 95% CI (–0.49, 0.14), $p = 0.280$) with a negligible heterogeneity ($I^2 = 0.0\%$, $P_{heterogeneity} = 0.918$) (Fig. 6B). Subgroup analyses indicated that the year of publication, sample size, and dose of resveratrol of the RCTs did not impact on the obtained effects (Table 3). Moreover, removing each study using the sensitivity analysis did not significantly change the final results (**Supplementary Fig. 10A**). The Begg test results indicated no evidence of small study effect ($p = 0.573$), but an irregularity was shown on the funnel plot. Thus, a trim and fill procedure was followed without imputing a new study (**Supplementary Fig. 10B**).

Five RCTs that were involved in five SRMAs evaluated the effect of resveratrol on the waist-to-hip ratio (WHR) of 246 patients with NAFLD. Combining their findings indicated that resveratrol intake did not significantly decrease WHR (WMD = –0.00, 95% CI (–0.02, 0.02), $p = 0.970$) of participants with a minor variety ($I^2 = 0.0\%$, $P_{heterogeneity} = 0.715$) (Fig. 6C). The sensitivity analysis indicated no significant change on the ES following excluding each trial (**Supplementary Fig. 11A**). Based on the Begg test, no considerable publication bias was seen ($p = 0.142$). However, an asymmetry was detected on the fun-

nel plot; hence, we conducted the trim and fill test with seven studies (two imputing), and the results did not change (**Supplementary Fig. 11B**).

In addition, pooling the results of four RCTs comprising 195 patients revealed that resveratrol intake did not significantly reduce the waist circumference (WC) of NAFLD patients (WMD = –1.86, 95% CI (–5.86, 2.14), p = 0.362) with a considerable variation (I^2 = 95.5%, $P_{heterogeneity}$ <0.001) (Fig. 6D).

4. Discussion

Non-alcoholic steatohepatitis (NASH) as one of the most common liver diseases, can result in liver cirrhosis, which is the main cause of hepatocellular carcinoma. An updated term for NAFLD is metabolically-dysfunction-associated steatotic liver disease (MASLD), which is a systemic disease linked to inflammation and metabolic disorders like T2DM and dyslipidemia [41]. It is a silent disease with ambiguous or nonexistent symptoms that endangers people's quality of life as well as the general public's health [42]. Therefore, its treatment and prevention play an important role in the hepatology of those disease types [1,43,44]. Due to the lack of suitable and approved medications for NAFLD, modification of lifestyle-related factors, such as nutrition, was recommended. It is indicated that resveratrol, a polyphenol rich in antioxidant properties, inhibits lipid accumulation, reducing TG levels in serum, and enhancing insulin sensitivity, seems to be a safe, natural, and efficient alternative treatment for NAFLD, especially when it results from obesity and/or insulin resistance [43,44,45]. The current umbrella review comprehensively summarized the previous SRMAs' findings regarding resveratrol supplementation impacts on liver enzymes, glycemic indices, inflammatory factors, lipid profiles, and anthropometric measures in 266 patients with NAFLD.

The hepatic enzymes serum levels are considered indicators of the progression of NAFLD because of their association with liver damage [46]. Previous research has reported different results regarding the effects of resveratrol administration on liver enzymes. However, pooling their findings in this umbrella meta-analysis revealed that resveratrol administration reduced serum ALT concentrations in subjects with NAFLD in comparison with the control group. Nevertheless, the impacts of resveratrol intervention on AST and GGT concentrations were not significant in these patients. ALT, one of the hepatic enzymes, is a key biomarker of hepatocellular injury, suggesting potential hepatoprotective effects [33]. Since elevated ALT levels are a sign of liver damage or injury, they are crucial for both diagnosing and tracking the development of liver disorders and conditions [47,48,49]. The beneficial effects of resveratrol in reducing ALT levels may be because of its capacity to influence hepatic apoptotic processes and halt the progression of fatty liver disease [43,45]. Resveratrol has been shown in a meta-analysis of preclinical research to have therapeutic promise for hepatic fibrosis and hepatoprotective benefits by reducing ALT and AST levels and elevated albumin expression [50]. Additionally, it has been suggested that the renin-angiotensin system (RAS) has a significant part in developing liver illnesses such as NAFLD and metabolic syndromes [51,52]. NAFLD has been linked to an imbalance between the RAS axis [53]. Hepatic steatosis, oxidative stress, inflammation, insulin resistance, and fibrosis all increase when the RAS axis is activated by reducing fatty acid oxidation [53,54,55]. NAFLD is thought to be improved by blocking this axis [53,56]. Resveratrol's capacity to modulate the RAS axis in several pathological conditions may contribute to its beneficial effects in patients with NAFLD [57]. This suggests that resveratrol medication reduces the risk of NAFLD onset and progression [29], possibly by modulating ALT levels. However, the rather small number of included studies in this regard and the variety among them prevent the clear demonstration of resveratrol's ability to improve liver function and relieve NAFLD; and resveratrol's effects on other enzymes have been less well established.

Evidence demonstrated that several factors, including insulin resistance, pro-inflammatory cytokines, and obesity, greatly contribute to the NASH process and result in metabolic abnormalities in subjects with NAFLD. Management of these underlying factors could be a useful approach in NAFLD control [58,59,60,61]. According to the findings of this study, the effects of resveratrol on glycemic factors in individuals with NAFLD were not considerable. However, the evidence suggests that resveratrol treatment could improve glycemic control, perhaps by enhancing cellular oxidative stress, triggering inflammatory pathways, and inhibiting inflammatory gene expression, which can prevent inflammation [62,63]. Moreover, it is indicated that resveratrol treatment leads to the activation of AMP-activated protein kinase (AMPK) and SIRT1, which leads to enhanced insulin sensitivity and reduced hepatic gluconeogenesis [64,65]. Additionally, resveratrol, by enhancing Insulin Receptor Substrate-1/Phosphoinositide 3-kinase/Protein Kinase B (IRS-1/PI3K/Akt) pathway activity, enhances skeletal muscle and adipose tissue glucose uptake [66].

