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The efficacy of resveratrol supplementation on inflammation and oxidative stress in type-2 diabetes mellitus patients: randomized double-blind placebo meta-analysis

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Background: The effects of resveratrol supplementation on inflammation and oxidative stress in patients with type 2 diabetes mellitus (T2DM) were controversial. A meta-analysis was performed to assess the changes in levels of inflammation and oxidative stress in patients with T2DM.

Methods: Relevant literatures before November 6, 2024 were screened through Web of Science,Embase,the Cochrane Library and other sources (ClinicalTrials, ProQuest Dissertations and Theses). The quality of the literature was evaluated according to the Cochrane Handbook of Systematic Reviews. The study quality was assessed using the risk-of-bias 2 tool and the Grading of Recommendations Assessment,Development and Evaluation (GRADE) system. Review Manager 5.3 conducted meta-analysis of the data included in the literature.

Results: This meta-analysis was conducted in six randomized controlled trials involving 533 participants. Our results showed that supplementation with resveratrol significantly reduced C-reactive protein levels(SMD = -1.40, 95%CI (-2.60, -0.21), P = 0.02; Level of evidence: low), lipid peroxide levels (SMD = -0.99, 95%CI(-1.36, -0.61), P < 0.00001; Level of evidence: low), 8-isoprostanes (SMD = -0.79, 95%CI(-1.16, -0.42), P < 0.0001; Level of evidence: low) and oxidative stress score (SMD = -1.62, 95%CI(-2.49, -0.75), P = 0.0003; Level of evidence: very low). In addition, compared to placebo, Supplementation with resveratrol significantly increased glutathione peroxidase levels (SMD = 0.38, 95% CI(0.03, 0.74), P = 0.04; Level of evidence:low) and catalase levels (SMD = 0.33, 95%CI(0.03, 0.63), P = 0.03; Level of evidence: low). However, no significant difference was observed in improving interleukin-6 levels (SMD = -1.35, 95%CI

(-2.75, -0.05), P = 0.06; Level of evidence: very low), tumor necrosis factor α levels (SMD = -3.30, 95%CI(-7.47, 0.87), P = 0.12; Level of evidence: very low), superoxide dismutase levels (SMD = 0.39, 95%CI(-0.26, 1.04), P = 0.24; Level of evidence: very low), total antioxidant capacity levels (SMD = 0.39, 95%CI(-0.23, 1.00), P = 0.21; Level of evidence: very low) and malondialdehyde levels (SMD = -3.36, 95%CI(-10.30, 3.09), P = 0.29; Level of evidence: very low).

Conclusion: Resveratrol improved inflammation and oxidative stress in T2DM patients to some extent. This provides a new idea and method for clinical treatment. However, due to the limitations of the study, more large-sample, multi-center clinical studies are needed to verify this conclusion.

KEYWORDS

resveratrol, inflammation, antioxidant, meta-analysis, type-2 diabetes mellitus

Introduction

Diabetes mellitus (DM), a metabolic disease characterized by chronic hyperglycemia, has become an epidemic worldwide (1). The International Diabetes Federation (IDF) reports that the global prevalence of DM among people aged 20-79 is expected to be 10.5% (536.6 million cases) in 2021, rising to 12.2%(783.2 million cases) by 2045 (2). Type 2 diabetes mellitus (T2DM) is a disease characterized by high blood sugar symptoms caused by islet dysfunction and cell resistance to insulin (3, 4). Chronic high blood sugar can lead to serious complications, including kidney disease, neuropathy and retinopathy, as well as microangiopathy and large vascular disease, which can seriously affect patients' quality of life (5–8).

At present, the treatment of T2DM mainly includes drug therapy, diet control and exercise therapy (9–12). However, the current treatment plan still has some shortcomings, such as drug treatment may bring some side effects, diet control and exercise therapy need patients to adhere to for a long time, and the effect is limited. T2DM patients often have difficulty changing their eating habits, so they can easily turn to dietary supplements to control the disease (13, 14).

