

Review Article

The Effects of Grape/Grape Products on Inflammatory and Oxidative Stress Markers: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background. A growing body of evidence has demonstrated the multiple effects of the individual phenolic antioxidants of grapes. However, it is not clear whether grape and its derivatives exert anti-inflammatory effects. In this systematic review and meta-analysis, we sought to examine the effects of grape/grape products on inflammation and oxidative stress in adults. **Methods.** This study has been conducted based on the PRISMA checklist. A systematic literature search in PubMed, Scopus, ISI Web of Science, and the Cochrane Library was conducted, from inception until January 2022, to identify eligible trials. Mean differences and standard deviations were pooled using random-effects models. **Results.** Twenty-nine eligible trials were included. Grape and its products significantly increased the catalase activity ($n = 3$ studies, 64 participants; WMD = 5.49 U/mg protein, 95% CI: 4.76, 6.22; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.98), oxygen radical absorbance capacity ($n = 5$ studies, 206 participants; WMD = 90.06 $\mu\text{mol/l TE}$, 95% CI: 35.97, 144.15; $P = 0.001$; $I^2 = 35.6\%$; P-heterogeneity = 0.18), and total antioxidant capacity ($n = 4$ studies, 224 participants; WMD = 62.48 $\mu\text{mol/l}$, 95% CI: 31.62, 93.33; $P < 0.001$; $I^2 = 55.2\%$; P-heterogeneity = 0.08) and decreased thiobarbituric acid reactive substances levels ($n = 5$ studies, 153 participants; WMD = -0.17 nmol/mg, 95% CI: -0.31 , -0.03 ; $P = 0.02$; $I^2 = 34.2\%$; P-heterogeneity = 0.19). No significant change was observed for inflammatory markers. **Conclusion.** Although grape/grape products elicited increases in antioxidant agents, they had no significant effect on inflammatory factors. This may be related to the low levels of baseline inflammatory factors, as none of the included studies enrolled patients with acute inflammation. Further well-designed studies are warranted to examine grape's efficacy on inflammation and oxidative stress.

1. Introduction

Reactive oxygen species (ROS) are produced in the cells in small quantities [1] as a consequence of physiological oxidative metabolism, mitochondrial bioenergetics, and immune function [2]. They act as a regulatory agent in the signaling pathways including gene expression, receptor activation, and signal transduction as well as cell

differentiation, cell growth, metabolic adaptation, and immune responses [3]. The excess production of ROS in the cells which exceeds the ability of the antioxidant system to neutralize them is known as oxidative stress [4], which can damage cellular molecules including lipids, protein, and DNA [5]. Oxidative stress also activates various inflammatory processes, such as nuclear factor κB (NF- κB) and activating protein-1 (AP-1), leading to the synthesis and

secretion of pro-inflammatory cytokines [6]. Oxidative stress and inflammation have been shown to be associated with, and implicated in, various diseases including, diabetes, cardiovascular diseases [5], cancer, neurodegenerative diseases, and arthritis [7].

The cumulative evidence shows that dietary polyphenols are able to exert antioxidant activity, ROS scavenging properties, and anti-inflammatory functions which can alter the expression of pro-inflammatory cytokines [8]. Therefore, a possible approach to reduce oxidative stress [9] and inflammation is to add polyphenol-rich foods, such as grape or its products, to the diet [6]. Grapes are the major source of phenolic acids, proanthocyanidins, anthocyanins, flavonoids, and stilbenes [10]. The most common grape-derived products include raisins, juices, and wines [6], which are also reported to have a high nutraceutical level and are on the market in the form of powders, dried, and concentrated extracts [6, 9]. It has been shown that grape and its product consumption can reduce the risk factors for cardiovascular and neurodegenerative disease, diabetes, cancer, and cognitive decline [11].

The results of the human randomized controlled trials (RCTs) investigating the effect of grape and its products on inflammation and oxidative markers are controversial. For instance, a few studies have shown improvement in some inflammatory and oxidative stress biomarkers [12–14], while others have reported unchanged levels [15–17]. It is worth mentioning that recent meta-analyses on the effects of grape products on inflammation and oxidative stress are also equivocal. Indeed, some meta-analysis studies have reported significant benefits of grape polyphenols, grape seed extract, or grape products on CRP levels, total antioxidant activity (TAC), malondialdehyde (MDA), oxidized low-density lipoprotein (ox-LDL), and hs-CRP levels [18–20]. However, no significant effect on interleukin-6 (IL-6), tumor necrosis factor α (TNF- α), superoxide dismutase (SOD), oxygen radical absorbance capacity (ORAC), and glutathione peroxidase (GPx) has been observed [18, 19, 21].

A serious criticism of prior studies is that they did not examine the effects of whole grape fruit or its products. Moreover, grape derivatives such as extracted polyphenols or grape seed extract were included in the same analysis along with fresh grape. Therefore, ascertaining whether whole grape fruit and its products can be effective on inflammatory factors is still unanswered.

Therefore, we sought to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the effect of whole grape/grape products on inflammatory and oxidative markers in adults.

2. Methods

The present systematic review and meta-analysis was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The protocol of the present study was registered at the International Prospective Register for Systematic Reviews (PROSPERO) database (ID of CRD42022349904).

2.1. Search Strategy and Study Selection. To identify relevant studies, a systematic search was conducted in PubMed, Scopus, ISI Web of Science, and the Cochrane Library, from database inception to January 2022, without any restrictions for language or publication date. A combination of MeSH and non-MeSH terms related to “grape” and “study design” was applied. Further details on the search strategy and PICO components are provided in Tables S1 and S2, respectively. In addition, reference lists of all included studies were screened manually in order to find additional eligible trials.

2.2. Eligibility Criteria. Original randomized clinical trials with parallel or crossover design investigating the effects of grape or its products in comparison with a control/placebo group were eligible for inclusion in this study if they were conducted on an adult population (age >18 years), lasted for a 2-week intervention or more, and reported at least one of our key outcomes (including serum levels of oxidative stress (ox-LDL; MDA, SOD, ORAC, GPX, nitric oxide (NO), advanced oxidation protein products (AOPPs), thiobarbituric acid reactive substances (TBARSs), catalase (CAT), and Trolox equivalent antioxidant capacity (TEAC)) and inflammatory markers (TNF- α , hs/CRP, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1), and C3 protein) as mean \pm standard deviation (SD) (or other statistics that can be converted to mean \pm SD)), before/after or change during the study.

The exclusion criteria were as follows: (1) trials that administered grape seed, resveratrol, or any individual ingredient of grape; (2) trials conducted on pregnant or lactating women; and (3) trials that administered multiple intervention components that independent effect of grape/grape products could not be determined.

The initial abstract and full-text screening of all retrieved studies were executed independently by two authors (SS and RKM) according to inclusion and exclusion criteria, and disagreements were resolved by consensus with the third author (SA).

2.3. Data Extraction. Two authors (FD and SS) extracted the following data from eligible studies: (1) study characteristics including first author’s name, publication year, study location, study design, sample size, follow-up duration, type of intervention (grape, raisin, grape juice or powder), placebo, and dosage of intervention; (2) participant characteristics including sex, age, and health status; and (3) mean/SD or other convertible data of antioxidants and inflammatory markers before/after intervention or mean changes/SD during the follow-up period. Disagreements were resolved by consensus with the third author (SA). The dose of grape products was converted to cup equivalent unit using Food Patterns Equivalents Database (FPED) [23], to make the dose data of grape products comparable between trials.

PlotDigitizer software (<https://plotdigitizer.sourceforge.net/>) was used for extracting data only obtainable in graphical formats. The units of antioxidants and inflammatory markers were unified before analysis. For studies that administered multiple dosages or follow-up durations, the higher dosage or duration was included in the analysis.

2.4. Quality Assessment. The Cochrane risk of the bias tool for RCTs was used to assess the risk of bias based on the following six parameters: selection bias, performance bias, detection bias, attrition bias, reporting bias, and bias due to problems not covered elsewhere [24]. The eligible studies were classified as low risk, high risk, and unclear. Studies with low risk of bias for all criteria were judged as good quality, studies with one criterion not met or two criteria unclear were judged as fair quality, and studies with high risk of bias for two or more criteria were judged as poor quality.

2.5. Quality of Meta-Evidence. The quality of meta-evidence was assessed by applying the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [25, 26]. Data from RCTs were initially considered high quality and might be downgraded considering the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence for each outcome was classified as high, moderate, low, or very low. Two authors (RKM and SS) independently assessed the quality of evidence, and disagreements were resolved by consensus with the third author (SA).

