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Anti-inflammatory effects of resveratrol in patients with cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Chronic inflammation is one of the most important factors involved in the development and progression of cardiovascular disease (CVDs). Accumulating evidence has described the effect of resveratrol, a natural polyphenolic compound, on biomarkers of inflammation among patients with CVDs; however, findings are controversial. Here we performed a systematic review and meta-analysis of randomized controlled trials to evaluate the effect of resveratrol supplements on TNF-α, IL-6, and CRP levels in CVDs patients.

Methods: Online research was conducted in the following database: MEDLINE, EMBASE, Cochrane Library, Web of Science databases, and Scopus. This systematic review and meta-analysis were conducted to investigate the effects of resveratrol supplements on inflammatory biomarkers among patients with CVDs. The meta-analysis was performed using Comprehensive Meta-Analysis (CMA) V3 software.

Results: Six RCTs met the inclusion criteria and were selected for the current meta-analysis. Our results demonstrated that resveratrol significantly decreases serum levels of CRP (MD = −0.63, 95 % CI: −0.1.13, −0.12; p = 0.01), and TNF-α (MD = −0.55, 95 % CI: −1.04, −0.06; p = 0.02), however, resveratrol had not significant effect on serum concentration of IL-6 (MD = −0.12, 95 % CI: −0.52, 0.27; p = 0.53), in patients with CVDs.

Conclusion: Our results suggest that resveratrol can be used as a potential treatment in patients with CVD by reducing inflammatory conditions.

1. Introduction

Regardless of the etiology, cardiovascular diseases (CVDs) include various heart or/and blood vessel disorders, such as cerebrovascular disease, congenital heart disease, and coronary artery disease. CVDs are a major global health problem due to their persistently high incidence and mortality.[1, 2] They (CVDs) account for 17.3 million deaths annually, which is expected to increase to over 23.6 million by 2030.[3] Inflammation represents a complex cascade of molecular and cellular processes beneficial for host defense, tissue repair, and survival. However, it is well shown that prolonged or chronic inflammation plays a key role in the pathogenesis of several disorders, specially CVDs.[4, 5] Among various inflammatory markers that have been studied, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are two major proinflammatory cytokines, acting mainly as mediators of inflammatory response involved in the development of metabolic diseases such as CVDs and type 2 diabetes. These cytokines are potent triggers of C-reactive protein (CRP) production primarily by the liver. CRP is a key factor of the acute-phase reaction, which has long been considered a well-known inflammation marker. It also contributes to the pathogenesis of various metabolic disorders.[6, 7] Accumulating evidence shows that targeting chronic inflammation with anti-inflammatory drugs can reduce the progression and development of CVDs.[5, 8] However, long-term use of many traditional anti-inflammatory medications can

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seriously affect patients.[9] Recent studies demonstrate that complementary and alternative medicine (CAM) has a natural protective effect against acute and chronic inflammation in different inflammatory diseases.[10]

Resveratrol has recently been considered a choice for preventing and treating inflammatory conditions. This non-flavonoid polyphenolic compound is rich in grapes and red wine.[11] Resveratrol has been reported as an active constituent of red wine, which may be responsible for the "French paradox" phenomenon. It refers to the low incidence and mortality rate of CVDs despite a high intake of dietary cholesterol and saturated fat.[12] According to research, resveratrol may protect against ischemic stroke, heart failure, atrial fibrillation, metabolic syndrome, type 2 diabetes, hepatic steatosis, and cancer through numerous targets.[13–18]