Active substances from plants, including curcumin, pipeline, resveratrol, and carotene, are essential for health (15–19). Supplementation of these active substances can reduce the risk of cardiovascular disease, neurodegenerative diseases, T2DM, etc. (20–24). These supplements are not only designed to have anti-hyperglycemic effects, but also to reduce inflammatory responses and oxidative stress to prevent DM complications (1, 25, 26). Resveratrol is a natural polyphenolic compound found in grapes, peanuts and knotweed (27, 28). Recent studies have found that resveratrol has anti-inflammatory, antioxidant, hypoglycemic and other pharmacological effects (29). T2DM is a chronic metabolic disease in which patients are prone to inflammation and oxidative stress (30, 31). Resveratrol has strong antioxidant and anti-inflammatory effects, and can regulate the inflammatory response and oxidative stress level in the body through various ways, so it is expected to be an effective treatment option for T2DM patients (32). Therefore, it is of great significance to study the effects of resveratrol on inflammation and oxidative stress in T2DM patients.

In recent years, some studies in animal models of diabetes have shown that resveratrol supplementation can reduce inflammation and oxidative stress (33). However, clinical trials have shown controversial results (34–39). The effects of resveratrol supplementation on inflammation and oxidative stress in T2DM patients were unknown. The aim of this study was to investigate the effects of resveratrol on inflammation and oxidative stress in T2DM patients through a randomized double-blind placebo meta-analysis.

Abbreviations: T2DM, type 2 diabetes mellitus; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; MDA, malondialdehyde; TAC, total antioxidant capacity; CRP, C-reactive protein; LPO, Lipid peroxide; SOD, Superoxide dismutase; GPx, Glutathione peroxidase; Cat, Catalase; OSS, Oxidative stress score, GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Methods

Search strategy

We searched Pubmed, Web of Science,Embase,the Cochrane Library and other sources (ClinicalTrials, ProQuest Dissertations and Theses) for randomized controlled trials (RCTs) on the effects of resveratrol on inflammation and oxidative stress in patients withT2DM published from the beginning of the database to November 6, 2024. Use the following search terms: resveratrol, type-2 diabetes mellitus, randomized controlled trial, randomized, etc. Search strategies and search results for each database can be found in the Supplementary Materials.

Including and excluding criteria

Inclusion criteria

(1) Participants: Patients diagnosed with T2DM;
(2) Interventions: Oral resveratrol. The dosage and frequency of supplementation were not limited;
(3) Controls: The placebo was similar to the intervention group;
(4) Outcomes: Outcomes associated with oxidative stress and inflammatory response;
(5) Study design: Randomized controlled trial.

Exclusion criteria

(1) Animal experiments;
(2) The data in the article was not reliable;
(3) The original data cannot be extracted, and the full text of the literature cannot be obtained.

Data extraction

Two researchers performed literature screening, data extraction and cross-checking independently. In case of disagreement, discuss with the third party to resolve. The contents to be extracted include: (1) basic information included in the study; (2) Basic characteristics of population; (3) Details of interventions; (4) Key points for assessing the risk of bias; (5) Outcome data.

Risk of bias

The risk of bias of RCTs will be assessed using Cochrane risk of bias (RoB) 2 tool. The evaluation included 6 items: 1) the bias in the randomization process; 2) Bias away from established interventions; 3) Bias in outcome measurement; 4) Bias due to missing outcome data; 5) Bias in selective reporting of results; 6) Overall bias.

Certainty of the evidence

We will assess the certain of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. Since the original studies included were all RCTs, the evidence quality level was initially high, but it would be downgraded due to the risk of bias, inconsistency, incoherence, inaccuracy, and publication bias of the original study. The final quality of evidence was divided into four levels: "high", "moderate", "low" and "very low".

Data synthesis and statistical analysis

Meta-analysis was performed using RevMan 5.3 software. Continuous variables were expressed using standard mean difference (SMD) and its corresponding 95% confidence interval (CI). Statistical heterogeneity of test analysis: If $P \leq 0.1$ and $I(2) > 50\%$, it indicated that there was a large heterogeneity among the test results, and the random effects model was used for pooled analysis. On the contrary, the fixed effect model was used. Subgroup analysis was performed according to the dose of resveratrol. The stability of the meta-analysis results was verified by sensitivity analysis using the replacement effect model. The funnel plot was used to determine whether there was publication bias.