2.6. Statistical Analysis. The effect of grape products on the change in the outcomes of inflammation (hs-CRP, TNF- α , IL-6, IL-10, and monocyte chemoattractant protein-1 (MCP-1)) and oxidative stress (ox-LDL), ORAC, thiobarbituric acid reactive substances (TBARSs), TAC, carbonyl, MDA, catalase (CAT), and SOD were examined. We applied analysis for the outcomes, when three studies or more reported data. The mean differences (MDs) and their corresponding 95% confidence interval (CI) between intervention and control groups were used to calculate the effect size. For studies that did not report change values, SDs were calculated according to the formulas suggested by the Cochrane Handbook of Systematic Review [27]. For all inflammatory and oxidative stress markers, we used a correlation coefficient of 0.5, with the exception of MDA, which was 0.48. Weighted mean differences (WMDs) and their SDs were calculated by using the DerSimonian and Laird random-effects model [28]. Due to the small number of included studies for each outcome, a modified method for random-effects meta-analysis (the Hartung–Knapp–Sidik–Jonkman method) was used to reduce the error rate [29].

To evaluate the statistical heterogeneity between the studies, Cochran's Q test and I^2 statistic (I^2) were used [30]. In order to detect the sources of heterogeneity, predefined subgroup analyses were conducted for potential factors including sex (male, female, both), participants' health status (healthy, metabolic syndrome, cardiovascular disease, and hemodialysis), study type (parallel, crossover), duration of intervention (≤ 12 wk, > 12 wk), intervention type (fresh grape, dried grape (including pomace, raisin, powder), and grape extract (including juice, concentrate, extract)), dosage (< 150 gr, ≥ 150 gr), study location (Asia, Europe, USA, and south USA), and quality of studies (unclear, low, and high). Sensitivity analysis was conducted by the leave-one-out method to determine whether a single trial affects the overall

effect size [31]. For outcomes with at least 10 trials, publication bias was evaluated by the visual inspection of the funnel plot and assessed statistically by Begg's adjusted rank correlation and Egger's regression asymmetry tests [32]. In addition, meta-regression analysis was conducted to explain the between-study variation based on the dose and duration of the intervention. The effect of other variables could not be assessed, due to the incomplete data. Statistical analyses were performed using STATA version 17 (StataCorp). Two-sided P values < 0.05 were considered statistically significant.

3. Results

3.1. Study Selection and Characteristics. Our primary search identified 8610 potentially relevant references. After excluding duplicates ($n = 3426$) and initial screening, 100 records remained for the full-text screening. Finally, 29 articles were considered eligible for inclusion in the analyses and reported the following outcomes: hs-CRP ($n = 15$), TNF- α ($n = 10$), IL-6 ($n = 10$), MCP-1 ($n = 3$), ox-LDL ($n = 10$), ORAC ($n = 5$), TBARS ($n = 5$), TAC ($n = 4$), Carbonyl ($n = 3$), MDA ($n = 4$), CAT ($n = 3$), and SOD ($n = 3$) (Figure 1). The reviewers' agreement for including studies was high at the abstract screening (Cohen's kappa = 0.76) and full-text screening (Cohen's kappa = 0.81) phases.

Excluded studies, along with the reasons for exclusion, are shown in Supplemental Table 3.

The general characteristics of the included studies are summarized in Table 1. Studies were conducted in the USA [14, 16, 17, 34, 38, 39, 42, 47, 49, 50], Spain [12, 35, 36, 46, 52, 55], Greece [13, 43, 44], Brazil [15, 37, 41, 53], Iran [48, 51], France [45], Turkey [33], Canada [40], and Israel [54]. Nineteen studies had a parallel design [12, 13, 15, 33, 35–37, 40, 42–44, 47, 48, 50–55], and 10 had a crossover design [14, 16, 17, 34, 38, 39, 41, 45, 46, 49]. The duration of the intervention ranged from 2 to 52 weeks. The included studies administered grape ($n = 1$) [48], grape powder ($n = 6$) [14, 16, 17, 34, 39, 54], grape extract ($n = 4$) [40, 45, 52, 55], grape juice ($n = 11$) [12, 15, 35–38, 41, 42, 45, 50, 53], raisin ($n = 5$) [43, 44, 47, 49, 51], currants ($n = 1$) [13], and grape pomace ($n = 1$) [46]. All the included studies were conducted in both sexes, except for three studies that were exclusively conducted on women [14, 37] and men [34]. Fourteen studies enrolled healthy participants [14, 16, 17, 33, 37, 41, 42, 44, 45, 47, 49, 50, 53, 55], and others recruited patients with metabolic syndrome [34, 39, 46], hemodialysis [12, 35, 36], prediabetes /diabetes [40, 43], hypertension [38, 54], hyperlipidemia [48, 51], nonalcoholic fatty liver disease (NAFLD) [13], Parkinson [15], and stable coronary artery disease [52]. One study also reported the results in postmenopause and premenopause women separately; the effect sizes of both were included in the analysis [14].

3.2. Quality Assessment. The methodological quality of the included studies was assessed using the Cochrane collaboration tool. We found eight studies to have a good quality design [37, 40, 41, 44, 45, 50, 52, 54]: one study had fair quality [38] and the remaining had poor quality [12–17, 33–36, 39, 42, 43, 46–49, 51, 53, 55]. The most

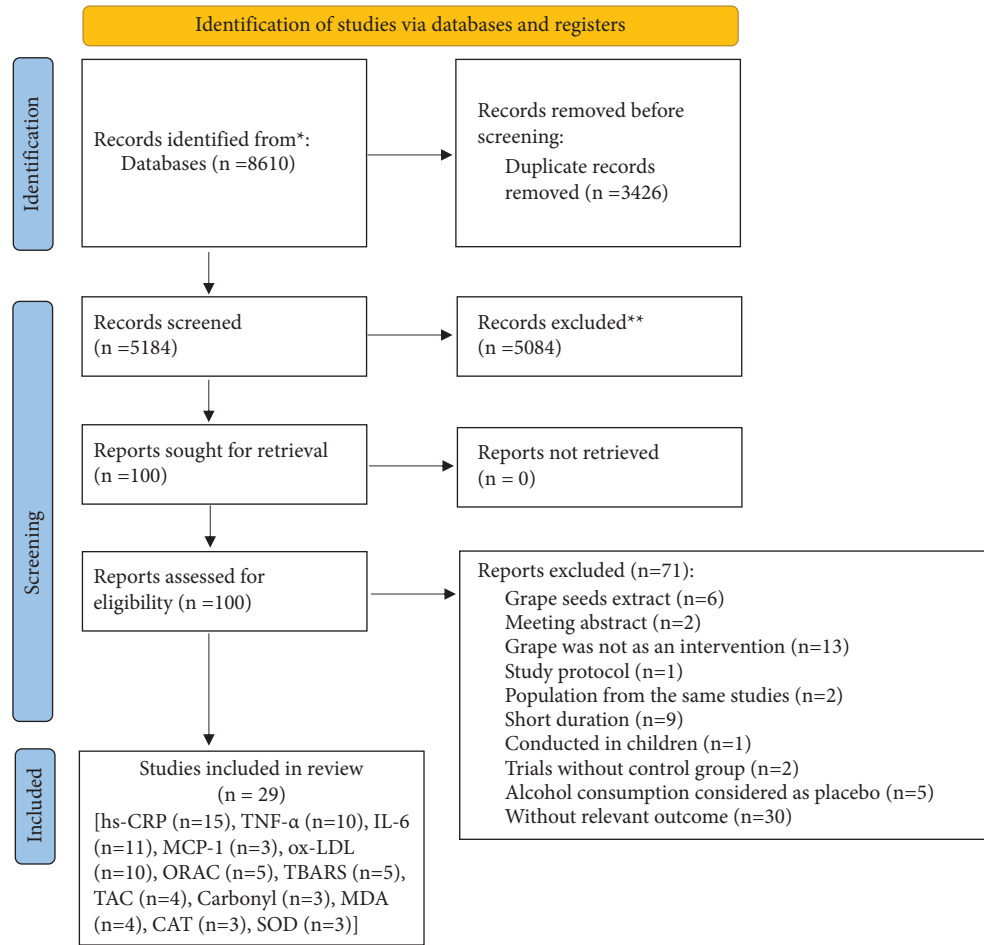


FIGURE 1: PRISMA flowchart of the selected trials.

contributing factors were random sequence generation and allocation concealment, details of the process of which were not explained (Table S4).