Numerous preclinical and human studies have shown the beneficial effects of resveratrol in CVDs.[19] However, the mechanisms underlying the role of resveratrol against the progression of CVDs are multifaceted. It has been demonstrated that the beneficial effects of resveratrol are mediated mainly through its anti-inflammatory and antioxidant functions.[20] In this regard, multiple mechanisms have been described for the anti-inflammatory effects of resveratrol in CVDs, including attenuation of monocyte adhesiveness to endothelial cells, suppression of NF-κB and JAK/STAT (Janus kinase/signal transducers and activators of transcription) signal pathways, upregulation of anti-inflammatory cytokines, and inhibition of the pro-inflammatory mediator's production such as TNF-alpha, IL-1β, and IL-6. [20, 21] However, results from different studies regarding resveratrol's effect on the inflammatory markers' levels in patients with CVDs are limited and controversial. Some difficulties in interpreting data may arise from different doses of resveratrol, and the duration of treatment has been administered in various human studies.[20] Furthermore, despite the enormous increase in published studies on resveratrol's health benefits, few are related to human clinical trials. [22] We performed a systematic review and meta-analysis to evaluate the impact of resveratrol on serum/plasma concentration of TNF-α, IL-6, and CRP in patients with CVDs by searching different databases for published RCTs.

2. Methods

2.1. Search strategy

Our study was designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[23] Independently two investigators searched electronic databases, including PubMed, Cochrane Library, Web of Science, and Scopus. Disagreements between extracted data were resolved by discussion with a third party. The search was limited to the RCTs published in English up to January 2022.

The search strategies included the following terms in titles and abstracts: (Resveratrol OR "3,4′,5-Trihydroxystilbene" OR "trans-Resveratrol" OR "cis-resveratrol" OR "Resveratrol's ") AND ("cardiovascular disease" OR "coronary artery disease" OR "CVD" OR "CAD") AND (" IL-6" OR "Interleukin 6" OR "C-reactive protein" OR "CRP" OR "tumor necrosis factor-α" OR TNF-α" "inflammation" OR "inflammatory mediator" OR "inflammatory marker"). We checked the reference lists of related studies to find further relevant articles.

2.2. Inclusion/exclusion criteria

Articles with the following inclusion criteria were included in this meta-analysis: (1) the study was RCT with either parallel or cross-over design; (2) the study investigated the effect of resveratrol on the inflammatory markers in CVD; (3) presentation of sufficient information (treatment/placebo) for TNF-α, IL-6, and CRP concentration. On the other hand, articles that met the following criteria were excluded**:** (1) studies with unclear inclusion and exclusion criteria; (2) not appropriate control or placebo groups in the research design; (3) intervention duration of less than one week; (4) inability to obtain adequate details about study methodology.

2.3. Extraction of data

The following items were extracted from eligible articles by using standard Excel forms: (1) first author's name; (2) year of publication; (3) the number of participants in the resveratrol and placebo groups; 4) age and BMI of study participants; (5) sample size in both treatment and placebo groups; (6) dose of resveratrol treatment; (7) duration of resveratrol treatment; (8) the mean and standard deviation (SD) of circulating inflammatory mediators in the treatment and placebo groups at baseline and the end of the study. The current meta-analysis treated each outcome as a separate study if the selected RCTs used varying doses and time points to determine their outcome.

2.4. Quality assessment

Methods described in the Cochrane Handbook for systematic reviews of interventions[24] were used to systematically assess the potential bias of the studies based on the following criteria: adequacy of sequence generation, allocation concealment, blinding, addressing incomplete outcome data, selective outcome reporting, and potential sources of bias. As recommended by Cochrane Handbook, a judgment of "yes" means a low risk of bias, whereas "no" means a high risk of bias. The label "unclear" means a risk of unknown or unclear bias. Each of the studies was classified as "weak" if it met less than two items for low risk of bias, "fair" if it met at least two items for low risk of bias, and "good" if it met at least three items for low risk of bias.

2.5. Publication bias assessment

A funnel plot was used to evaluate publication bias in the meta-analysis visually. The asymmetric funnel plot was further assessed using Begg's rank correlation and Egger's weighted regression tests for publication bias across the RCTs. The p-value of < 0.05 was considered statistically significant for all analyses. [25, 26]

2.6. Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis (CMA) V3 software. In this study, inflammatory markers concentration was treated as a continuous variable. We utilized mean differences (MDs) and 95 % confidence intervals (CI) to combine data and measure the effect sizes. A random-effects model was used to calculate MDs. [27] The statistical effect of clinical heterogeneity between studies was quantified using Cochrane's Q test and I^2 statistics. A p-value ≤ 0.1 for Cochran's Q test and the I-squared statistic value ≥ 50 % were considered significant heterogeneity between studies. We determined the possible sources of heterogeneity between the studies by subgroup analyses based on study duration ($\leq$9 weeks and $>$9 weeks) and amount of resveratrol supplementation ($\leq$15 mg/day and $>$15 mg/day) on meta-analysis outcome. We performed sensitivity analyses to estimate each study's effect on the validity of the overall MDs using the leave-one-out method.