Results

Characteristics of included studies

Through searching the database and other resources, a total of 578 articles were retrieved. 314 duplicates were excluded using Endnote literature management software. After reading the title and abstract, 237 articles were excluded. After reading the full text, eight literatures were excluded according to the inclusion criteria and exclusion criteria, and six (34–39) literatures were finally included (Figure 1). All trials were registered. There were two three-arm trials (34, 35), so we split them into two arm trials for analysis. One trial (35)was conducted in Mexico. One trial (38) was conducted in Pakistan. One trial (34) was conducted in Italy. The remaining three trials (36, 37, 39) were conducted in Iran. The dose of Resveratrol ranges from 40mg to 1000mg. The duration of intervention ranged from 4 to 24 weeks. The basic characteristics of the included literatures were shown in Table 1. The included RCTs were of high quality (Figure 2).

C-reactive protein

Seven studies (34–39) involving 563 participants reported C-reactive protein(CRP) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol significantly reduced CRP levels compared with placebo (SMD = -1.40, 95%CI(-2.60, -0.21), P = 0.02) (Table 2, Figure 3A). Sensitivity analysis was conducted by fixed effect model. Meta-analysis of this outcome were stable (SMD = -0.81, 95%CI(-1.00, -0.62), $P < 0.00001$)(Table 2).

Interleukin-6

Five studies (34, 36–38) involving 435 participants reported interleukin-6 (IL-6) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol did not reduce IL-6 levels compared to placebo