The GRADE assessment system showed that the quality of evidence was very low for the effect of grape products on carbonyl, ox-LDL, MDA, SOD, total antioxidant capacity (TAC), TNF- α , and MCP-1 and low for the remaining outcomes (catalase, ORAC, TBARS, hs-CRP, and IL-6) (Table S5).

4. Meta-Analysis

4.1. The Effect of Grape/Grape Products on Inflammatory Markers. Our results showed that grape/whole grape products had no significant effect on hs-CRP ($n = 15$ studies, 659 participants; WMD = -0.01 mg/L, 95% CI: $-0.14, 0.11$; $P = 0.82$; $I^2 = 0\%$, 95% CI: 0, 52; P-heterogeneity = 0.59) (Figure 2(a)), IL-6 ($n = 10$ studies, 310 participants; WMD = -0.04 pg/ml, 95% CI: $-0.44, 0.36$; $P = 0.85$; $I^2 = 0\%$, 95% CI: 0, 60; P-heterogeneity = 0.99) (Figure 2(b)), TNF- α ($n = 10$ studies, 310 participants; WMD = -0.04 pg/ml, 95% CI: $-0.25, 0.17$; $P = 0.68$; $I^2 = 70.8\%$, 95% CI: 46, 84; P-heterogeneity < 0.001) (Figure 2(c)), and MCP-1 ($n = 3$ studies, 55 participants; WMD = -4.96 pg/ml, 95% CI: $-14.04, 4.13$; $P = 0.28$; $I^2 = 0\%$, 95% CI: 0, 90; P-heterogeneity = 0.50) (Figure 2(d)).

The results of the subgroup analysis are presented in Tables S6–S8. The subgroup analysis revealed a significant reduction in hs-CRP levels following grape extract supplementation ($n = 5$ studies, 192 participants; WMD = -0.52 mg/L, 95% CI: $-0.99, -0.04$; $P = 0.03$; $I^2 = 0\%$; P-heterogeneity = 0.74) (Table S6). Moreover, TNF- α levels reduced in RCTs with crossover design ($n = 6$ studies, 140 participants; WMD = -0.17 pg/ml, 95% CI: $-0.32, -0.02$; $P = 0.03$; $I^2 = 0\%$; P-heterogeneity = 0.76), when intervention lasted for less than 12 weeks ($n = 7$ studies, 200 participants; WMD = -0.16 pg/ml, 95% CI: $-0.24, -0.09$; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.84), when grape extract was used ($n = 2$ studies, 110 participants; WMD = -0.16 pg/ml, 95% CI: $-0.25, -0.07$; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.61), in studies that were conducted in the USA ($n = 6$ studies, 188 participants; WMD = -0.16 pg/ml, 95% CI: $-0.31, -0.01$; $P = 0.03$; $I^2 = 0\%$; P-heterogeneity = 0.75), and when studies enrolled healthy subjects ($n = 5$ studies, 157 participants; WMD = -0.16 pg/ml, 95% CI: $-0.24, -0.09$; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.99) (Table S7).

4.2. The Effect of Grape/Grape Products on Oxidative Stress Markers. Grape/grape products showed a significant increase in levels of catalase ($n = 3$ studies, 64 participants;

TABLE 1: Characteristics of eligible randomized controlled trials that investigated the effect of the grape and its products on inflammatory and oxidative stress biomarkers in adults.

Author (year)	Country	Sample size/sex	Mean age intervention/control	Duration (week)/study design	Population characteristics	Type of intervention (gr/day)	Intervention in placebo group (gr/day)	Outcomes
Amoutzopoulou et al. (2013) [33]	Turkey	89 (high hardaliye: 39 Low hardaliye: 33 C: 17)/both	High hardaliye: 37.44 Low hardaliye: 32.79 C: 34.18	6/P	Healthy adults	High hardaliye (500)/Low hardaliye (250)	Not receiving intervention	↔TAC ↓MDA
Bardagjy et al. (2018) [16]	USA	20 (I: 20, C: 20)/both	48.6	4/C	Healthy obese	Freeze-dried whole grape powder (60)	Placebo	↔CRP ↔IL-6 ↔MCP-1 ↔ox-LDL ↔TNF-a
Barona et al. (2012) [34]	USA	24 (I: 40, C: 38)/M Dyslipidemia: 11 Nondyslipidemia: 13	Dyslipidemia: 48.1 Nondyslipidemia: 53.9	4/C	Metabolic syndrome	Lyophilized whole grape powder (46)	Macronutrient-matched placebo	↔TNF-a ↔IL-6 ↔IL-8 IL-10 (Dyslipidemia: ↓ Non-dyslipidemia: ↑)
Castilla et al. (2006) [12]	Spain	38 (I: 26, C: 12)/both	62/59.2	2/P	Hemodialysis	Concentrated red grape juice (100)	Not receiving intervention	↓ ox-LDL ↑TEAC ↓MCP-1 ↔CRP
Castilla et al. (2008) [35]	Spain	16 (I: 8, C: 8)/both	Range: 33–79 y	2/P	Hemodialysis	Concentrated red grape juice (1000)	Not receiving intervention	↓ ox-LDL ↓MCP-1 ↔CRP
Corredor et al. (2016) [36]	Spain	39 (I: 25, C: 14)/both	66.16/59.71	24/P	Hemodialysis	Unfermented grape juice (100)	Not receiving intervention	↔CRP ↔TBARS ↔Carbonyl ↔SOD ↔CAT ↓IL-6
Dani et al. (2020) [37]	Brazil	20 (I: 10, C: 10)/F	68/72	4/P	Healthy elderly women	Grape juice and exercise (400)	Placebo and exercise	↔TBARS ↔Carbonyl ↔CAT ↔GPX ↔SOD
De Oliveira et al. (2021) [15]	Brazil	19 (I: 10, C: 9)/both	68.33/65.5	4/P	Parkinson	Grape juice (400) + aquatic exercise	No grape juice + aquatic exercise	↔TBARS ↔Carbonyl ↔CAT ↔GPX ↔SOD
Dohadwala et al. (2010) [38]	USA	59 (I: 59, C: 59)/both	40/44	8/C	Prehypertension and stage 1 hypertension	Grape juice (595)	Placebo juice	↔CRP

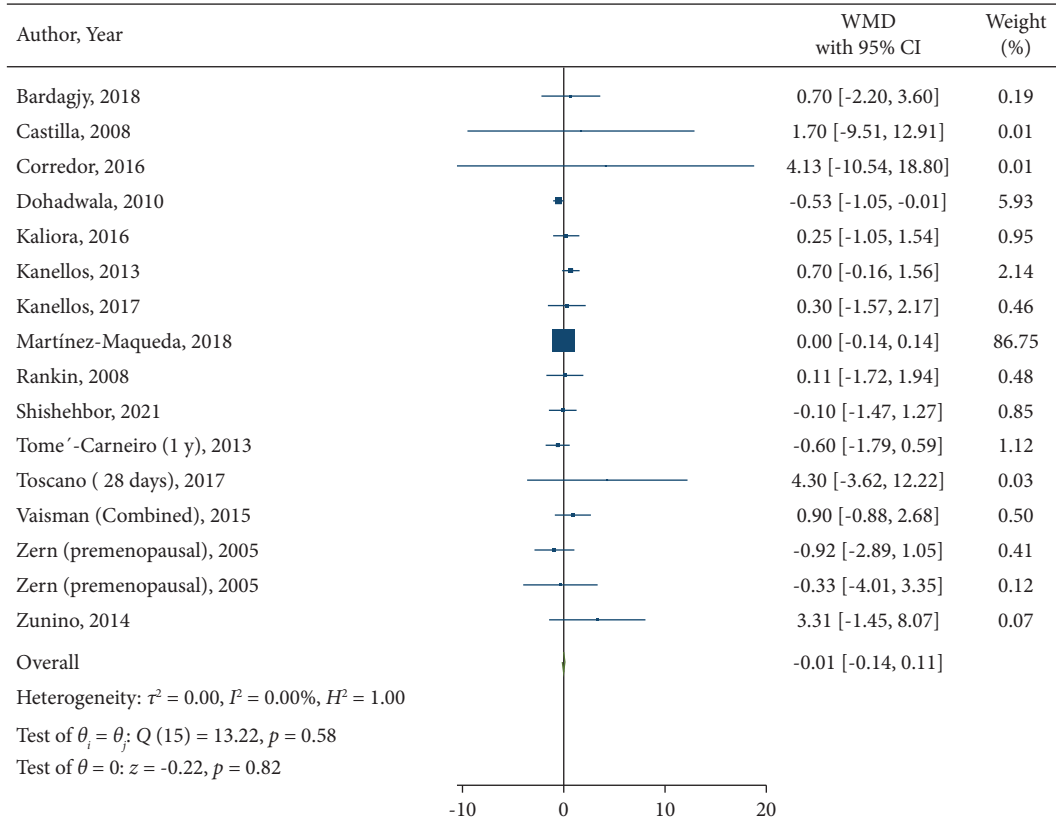
TABLE 1: Continued.