3. Results

3.1. Study selection and characteristics

The initial online search from four central databases, Web of Science, Scopus, Cochrane Library, and PubMed, up to January 2022 yielded 394 articles, of which 102 studies were excluded due to duplication. Two hundred fifty non-relevant papers were removed after screening the titles and abstracts. Then 42 articles were selected, and their full texts

were evaluated. After careful assessment, 36 articles were excluded; thus, six studies met the inclusion criteria and were selected for the current meta-analysis. The PRISMA flow diagram summarizes the study selection process in Fig. 1. The overall number of participants was 415, ranging from 9 to 30 subjects in each study. Six RCTs with nine effect sizes were included in the analysis. These studies were published between 2012 and 2019. Six, four, and three of these trials reported the effects of resveratrol on the levels of CRP, TNF-α, and IL-6, respectively. The resveratrol was used at the dose of 500 mg/day in one trial; however, most RCTs have used a dose of ≤ 100 mg/day. The duration of patient follow-up ranged from 4 to 52 weeks. The inflammatory markers in the intervention group were compared to the placebo group in all RCTs. In Table 1, study characteristics are presented in detail.

3.2. The effects of resveratrol on inflammatory factors

In total, six RCTs with nine effect sizes show that, resveratrol significantly reducethe levels of TNF-α (MD = −0.55, 95 % CI: −1.04, −0.06; p = 0.02), and CRP (MD = −0.63, 95 % CI: −0.1.13, −0.12; p = 0.01) in the serum/plasma of CVDs patients. Whereas resveratrol does not have any significant effect on IL-6 concentration (MD = −0.12, 95 % CI: −0.52, 0.27; p = 0.53) (Fig. 2). There was no statistically significant heterogeneity between studies for TNF-α (I2 = 0.00 %; p = 0.76), CRP (I2 = 3.99 %; p = 0.33), and IL-6 (I2 = 0.00 %; p = 0.99).

3.3. Subgroup analysis

Although the level of heterogeneity was not high, we conducted subgroup analyses based on two moderator variables: study duration (≤9 weeks and >9 weeks) and amount of resveratrol supplementation (≤15 mg/day and >15 mg/day). Subgroup analyses showed that consumption of > 15 mg/day resveratrol for CRP (MD = −1.11; p = 0.01), and TNF-α (MD = −1.16; p = 0.01) significantly reduced CRP and TNF-α levels. Whereas consumption of ≤ 15 mg/day resveratrol not significantly effect on CRP (MD = −0.37; p = 0.23), and TNF-α levels (MD = −0.4; p = 0.18), in CVD patients. Details of the subgroup analysis are presented in Table 2. Subgroup analyses were not conducted for IL-6 concentration because of the small number of publications on our review in CVD patients (Fig. 3).