According to the findings, administration of resveratrol did not improve the lipid profile concentrations. Nevertheless, it is indicated that resveratrol has a hypocholesterolemic effect because of its phenolic hydroxyl compounds [67]. There are some possible mechanisms through which resveratrol could improve lipid profile, such as promoting the neutral sterols and bile acids excretion from the liver to the stool [68,69]. In fact, enhancing the amount of lipid secretion from the body is one of the ways to reduce the lipid profile with resveratrol [70]. During resveratrol transition through the gut, it is taken up by the liver and is metabolized to resveratrol glucuronide [71,72,73,74]. Resveratrol glucuronide can decrease the synthesis of cholesterol in the

liver [75]. Additionally, it causes unsaturated fatty acids oxidation and reduces circulating cholesterol levels [67].

This meta-analysis indicated that resveratrol intake did not decrease TNF-α or hs-CRP levels in NAFLD patients. The absence of significant improvements in inflammatory cytokines suggests that resveratrol's effects may be localized within hepatic tissue and not reflected systemically. It was reported that resveratrol may inhibit the nuclear factor kappa beta signaling pathway and reduce proinflammatory cytokines that cause insulin resistance [76]. On the other hand, resveratrol could decrease oxidative stress by chelation of metal catalysts, inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and activation of antioxidant enzymes [77]. These support the hypothesis that resveratrol may alleviate liver oxidative stress and inflammation, both of which are central in NAFLD pathogenesis and hepatocyte damage [78].

Some of the previous studies reported the improvement in obesity measures following resveratrol intervention [34,79]. Combining their findings in this study indicated a considerable decrease in the body weight of patients following resveratrol supplementation, but not in BMI and abdominal obesity. Reduction in body weight of participants was aligned with the evidence showing that resveratrol may influence energy metabolism and adipogenesis [80,81]. According to research on animals, resveratrol consumption may reduce weight gain by increasing energy expenditure [8,82,83]. It was shown that resting metabolic rate increased after resveratrol administration through inducing gene expression of skeletal muscle *SIRT1* and *AMPK*, which suggests potential beneficial exercise-mimetic effects [84]. Moreover, it was reported that resveratrol has anti-obesity effects on white adipose tissue via different mechanisms, including induction of adipocyte apoptosis, promotion of white adipocytes browning, a reduction in fat accumulation and adipogenesis, inhibiting the proliferation and differentiation of preadipocytes, and upregulation of miRNAs that contribute to the triacylglycerol metabolism in white adipose tissue and antiadipogenic [85,86]. It should be noted that the inconsistency in central obesity outcomes could be explained by differences in baseline anthropometric characteristics, dietary intake, and lifestyle behaviors that were not uniformly controlled across studies [87]. Regarding BMI, the effects of resveratrol were also inconsistent with body weight. Because BMI is a measurement of body fat according to height and weight, presenting the overall body weight and composition, these impacts might take longer to show up.

These findings indicate that while resveratrol may benefit hepatic health by decreasing ALT levels and promoting weight reduction, its broader metabolic effects in NAFLD populations remain unclear or inconsistent. These discrepancies in the existing evidence may be connected to various study designs, participants' characteristics such as baseline metabolic status, lifestyle and diet, comorbid conditions, formulations and dosages of resveratrol, and duration of supplementation. Therefore, future trials should consider these points, especially the anthropometric characteristics of participants, to clarify the effects of resveratrol on patients with NAFLD.

5. The Strengths and Limitations

This study has certain advantages and disadvantages. Two separate authors conducted a thorough, systematic search for the current umbrella meta-analysis. Furthermore, we pooled the results of RCTs rather than the meta-analyses to prevent overlap of the original RCTs' results included in more than one meta-analysis. However, the RCTs' heterogeneity was relatively high, which was likely because of different intervention dosages and durations among the studies. The findings of the publication bias assessments (Begg's test and funnel plots) and subgroup analyses should be interpreted with caution, as they involved a relatively small number of studies.

6. Conclusion

The findings suggest that resveratrol intervention may have modest effects on ALT levels and body weight in adults with NAFLD; nevertheless, the evidence is limited and inconsistent. The effects of resveratrol in modulating glycemic indices, inflammatory factors, lipid profiles, BMI, and central obesity of NAFLD patients were not considerable. Therefore, well-designed RCTs are necessary to recognize the accurate roles of resveratrol in these patients.

Availability of Data and Materials

Upon reasonable request, the corresponding author [rafrafm@tbzmed.ac.ir] will provide the supporting data for the study's conclusions.

Author Contributions

All authors contributed to the conception and design of this review umbrella. RMG and SS carried out the search and data extraction, and RMG wrote the first draft of the manuscript. MR and AAE commented on the previous version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Ethical Committee of Tabriz University of Medical Sciences, Tabriz, Iran (ethical code: IR.TBZMED.VCR.REC.1403.280), the vice-chancellor, and the Nutrition Research Center of Tabriz University of Medical Sciences, Tabriz, Iran (ID: 75526) accepted and registered the study's protocol.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR48116.

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