Author (year)	Country	Sample size/sex	Mean age intervention/control	Duration (week)/study design	Population characteristics	Type of intervention (gr/day)	Intervention in placebo group (gr/day)	Outcomes
Duclos (2017) [39]	USA	19 (I: 19, C: 19)/both	30–70	4/C	Metabolic syndrome	Freeze-dried grape powder (60)	Matched placebo	↔AOPPs ↔TBARS ↔TNF- α ↔MCP-1 ↔IL-6
Evans et al. (2014) [40]	Canada	25 (I: 13, C: 12)/both	46.1/38	6/P	Prehypertensive, overweight, and/or prediabetic	Whole grape extract (0.35)	Microcrystalline cellulose	↔TAC ↔SOD ↔ox-LDL
Goulart et al. (2020) [41]	Brazil	20 (I: 20, C: 20)/both	17.8	2/C	Judo athlete	Grape juice (400)	Placebo	↔Carbonyl ↔TBARS ↑TAC ↓SOD ↔CAT
Hollis et al. (2009) [42]	USA	51 (I: 25, C: 26)/both	22/28	12/P	Healthy adults	Concord grape juice (480)	Not receiving intervention	↔ORAC
Kaliora et al. (2016) [13]	Greece	44 (I: 23, C: 21)/both	50.7/51.6	24/P	NAFLD with nonsignificant fibrosis	Corinthian currants (36) + dietary counseling	Dietary counseling	↔CRP ↓IL-6 ↔ox-LDL ↔TNF- α
Kanellos et al. (2013) [43]	Greece	48 (I: 26, C: 22)/both	63.7/63	24/P	Diabetes (type 2)	Raisin (36)	Usual dietary habit	↔hs-CRP ↔IL-6 ↔TNF- α ↑TAP ↔ox-LDL
Kanellos et al. (2017) [44]	Greece	33 (I: 20, C: 13)/both	30.8/29.8	4/P	Healthy smokers	Raisin (90)	Not receiving intervention	↔CRP ↔MDA ↔AOPPs ↔NO
Lafay et al. (2009) [45]	France	20 (I: 20, C: 20)/both	21.6	4/C	Elite athletes	Grape extract (0.4)	Maltodextrin	↑ORAC ↔Ox-LDL ↔SOD ↔GPx ↔CAT
Martínez-Maqueda et al. (2018) [46]	Spain	48 (I: 25, C: 23)/both	Range: 20–65 Mean: 42.6	6/C	Metabolic syndrome	Dried grape pomace (8)	Not receiving intervention	↔hs-CRP
Puglisi et al. (2008) [47]	USA	22 (I: 10, C: 12)/both	57.8/55	6/P	Men and postmenopausal women	Raisin (150) + walk	Walk	↔TNF- α
Rahbar et al. (2015) [48]	Iran	69 (Red grape: 22, White grape: 24, C: 23)/both	Red grape: 50.5 White grape: 50.6 C: 52.5	8/P	Hypercholesterolemic adults	Condori red grapes/Shahroodi white grape (500)	5 servings of other fruits except grapes	↓TBARS ↑TAC

TABLE 1: Continued.

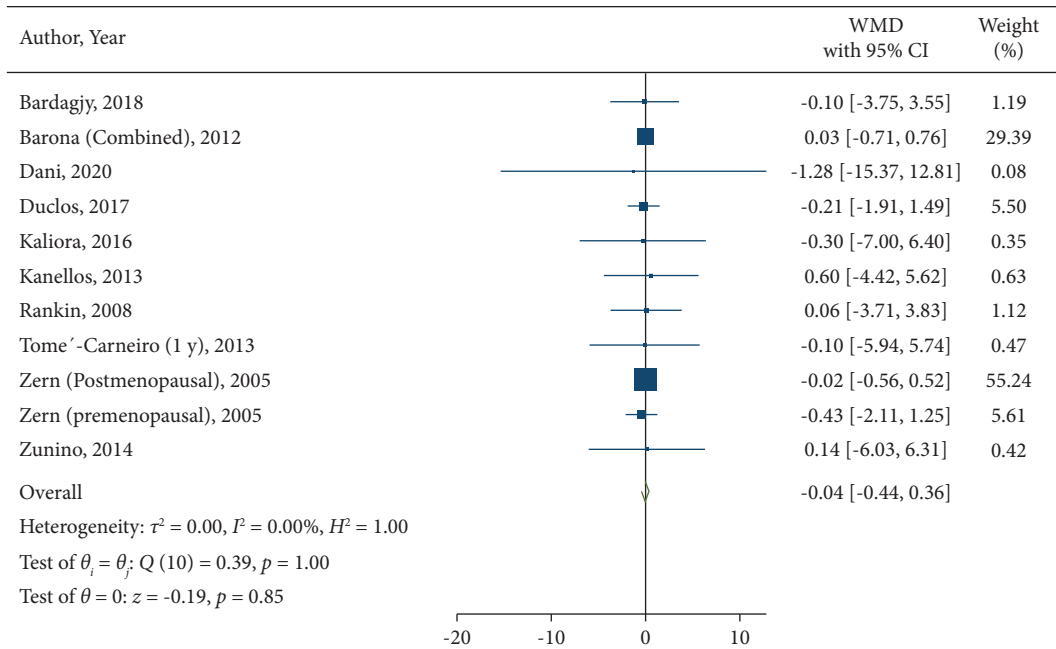
Author (year)	Country	Sample size/sex	Mean age intervention/control	Duration (week)/study design	Population characteristics	Type of intervention (gr/day)	Intervention in placebo group (gr/day)	Outcomes
Rankin et al. (2008) [49]	USA	17 (I: 17, C: 17)/both	26.5	2/C	Overweight	Raisin (90)	Isocaloric placebo	↔CRP ↔IL-6 ↑ORAC
Rowe et al. (2011) [50]	USA	78 (I: 40, C: 38)/both	Range: 50–75 Mean: 57.9	9/P	Healthy individuals	Concord grape juice (260)	Concord grape-flavored placebo	↔ORAC
Shishehbor et al. (2021) [51]	Iran	38 (I: 20, C: 18)/both	39.11/42.8	5/P	Hyperlipidemic patients	Black seed raisin (90)	Not receiving intervention	↔hs-CRP ↑TAC ↔MDA
Tomé-Carneiro et al. (2013) [52]	Spain	50 (I: 25, C: 25)/both	58/59	52/P	Patients with stable coronary Artery disease	Grape extract (0.35)	Maltodextrin	↔hs-CRP ↔TNF-α ↔IL-6 ↔IL-10 ↔IL-6/IL-10
Toscano et al. (2017) [53]	Brazil	28 (I: 15, C: 13)/both	42.7/36.3	4/P	Recreational runners	Grape juice (680)	Isocaloric juice	↔MDA ↑TAC ↔hs-CRP
Vaisman and Niv (2015) [54]	Israel	45 (not mentioned separately)/both	57.6/56.4	12/P	Pre- and mild hypertension	Red grape cell powder (0.4)	Colored maltodextrin powder (0.2)	↔CRP
Yubero et al. (2013) [55]	Spain	60 (I: 30, C: 30)/both	Range: 34–65 Mean: 51	8/P	Healthy	Polyphenol-rich pomace grape extract supplement (Eminol) (0.7)	Maltodextrin	↔TNF-α ↑ORAC ↔ox-LDL
Zern et al. (2005) [14]	USA	24 (I: 24, C: 24)/F	39.7	4/C	Premenopausal women	A lyophilized grape powder (36)	Equal ratio of fructose and dextrose	↔hs-CRP ↔IL-6 ↓TNF-α ↔hs-CRP ↔IL-6 ↓TNF-α
Zunino et al. (2014) [17]	USA	59 (I: 24, C: 24)/both	F: 34.7/M: 37.1	3/C	Healthy obese	A lyophilized grape powder (36)	Equal ratio of fructose and dextrose	↔IL-1b ↔IL-6 ↔IL-8 ↔TNF-α ↔CRP ↔ORAC ↔ox-LDL

High-sensitivity C-reactive protein; IL: interleukin; TNF: tumor necrosis factor; TAP: antioxidant potential; ox-LDL: oxidized low-density lipoprotein; NO: nitric oxide; MDA: malondialdehyde; AOPPs: advanced oxidation protein products; TBARS: thiobarbituric acid reactive substances; CAT: catalase; GPX: glutathione peroxidase; SOD: superoxide dismutase; TEAC: Trolox equivalent antioxidant capacity; MCP-1: monocyte chemoattractant protein-1; ORAC: oxygen radical absorbance capacity; TAC: total antioxidant capacity; F: female; P: parallel; C: crossover.