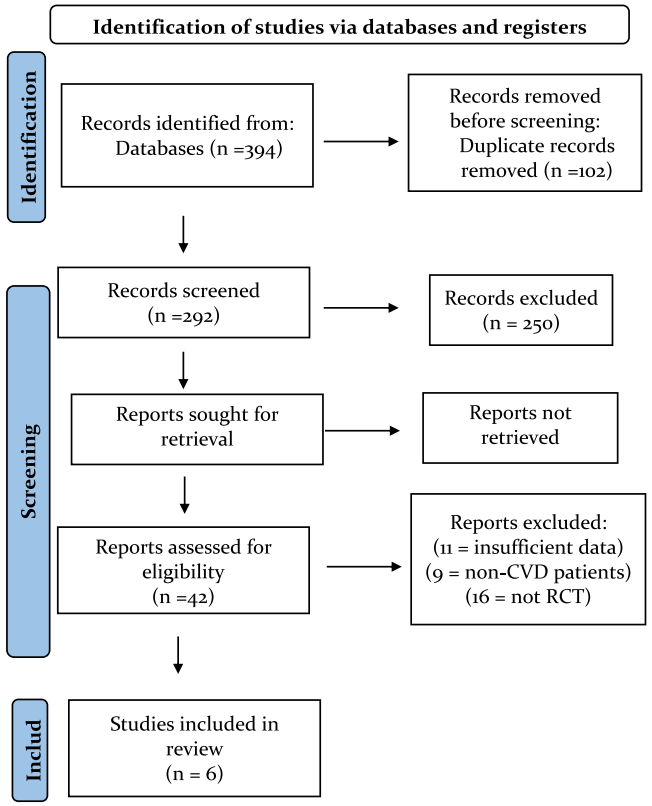

Fig. 1. flow diagram of study selection, inclusion, and exclusion of RCTs.

Table 1
Demographic characteristics of the RCTs included in the systematic review and meta-analysis.

Author-Year	Country	Dose (mg/day)	Duration (day)	Placebo sample size	Resveratrol sample size
Hosseini-2019	Iran	500	28	28	28
Chekalina-2016	Ukraine	100	60	30	30
Militaru-2013	Romania	20	60	30	29
Carneiro-B1–2013	Spain	8.1	180	25	25
Carneiro-B2–2013	Spain	12.5	360	25	25
Magyar-2012	Hungary	10	90	20	20
Carneiro-C1–2012	Spain	8.1	180	25	25
Carneiro-C2–2012	Spain	16.2	360	25	25

3.4. Sensitivity and publication bias

Out of the six RCTs in our systematic review and meta-analysis, four trials were scored as "good" quality, [28–31] while two RCTs were "fair" quality based on Cochrane Collaboration's tool. [32, 33] More detailed data on the quality assessment are presented in Table 3. The sensitivity analyses demonstrated no significant differences between overall results. The removal of each trial from the analysis did not cause a significant alteration in the overall effect size. The funnel plots for TNF-α, IL-6 and CRP were not visually symmetric (Fig. 4); Egger's weighted regression (p value = 0.85 for TNF-α, p value = 0.13 for IL-6 and p = 0.22 for CRP) and Begg's rank correlation (p value = 0.36 for TNF-α, p value = 0.06 for IL-6 and p value = 0.17 for CRP) showed no publication bias in included trials.

4. Discussion

To the best of our knowledge, the current study is the first systematic review and meta-analysis to find the effect of resveratrol on the concentration of inflammatory markers (TNF-α, IL-6, and CRP) in patients with CVDs. The role of inflammation in the progression of atherosclerosis and susceptibility to CVDs is well known. High TNF-α, IL-6, and CRP levels have been demonstrated in CVD patients.[34–36] It should be noted that these inflammatory markers are involved in the immunological process that triggers vascular remodeling and plaque deposition. These are also associated with an increased risk of CVDs. [37–40] Resveratrol is one of the natural compounds that can help prevent and treat CVDs. The protective effects of resveratrol against cardiovascular complications, such as atherosclerosis, hypertension, and heart failure, recently have become a topic of interest for researchers. [36, 41] Several studies recommended that resveratrol could improve the inflammatory state in inflammation-related diseases. [42–45]

The current meta-analysis demonstrated that resveratrol significantly decreases CRP and TNF-α concentration; however, it did not significantly affect the serum concentration of IL-6 in patients with CVDs. Consistent with our results, Militaru and colleagues in a RCT, including subjects with stable angina pectoris with an oral intake of 20 mg/day resveratrol, revealed a significant reduction of CRP in the