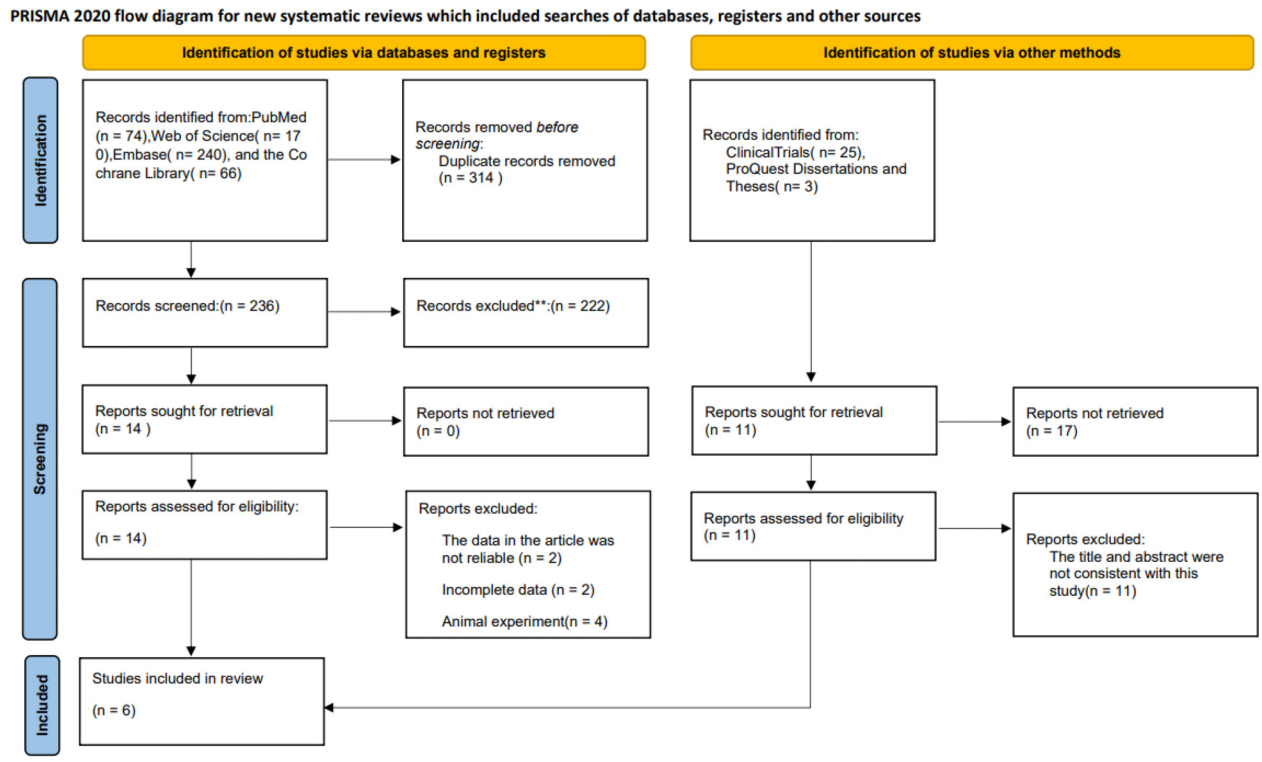

FIGURE 1
Flow diagram of study selection.

(SMD = -1.35, 95%CI(-2.75, -0.05), P = 0.06) (Table 2, Figure 3B). Sensitivity analysis was conducted by fixed effect model. The meta-analysis of this outcome was reversed (SMD = -0.53, 95% CI(-0.74, -0.32), P < 0.00001)(Table 2). This suggests that resveratrol may significantly reduce IL-6 levels in T2DM patients (Table 2).

Tumor necrosis factor α

Three studies (36–38) involving 198 subjects reported tumor factor α(TNF-α) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol did not significantly reduce TNF-α levels compared to placebo (SMD = -3.30, 95%CI(-7.47, 0.87), P = 0.12) (Table 2, Figure 3C). Sensitivity analysis was conducted by fixed effect model. The meta-analysis of this outcome was reversed(SMD = -0.83, 95%CI(-1.24, -0.43), P < 0.0001). This suggests that resveratrol may significantly reduce TNF-α levels in T2DM patients (Table 2).

Lipid peroxide

Two studies (35) involving 125 participants reported lipid peroxide(LPO) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol significantly reduced LPO levels compared to placebo (SMD = -0.99, 95%CI(-1.36, -0.61), P < 0.00001) (Table 2, Figure 4A). Random effects model was used for sensitivity analysis. Meta-analyses of this outcome were stable (SMD = -0.99, 95%CI(-1.36, -0.61), P < 0.00001)(Table 2).

8-isoprostanes

Two studies (35) involving 125 participants reported 8-isoprostanes levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol significantly reduced 8-isoprostanes levels compared with placebo (SMD = -0.79, 95%CI(-1.16, -0.42), P < 0.0001) (Table 2, Figure 4B). Random effects model was used for sensitivity analysis. Meta-analyses of this outcome were stable (SMD = -0.79, 95%CI(-1.29, -0.29), P = 0.002)(Table 2).

Superoxide dismutase

Three studies (35, 39) involving 171 participants reported superoxide dismutase (SOD) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol did not significantly increase SOD levels compared with placebo (SMD = 0.39, 95%CI(-0.26, 1.04), P = 0.24) (Table 2, Figure 4C). Sensitivity analysis was conducted by fixed effect model. The meta-analysis of this outcome was reversed (SMD = 0.43, 95% CI(0.12, 0.74), P = 0.006). This suggests that resveratrol may significantly increase SOD levels in T2DM patients (Table 2).

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TABLE 1 Characteristics of the included randomized controlled trials.