Random-effects DerSimonian-Laird model

(a)



Random-effects DerSimonian-Laird model

(b)

FIGURE 2: Continued.

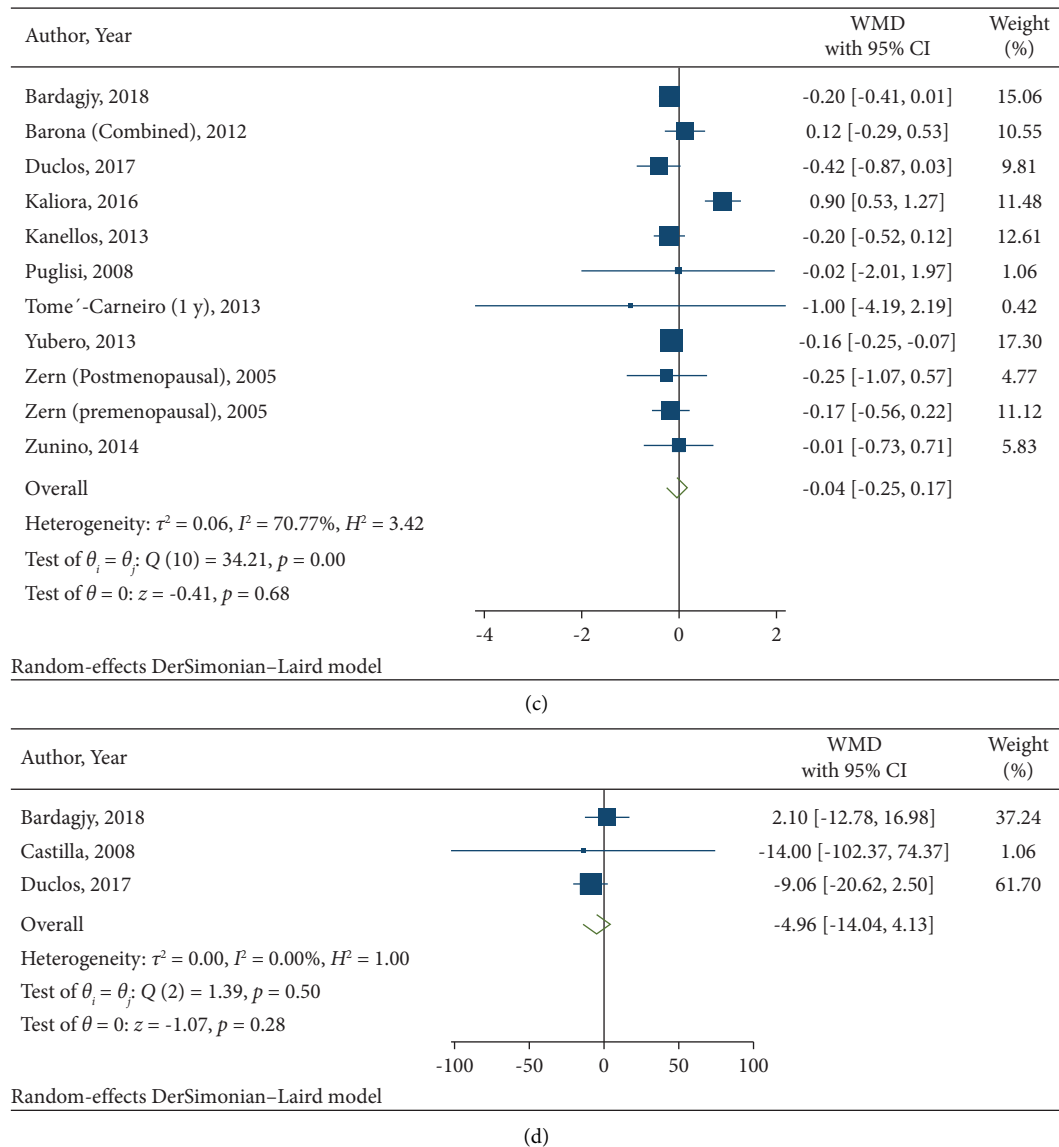


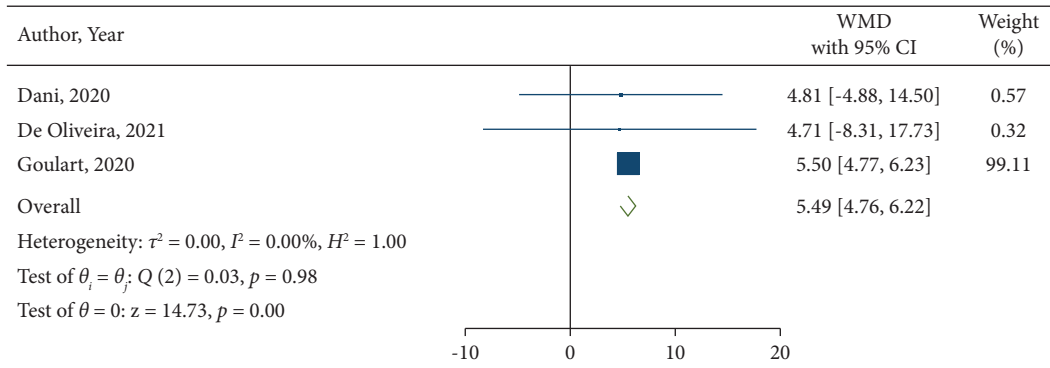
FIGURE 2: The effect of grape/grape products on hs-CRP (a), IL-6 (b), TNF- α (c), and MCP-1 (d) using random meta-analysis of randomized controlled trials.

WMD = 5.49 U CAT/mg protein, 95% CI: 4.76, 6.22; $P < 0.001$; $I^2 = 0\%$, 95% CI: 0, 90; P-heterogeneity = 0.98) (Figure 3(a)), ORAC ($n = 5$ studies, 206 participants; WMD = 90.06 $\mu\text{mol/l TE}$, 95% CI: 35.97, 144.15; $P = 0.001$; $I^2 = 35.6\%$, 95% CI: 0, 76; P-heterogeneity = 0.18) (Figure 3(b)), and TAC ($n = 4$ studies, 224 participants; WMD = 62.48 $\mu\text{mol/l}$, 95% CI: 31.62, 93.33; $P < 0.001$; $I^2 = 55.2\%$, 95% CI: 0, 85; P-heterogeneity = 0.08) (Figure 3(c)), while they showed a significant reduction in TBARSs ($n = 5$ studies, 153 participants; WMD = -0.17 nmol/mg, 95% CI: -0.31 , -0.03 ; $P = 0.02$; $I^2 = 34.2\%$, 95% CI: 0, 75; P-heterogeneity = 0.19) (Figure 3(d)).