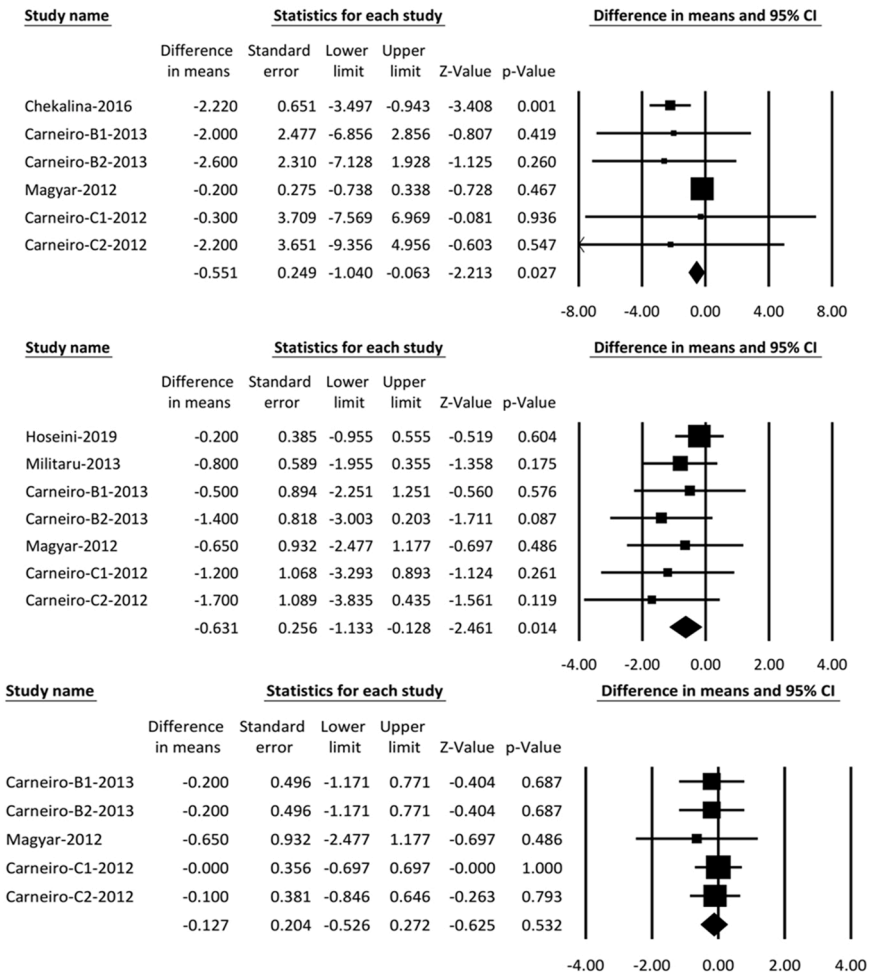

Fig. 2. The results of the overall mean difference for the effects of resveratrol on the inflammatory markers. MD was calculated as mean difference intervention versus the placebo difference for each inflammatory marker in CVDs. (A) CRP, (B) TNF-α, (C)IL-6.

Table 2
Subgroup analysis to assess the effect of resveratrol on inflammatory marker in CVD patients.

CRP		Mean difference	p-Value	95 % confidence interval	I^2	p heterogeneity
Dose of RES	≤ 15	-0.37	0.23	-0.99, 0.24	0.00	0.82
	> 15	-1.11	0.01	1.97, − 0.25	0.00	0.70
Duration (weeks)	≤ 9	-0.4	0.18	-1.00, 0.18	0.00	0.67
	> 9	-1.16	0.01	-2.09, − 0.23	0.00	0.83
TNF-a						
Dose of RES	≤ 15	-0.22	0.41	-0.75, 0.31	0.00	0.78
	> 15	-2.24	0.00	-3.45, − 1.03	0.00	0.98
Duration (weeks)	≤ 9	-0.5	0.04	-1.00, 0.00	87.75	0.04
	> 9	-2.00	0.15	-4.7, 0.77	0.00	0.96

intervention group to the control group at the 30-day and 60-day visits. Also, the results of some studies suggested that a one-year consumption of resveratrol-rich grape significantly reduced TNF-α and CRP levels in seventy-five patients undergoing primary prevention CVDs; however, IL-6 levels remained unchanged. [30, 31] Furthermore, Chekalina et al. reported that 100 mg/day of resveratrol for two months decreased plasma levels of TNF-α in CVD patients. [29] In another study, Magyar et al. reported that 10 mg of resveratrol daily for two months led to a significant decrease in the concentration of TNF-α and CRP in patients with stable coronary artery disease. [33]