Study, year	Country	Registration number	Participants		Ages		Intervention		Dose	Duration
			Treatment group	Control group	Treatment group	Control group	Treatment group	Control group		
García-Martínez et al., 2023	Mexico	ISRCTN15172592	37	28	66 ± 6	64 ± 5	Resveratrol	Placebo	1000 mg	24 weeks
			32		64 ± 7		Resveratrol		500 mg	
Mahjabeen 2022	Pakistan	SLCTR/2018/019	55	55	49.42 ± 9.04	50.02 ± 12.57	Resveratrol	Placebo	200 mg	24 weeks
Khodabandehloo et al., 2018	Iran	IRCT2015080223336N2	25	20	56.48 ± 6.72	61.10 ± 5.61	Resveratrol	Placebo	800 mg	12 weeks
Seyyedebrahimi et al., 2018	Iran	IRCT2015072523336N1	23	23	54.96 ± 6.37	58.72 ± 6.06	Resveratrol	Placebo	800 mg	8 weeks
Javid et al., 2019	Iran	IRCT2015012420765N1	21	22	30-60		Resveratrol	Placebo	480 mg	4 weeks
Bo et al., 2016	Italy	NCT02244879	65	62	65.0 ± 7.6	65.4 ± 8.8	Resveratrol	Placebo	500 mg	24 weeks
			65		64.9 ± 8.6		Resveratrol		40 mg	

Glutathione peroxidase

Two studies (35) involving 125 participants reported glutathione peroxidase (GPx) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol significantly increased GPx levels compared to placebo (SMD = 0.38, 95%CI(0.03, 0.74), P = 0.04) (Table 2, Figure 4D). Random effects model was used for sensitivity analysis. Meta-analyses of this outcome were stable (SMD = 0.38, 95%CI(0.03, 0.74), P = 0.04)(Table 2).

Catalase

Three studies (35, 39) involving 171 participants reported catalase (Cat) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol significantly increased Cat levels compared to placebo (SMD = 0.33, 95%CI(0.03, 0.63), P = 0.03) (Table 2, Figure 4E). Random effects model was used for sensitivity analysis. Meta-analyses of this outcome were stable (SMD = 0.33, 95%CI(0.03, 0.63), P = 0.03)(Table 2).

Total antioxidant capacity

Three studies (35, 36) involving 168 participants reported Total antioxidant capacity(TAC) levels before and after treatment in patients with T2DM. The results of the meta-analysis showed that resveratrol did not significantly increase TAC levels compared to placebo(SMD = 0.39, 95%CI(-0.23, 1.00), P = 0.21) (Table 2, Figure 4F). Sensitivity analysis was conducted by fixed effect model. The meta-analysis of this outcome was reversed (SMD = 0.40, 95%CI (0.09, 0.71), P = 0.01). This suggests that resveratrol may significantly increase TAC levels in patients with T2DM (Table 2).

Oxidative stress score

Two studies (35) involving 125 subjects reported oxidative stress scores (OSS) in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol significantly reduced OSS compared to placebo(SMD = -1.62, 95%CI(-2.49, -0.75), P = 0.0003) (Table 2, Figure 4G). Sensitivity analysis was conducted by fixed effect model. Meta-analyses of this outcome were stable (SMD = -1.58, 95%CI(-1.99, -1.17), P < 0.00001)(Table 2).

Malondialdehyde

Two studies (38, 39) involving 156 participants reported malondialdehyde (MDA) levels in patients with T2DM before and after treatment. The results of the meta-analysis showed that resveratrol did not significantly reduce MDA levels compared to placebo(SMD = -3.36, 95%CI(-10.30, 3.09), P = 0.29) (Table 2, Figure 4H). Sensitivity analysis was conducted by fixed effect model. The meta-analysis of this outcome was reversed (SMD = -1.87, 95%