The overall analysis showed no significant effect of grape products on carbonyl ($n = 3$ studies, 64 participants; WMD = -3.27 nmol/mg, 95% CI: -18.30 , 11.77; $P = 0.67$; $I^2 = 87\%$, 95% CI: 63, 95; P-heterogeneity < 0.001) (Figure 4(a)), ox-LDL ($n = 10$ studies, 385 participants; WMD = -3.19 U/L, 95% CI: -6.64 , 0.25; $P = 0.07$; $I^2 = 63.7\%$, 95% CI: 28, 82;

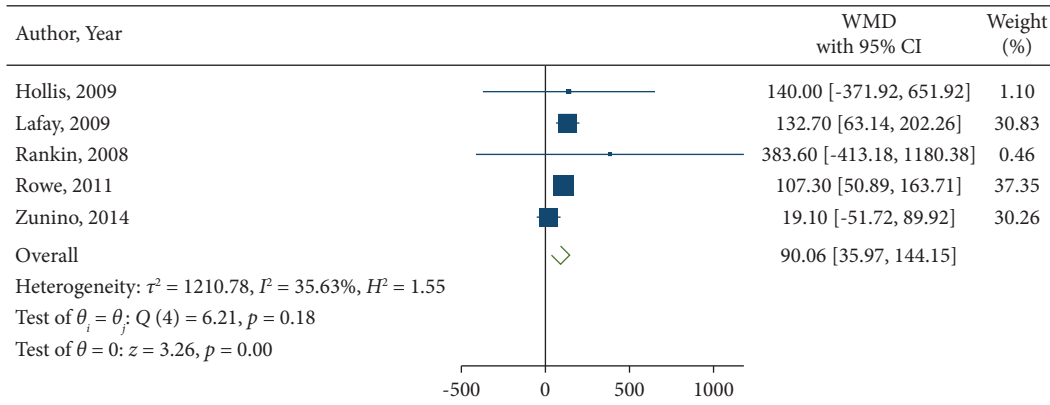
P-heterogeneity = 0.003) (Figure 4(b)), MDA ($n = 4$ studies, 193 participants; WMD = -0.09 $\mu\text{mol/l}$, 95% CI: -0.50 , 0.33; $P = 0.68$; $I^2 = 56.5\%$, 95% CI: 0, 86; P-heterogeneity = 0.07) (Figure 4(c)), and SOD ($n = 3$ studies, 64 participants; WMD = 4.95 U SOD/mg of protein, 95% CI: -0.14 , 10.04; $P = 0.06$; $I^2 = 93.5\%$, 95% CI: 84, 97; P-heterogeneity < 0.001) (Figure 4(d)).

In the subgroup analysis, we found that ox-LDL levels were reduced significantly in hemodialysis patients ($n = 2$ studies, 54 participants; WMD = -10.25 U/L, 95% CI: -15.42 , -5.07 ; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.89), in studies that were conducted in European countries ($n = 7$ studies, 281 participants; WMD = -6.43 U/L, 95% CI: -7.32 , -5.54 ; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.53), and in studies with parallel design ($n = 7$ studies, 281 participants; WMD = -6.42 U/L, 95% CI: -7.31 , -5.54 ; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.56). Additionally, grape extract



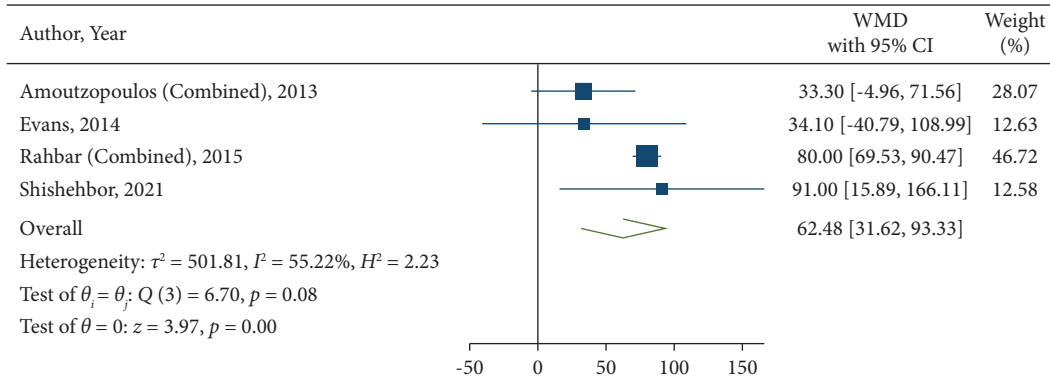
Random-effects DerSimonian–Laird model
 Sorted by: StudyFirstAuthorYear

(a)



Random-effects DerSimonian–Laird model
 Sorted by: AuthorYear

(b)



Random-effects DerSimonian–Laird model
 Sorted by: StudyFirstAuthorYear

(c)

FIGURE 3: Continued.

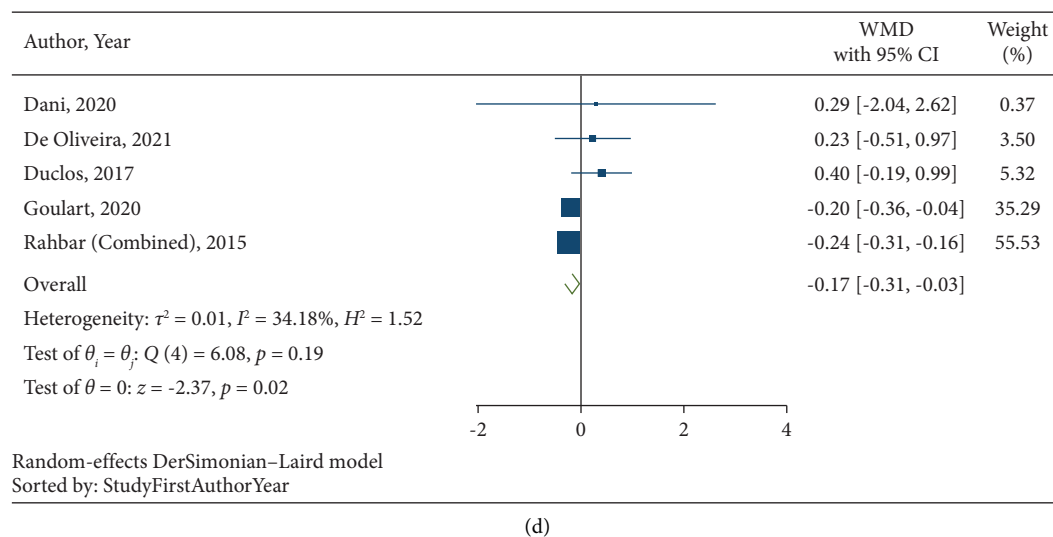


FIGURE 3: The effect of grape/grape products on catalase (a), ORAC (b), TAC (c), and TBARSs (d) using random-effects meta-analysis of randomized controlled trials.

supplementation significantly reduced ox-LDL ($n = 6$ studies, 209 participants; WMD = -6.46 U/L, 95% CI: -7.35 , -5.57 ; $P < 0.001$; $I^2 = 0\%$; P-heterogeneity = 0.51) (Table S9).

4.3. The Qualitative Systematic Review

4.3.1. Advanced Oxidation Protein Products (AOPPs). Three studies reported the effect of raisin [44], black current [56], and freeze-dried grape [39] on AOPP levels. The data from the articles could not be analyzed because the unit reported in one of the articles could not be converted and equated. No significant effect was observed in all three studies.

4.3.2. Paraoxonase (PON1). The effect of the freeze-dried grape extract on the PON1 activity has been investigated in adults with metabolic syndrome. The results showed that grape supplementation did not significantly change the PON1-arylesterase activity and PON1-lactonase activity compared with placebo [57].

4.3.3. Homocysteine (Hcy). In healthy adults, a traditional fermented grape-based drink “hardaliye” in two different dosages (250 and 500 mL) significantly reduced the serum Hcy concentrations ($P < 0.001$) [33].

4.3.4. GPx. The grape extract and powder supplementation (400 mg/day) could not significantly change GPx levels in elite athletes [45] and hemodialysis patients [58], respectively. Grape juice consumption (400 ml/day) in patients with Parkinson’s disease for 4 weeks significantly reduced GPx levels compared to the placebo group [15]. The data of the articles could not be analyzed because the unit reported in one of the articles could not be converted and equated.

4.3.5. Nitric Oxide. In one study, raisin consumption showed no significant effect on nitric oxide in healthy smokers [44].

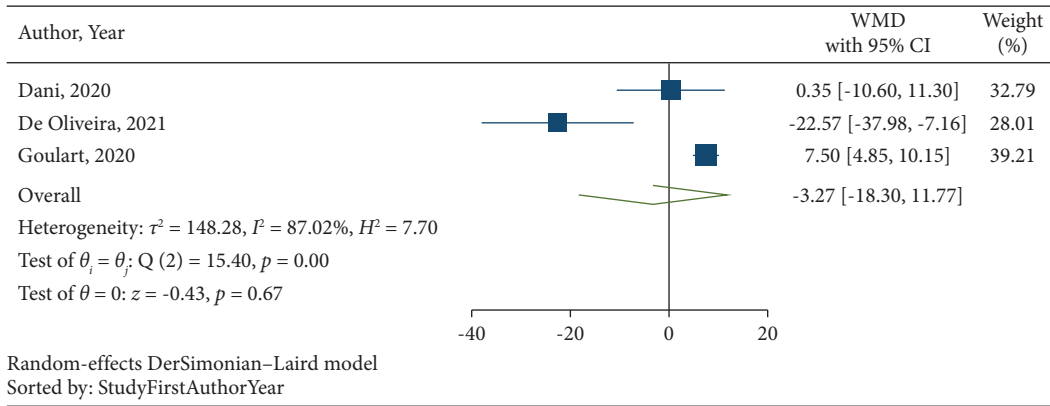
4.3.6. Complement Component 3-Protein (C3). One study reported the effect of dietary supplementation with concentrated red grape juice on C3 in hemodialysis patients, which had no significant differences between the intervention and control groups [35].