A previous meta-analysis of RCTs, including adults aged 18–75, reported that resveratrol significantly decreases CRP levels. Still, it could not change IL-6 and TNF-α concentrations. [46] Also, a recent meta-analysis by Gorabi et al. revealed that resveratrol consumption reduces the levels of CRP in the serum of patients with systematic inflammation due to various disorders.[47] Furthermore, in a separate meta-analysis, Koushki et al. and Omraninava et al., agreeing with our study's results, showed a potential preventive effect of resveratrol supplementation on inflammatory markers. [6, 45] However, unlike our study, these meta-analyses were not performed on a specific type of disease; given that resveratrol has a largely different effect in different kinds of patients, the results of these studies may be affected by these conditions. [16,48,49] So, we investigated the effect of resveratrol only in patients with CVDs.

Inconsistent with our results, a meta-analysis by Sahebkar et al. concluded that resveratrol consumption does not significantly reduce CRP levels in various disorders.[50] One of the most important reasons for these inconsistencies may be the low bioavailability of resveratrol, so a

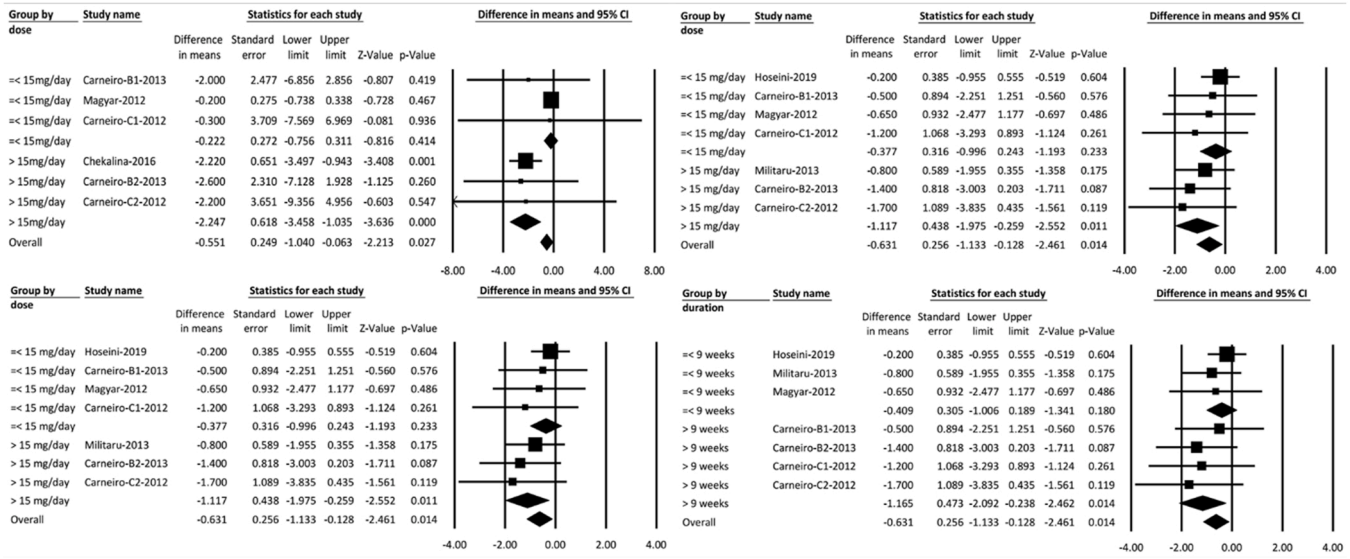

Fig. 3. Subgroup analysis to assess the effect of resveratrol on the inflammatory marker in CVD patients.

Table 3
Quality assessment of studies selected for analysis.

Study	Random sequence generation	Allocation concealment	Blinding	Blinding of participants and personnel	Blinding of outcome assessment	Selective reporting	Overall quality
Hoseini (2019)	unclear	yes	yes	unclear	yes	yes	Good
Chekalina (2016)	unclear	yes	yes	unclear	yes	yes	Good
Militaru (2013)	unclear	No	unclear	yes	No	yes	Fair
Carneiro-B (2013)	unclear	yes	yes	unclear	yes	yes	Good
Magyar (2012)	unclear	unclear	No	unclear	unclear	yes	Fair
Carneiro-C (2012)	unclear	yes	yes	unclear	yes	yes	Good

Yes: low risk of bias, No: high risk of bias, Unclear: unclear risk of bias

low dose of resveratrol and short duration of intervention in some RCTs could not significantly affect serum levels of inflammatory markers.[51–53] Therefore, some studies have suggested that mixing resveratrol with other compounds or using effective drug delivery systems by nanotechnology strategies reduces resveratrol metabolism and increases bioavailability.[50] As well as, emerging research suggested that combining resveratrol with other compounds may have a greater synergistic effect than each ingredient alone. For example, resveratrol could be as helpful in treating significant diabetes-related complications like glucose and insulin concentration in individuals using metformin.[19, 54] However, these findings are still preliminary, and well-designed clinical investigations are needed to corroborate them. In this study, we found no significant evidence of the effect of resveratrol on IL − 6 concentration. Although the inhibitory effects of resveratrol on IL − 6 have been demonstrated in vitro studies,.[55] Given the strong association between TNF-α and IL − 6, we had expected to observe a decreasing influence of resveratrol on IL − 6. However, a relatively small number of pooled participants likely does not provide sufficient statistical power to estimate the intervention effect.

The results of a study by Santana et al. showed that the effect of resveratrol could be customized according to the patient's condition, duration of treatment, and dose of resveratrol.[48] This study performed a subgroup analysis to investigate this issue in CVDs patients based on dose and time of intervention. According to the subgroup analysis results, the overall effect size for studies that assessed the effect of resveratrol with a dose of > 15 mg/day significantly decreased CRP and TNF-α levels. However, the overall effect size for studies with a dose of resveratrol consumption ≤ 15 mg/day did not show a statistically significant decrease in CRP and TNF-α concentration. It can be suggested that increasing the dose of resveratrol can more effectively reduce the CRP and TNF-α concentrations in CVD patients.

This study has some limitations: (1) due to the small number of studies, we could not better evaluate the effect of resveratrol on inflammatory markers; (2) in this study, only English articles were used; (3) it would be fascinating to see if these findings are equivalent to actual red wine consumption, but such comparisons would be difficult due to the scarcity of data; (4) the studies had different sample sizes, intervention durations, and resveratrol doses, so the results obtained in the present study may be biased; (5) finally, most articles did not report information about the drugs used by patients. Therefore, some of these drugs may have anti-inflammatory activity and affect the results. Our study also has several strengths: (1) this article is the first meta-analysis that examined the resveratrol effect on TNF-α, IL-6, and CRP concentrations in CVD patients; (2) we did not limit our search to specific publication date; (3) although heterogeneity was not high, we performed subgroup analyses based on intervention duration and dose of resveratrol; (4) unlike previous studies, our study was performed only on CVD patients, and therefore, the results are less affected by the different effects of resveratrol in different diseases; (5)finally, our results remained stable even in sensitivity analyses. Overall, the results of this review should be interpreted with caution, given its limitations and strengths.

5. Conclusions

In conclusion, in agreement with most of the studies included in the meta-analysis, we found a potential preventive effect of resveratrol supplementation on inflammatory conditions in CVD patients. The beneficial effects of resveratrol could represent an interesting pharmacological approach for preventing and treating CVDs. However, the low