4.3.7. IL-1 β . Two trials examined the effects of dietary grape powder and grape on IL-1 β in obese and healthy subjects, respectively. Zunino et al. reported no significant difference in IL-1 β concentrations between groups [17]. In Ammollo’s study, grape intake did not show any significant change in the plasma levels of IL-1 β in intervention and control groups, while a significant reduction in the release of IL-1 β by lipopolysaccharide (LPS-) stimulated blood cells was observed in the intervention group compared with the control group [59].

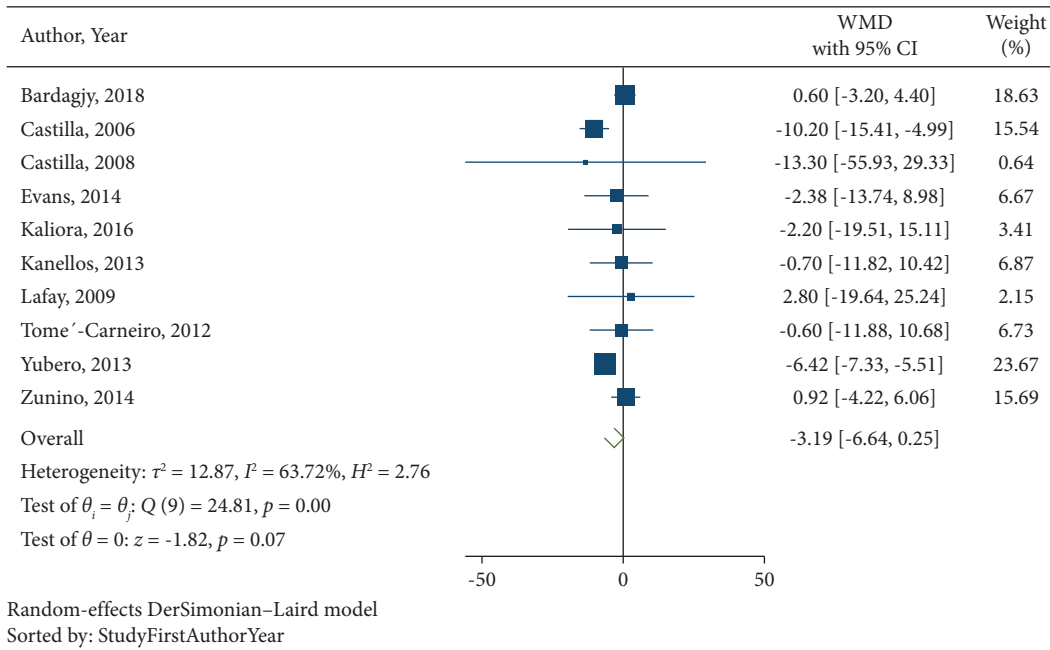
4.3.8. IL-18. One study showed a significant reduction in IL-18 after grape consumption for one year in patients receiving primary CVD prevention, but it was not significant in comparison with the control group [60].

4.3.9. IL-6/IL-10. Two studies explored the effects of grape extract supplementation in patients with stable coronary artery disease [52] and those on primary CVD prevention [60]. In both studies, grape extract supplementation did not change the IL-6/L-10 ratio significantly.

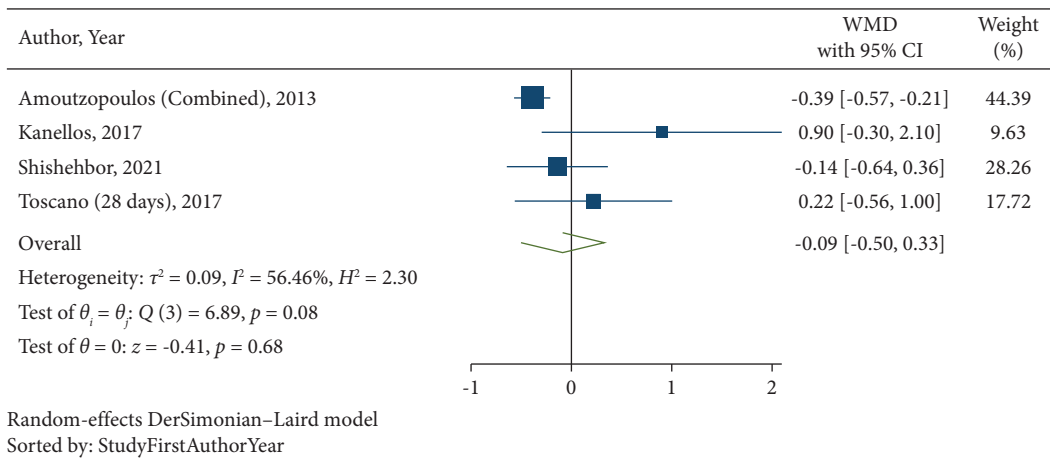
4.3.10. IL-8. Two trials evaluated the effect of the grape powder supplement on plasma concentration and LPS-stimulated monocytes’ production of IL-8 in obese [17]



(a)



(b)



(c)

FIGURE 4: Continued.

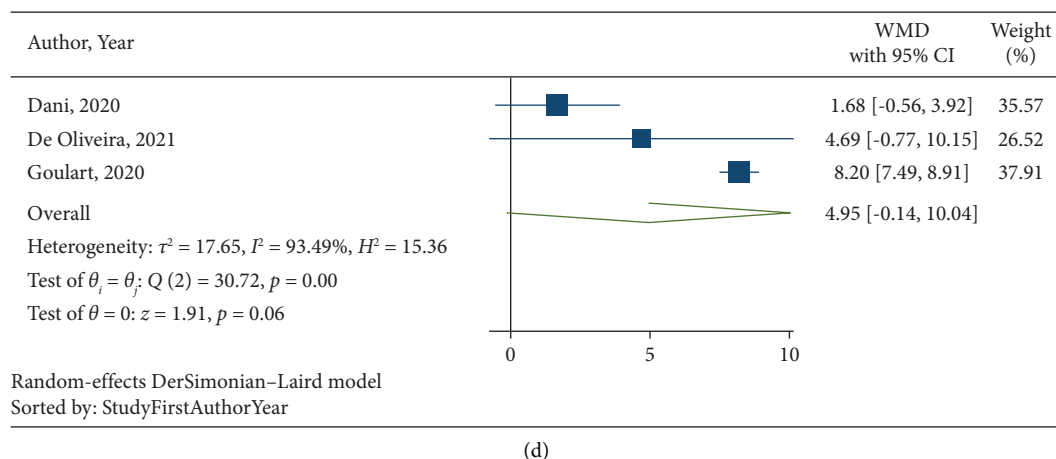


FIGURE 4: The effect of grape/grape products on carbonyl (a), ox-LDL (b), MDA (c), and SOD (d) using random-effects meta-analysis of randomized controlled trials.

and men with metabolic syndrome [34]. Grape powder supplementation did not significantly alter the IL-8 levels between the intervention and control groups in both studies.

4.3.11. IL-10. The effect of the grape extract and grape powder on IL-10 was investigated in three trials. However, a contradictory result was reached. A study showed that grape consumption increased IL-10 levels in patients with metabolic syndrome [34], while another study revealed no significant change in patients with stable coronary artery disease [52] and patients undergoing primary prevention of cardiovascular disease [60].

4.4. Sensitivity Analysis, Publication Bias, and Hartung–Knapp–Sidik–Jonkman Method-Based Analysis. To assess the robustness of the overall effect, a leave-one-out sensitivity analysis was performed, and the results were stable for IL-6, hs-CRP, and TNF- α . However, excluding the study by Bradagjy et al. [16] changed the results to a significant reduction in the ox-LDL levels (WMD = -4.45 U/L, 95% CI: -7.60 , -1.30 ; $P = 0.006$; $I^2 = 39.03\%$; P-heterogeneity = 0.11).