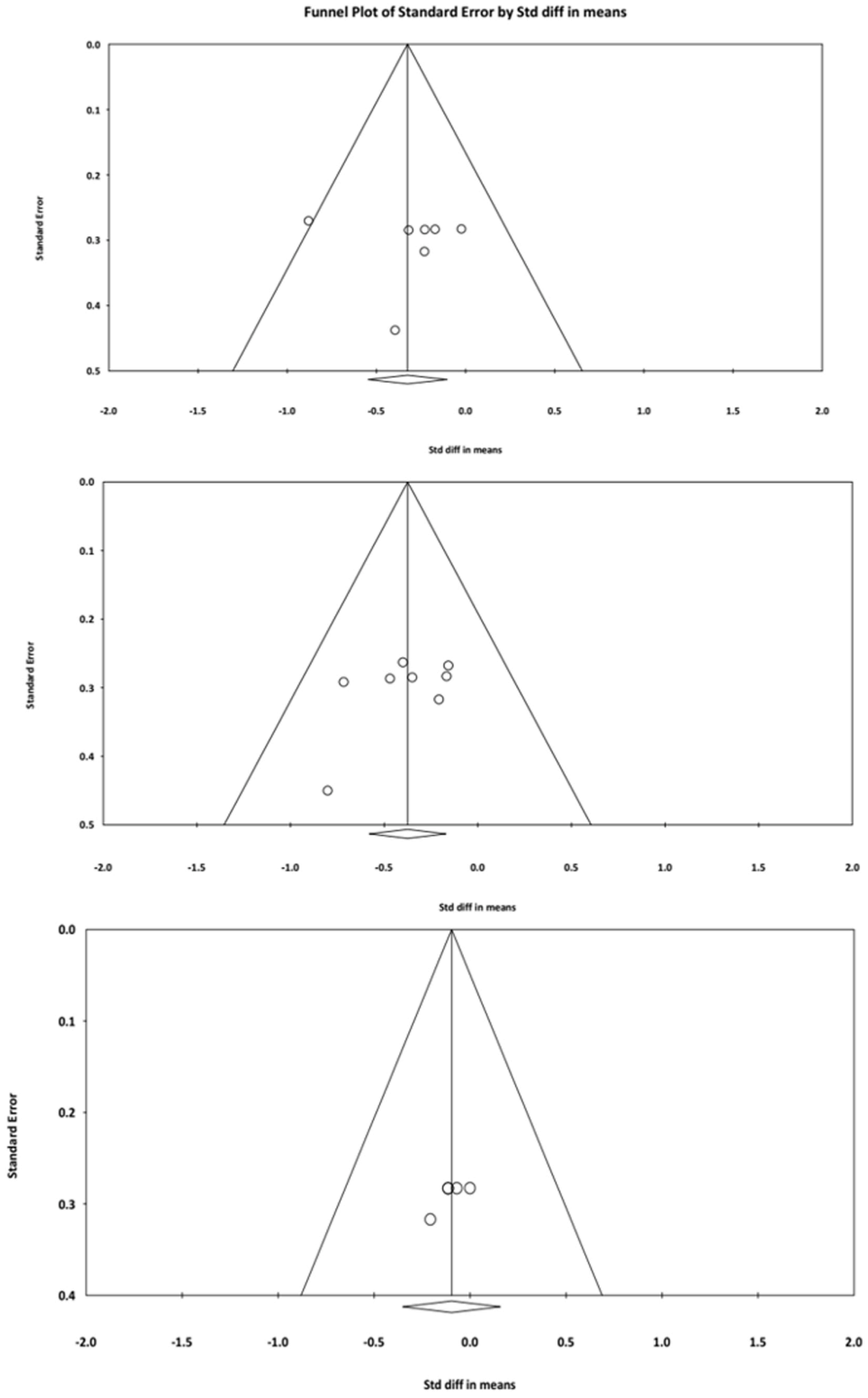

Fig. 4. The results of publication bias with funnel plot for (A) CRP. (B) TNF-α, Visual inspection of the funnel plot revealed no evidence of publication bias for TNF-α and CRP. The funnel plot was not drawn because of the low number of triads for IL-6.

bioavailability, dose of resveratrol, and duration of therapy are crucial factors for interpreting clinical studies. Accordingly, larger RCTs are required to investigate these points and explore the effects of resveratrol supplementations.

Conflict of Interest

The authors declare that they have no conflict of interest.

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