Publication bias was assessed for the effect of grape products on levels of hs-CRP, TNF- α , IL-6, and ox-LDL. The visual inspection of the funnel plots revealed no sign of asymmetry, which was also confirmed by Egger's and Begg's tests.

The Hartung–Knapp–Sidik–Jonkman method meta-analysis changed the results to a significant reduction for ox-LDL levels (WMD = -3.28 U/L, 95% CI: -6.47 , -0.09 ; $P = 0.5784\%$; P-heterogeneity = 0.003) and a significant increase for SOD levels (WMD = 5.02 U SOD/mg of protein, 95% CI: 1.1, 8.94; $P = 0.01$; $I^2 = 88.75\%$; P-heterogeneity = 0.0) (Table S10).

4.5. Meta-Regression. No significant associations were found between LFDs compared with HFDs on CRP, TNF, LDL-ox, and IL-6 and dose or duration of the intervention in meta-regression analysis (Supplementary Table 11).

5. Discussion

In the present meta-analysis, we pooled data from RCTs examining the effect of grape products on inflammation and oxidative stress markers in adults. Our main results showed that grape products significantly increased the catalase activity, ORAC, TAC, and decreased TBARS levels. We also found the grape extract may have more beneficial effects on inflammatory markers, including CRP, ox-LDL, and TNF- α , as compared to the other types of intervention (fresh grape or dried grape).

There are bidirectional communications between oxidative stress and inflammation; indeed, both are able to activate and aggravate each other in a direct or indirect manner [61]. Frequent exposure to ROS leads to cell damage and consequently induces proinflammatory pathways. Oxidative damage can induce the release of TNF- α from the cells, which binds to its cell surface receptors, leading to NF- κ B inflammasome activation [61]. As a result of NF- κ B signaling activation, other proinflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , are produced [61–63]. Grapes are known as one of the main sources of antioxidants due to their high polyphenol content [64]. Polyphenols are capable of enhancing antioxidant enzyme activities directly or indirectly through the activation of Keap1/Nrf2/ARE and sirtuin 1 (Sirt1) signaling pathways, which can enhance the expression of antioxidant genes [65]. Moreover, polyphenols can suppress the NF- κ B pathway, toll-like receptor (TLR), and expression of inflammatory genes, consequently [66].

Although we found no significant effect of grape and its products on inflammatory markers in the overall analysis, it seems grape extracts can reduce inflammatory markers. It may be associated with the higher dose of antioxidant in the grape extract compared to fresh grape. On the other hand, none of the included studies investigated patients with pre-existing acute inflammation, so the low level of inflammatory factors was not affected by the short-term intervention. In line with our results, a meta-analysis of eight studies regarding grape polyphenols did not show any significant effect on hs-CRP, IL-6, and TNF- α [21]. In

another meta-analysis, grape products had no significant effect on IL-6 and TNF- α , while they showed a significant effect on CRP levels [18]. However, two meta-analyses showed grape seed extract supplementation [20] and grape products containing polyphenols significantly reduced the CRP levels [19]. The inconclusive findings in the extant literature may be related to the different eligibility criteria used by the studies. For example, in the meta-analysis of grape products containing polyphenols, red wine and resveratrol interventions were also included in the analysis, which might distort our understanding of the actual effect of grape and its derivatives.

We also found that grape supplementation significantly increased catalase, ORAC, and TAC and decreased the TBARS levels. However, no significant changes were observed regarding carbonyl, ox-LDL, MDA, and SOD levels. The results of recent meta-analyses are also equivocal. In one study, grape products had no significant effect on TAC and MDA levels [18]. In another study, grape products containing polyphenols showed a significant increase in TAC, whereas they did not have any significant effect on SOD, MDA, ORAC, and GPx levels [19]. Moreover, grape seed extract supplementation significantly decreased MDA and ox-LDL along with eliciting an increase in TAC levels [20].

In the subgroup analysis, grape and its products significantly reduced the ox-LDL levels in hemodialysis patients. Hemodialysis patients exhibit oxidative stress throughout dialysis due to the accumulation of oxidative products (such as ox-LDL) and insufficient antioxidant ability [67]. Grape polyphenols are able to reduce lipid levels through pancreatic lipase inhibition, lipoprotein synthesis reduction in hepatocytes, and increasing fatty acid metabolism [68].

The present study has several strengths that should be acknowledged. To the best of our knowledge, this is the largest and most comprehensive meta-analysis to have examined the effects of grape/whole grape products on circulating levels of inflammatory and oxidative markers in adults. In addition, only RCTs were included in our study, permitting causal statements to be made. Previous meta-analyses regarding the effect of grape/grape products on oxidative and inflammatory markers have some limitations such as including grape seed and grape products containing polyphenols, which failed to show the real effect of grape and whole grape products on these factors. Furthermore, our search was more comprehensive, and we included all the studies with grape intervention without any missing publications. Moreover, it has been reported that I^2 has not enough power to show heterogeneity in meta-analysis with small number of studies [69], so the CI for I^2 has been reported in our study to avoid misconceptions.

However, despite the strengths outlined above, there are some potential limitations worth noting. First, the number of included studies for most outcomes (except for hs-CRP, IL-6, TNF, and ox-LDL) was small, which could affect the results' validity. Second, several factors including sex, age, environmental factors, diet, and genetics might affect the bioavailability of polyphenols and physiological responses to oxidative stress [64], and we were unable to include all these

variables in our subgroup analysis. Third, although all the eligible studies administered grape and its products, there was a wide variety of the interventions or grapes, which might affect the products' antioxidant content due to different processing methods. This is probably the reason for the observed significant result regarding the geographical location for TNF- α and ox-LDL. It is suggested that future studies focus on the composition of nutrients of grapes depending on the geographical location of plant growth and their health effects. Fourth, based on the CI of I^2 , there was a considerable heterogeneity between studies for all outcomes, which we could not find the source of it. Fifth, some of the included studies used untreated group and some others used placebo as the control group. Although in dietary intervention studies, the criteria of a placebo group may not be possible to achieve, untreated groups are accepted as a control group in these studies. However, blinding in these studies may not be possible, but it may not matter for objective outcomes. Nevertheless, a subgroup analysis was performed and no significant differences between placebo- and untreated control studies were found (data not shown). Sixth, the methodological quality of most of the included studies was poor, and the certainty of evidence was low and very low for all the outcomes, mainly due to the small sample size for each outcome that did not reach the optimal information size, which means the observed results may change when further studies are added to the present analyses. Lastly, the compliance rate for most included studies was not mentioned, which might affect the results.

6. Conclusion

In conclusion, grape products can significantly improve some biomarkers of oxidative stress, although appear to have no significant effect on reducing inflammation in an adult population. Low certainty of evidence emphasizes the need to further good quality of randomized clinical trials to clarify the actual effect of grape and its derivatives on oxidative stress and inflammation.

Data Availability

The raw data required to reproduce these findings are available from the corresponding author.

Disclosure

The financial source had no role in the implementation, writing, or submitting the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

SA and SS designed the review; RKM and SS conducted the major database search according to search strategy; FD and SS did data extraction; SS performed the analysis; FD, CC, and SA wrote the manuscript's draft; and all authors have

read and evaluated the final version of the manuscript precisely and approved it and agree with its submission to the Journal of Food Biochemistry.

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Supplementary Materials

Table S1: Literature search strategy terms. Table S2: PICO criteria for inclusion and exclusion of trials. Table S3: References of the excluded studies with reasons for exclusion. Table S4: Risk of bias assessment according to the Cochrane criteria for the studies regarding the effect of grape/grape products on inflammation and oxidative stress markers. Table S5: Assessing the quality of evidence regarding the effect of grape/whole grape products on oxidative stress and inflammatory markers by the GRADE system. Table S6: Subgroup analysis to assess the effect of grape/whole grape products on high-sensitivity C-reactive protein (hs-CRP) levels. Table S7: Subgroup analysis to assess the effect of grape/whole grape products on tumor necrosis factor alpha (TNF- α) levels. Table S8: Subgroup analysis to assess the effect of grape/whole grape products on interleukin 6 (IL-6) levels. Table S9: Subgroup analysis to assess the effect of grape/whole grape products on oxidized low-density lipoprotein (Ox-LDL) levels. Table S10: Subgroup analysis to assess the effect of grape/whole grape products on inflammatory and oxidative stress markers using DerSimonian–Laird and Hartung–Knapp–Sidik–Jonkman methods. Table S11: Meta-regression analysis of the potential source of heterogeneity. (*Supplementary Materials*)

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