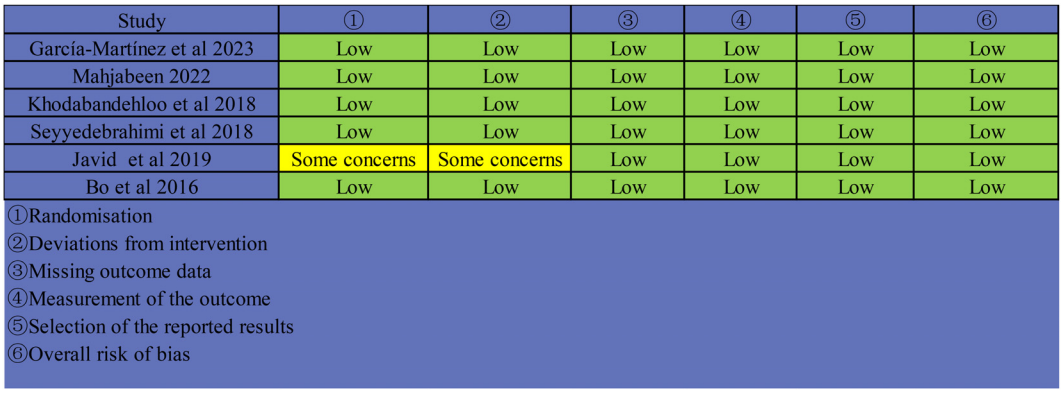

FIGURE 2
Risk of bias assessment by cochrane risk-of-bias tool for included RCTs.

CI(-2.38, -1.37), P < 0.00001). This suggests that resveratrol may significantly reduce MDA levels in T2DM patients (Table 2).

Adverse event

All studies investigated the occurrence of adverse events. The results showed that resveratrol had a high safety profile with no adverse events.

Subgroup analysis

We performed subgroup analyses of CRP and IL-6 based on the dose of resveratrol (< 500mg vs ≥ 500mg). The results showed that no difference was observed whether the dose of resveratrol was < 500mg or ≥ 500mg (P > 0.05)(Table 3).

Publication bias analysis

We conducted a publication bias analysis for CRP. The results showed that the funnel plot was asymmetrical and there may be publication bias (Figure 5).

Evidence quality evaluation

The quality of evidence for each outcome measure was assessed using the GRADE system. RCTs without major defects are by default the highest level of evidence in GRADE. The quality of the evidence was evaluated and processed according to 5 downgrade factors and 3 upgrade factors. The evidence quality of 5 outcome indicators was low, and the rest was very low (Table 4).

TABLE 2 Sensitivity analysis of each outcomes.

Outcomes	Pooled analysis results			Change model analysis results		
	Model	SMD(95%CI)	*P*-value	Model	SMD(95%CI)	*P*-value
C-reactive protein	Random	**-1.40(-2.60, -0.21)**	**0.02**	Fixed	**-0.81(-1.00, -0.62)**	**P < 0.00001**
Interleukin-6	Random	-1.35(-2.75, 0.05)	0.06	Fixed	**-0.53(-0.74, -0.32)**	**P < 0.00001**
Tumor necrosis factor α	Random	-3.30(-7.47, 0.87)	0.12	Fixed	**-0.83(-1.24, -0.43)**	**P < 0.0001**
Lipid peroxide	Fixed	**-0.99(-1.36, -0.61)**	**P < 0.00001**	Random	**-0.99(-1.36, -0.61)**	**P < 0.00001**
8- isoprostanes	Fixed	**-0.79(-1.16, -.042)**	**P < 0.0001**	Random	**-0.79(-1.29, -0.29)**	**0.002**
Superoxide dismutase	Random	0.39(-0.26, 1.04)	0.24	Fixed	**0.43(0.12, 0.74)**	**0.006**
Glutathione peroxidase	Fixed	**0.38(0.03, 0.74)**	**0.04**	Random	**0.38(0.03, 0.74)**	**0.04**
Catalase	Fixed	**0.33(0.03, 0.63)**	**0.03**	Random	**0.33(0.03, 0.63)**	**0.03**
Total antioxidantcapacity	Random	0.39(-0.23, 1.00)	0.21	Fixed	**0.40(0.09, 0.71)**	**0.01**
Oxidative stress score	Random	**-1.62(-2.49, -0.75)**	**0.0003**	Fixed	**-1.58(-1.99, -1.17)**	**P < 0.00001**
Malondialdehyde	Random	-3.60(-10.30, 3.09)	0.29	Fixed	**-1.87(-2.38, -1.37)**	**P < 0.00001**

SMD, Standard mean difference; CI, Confidence interval; Bold characters indicate statistically significant differences.
Bold font indicates that the difference is statistically significant.

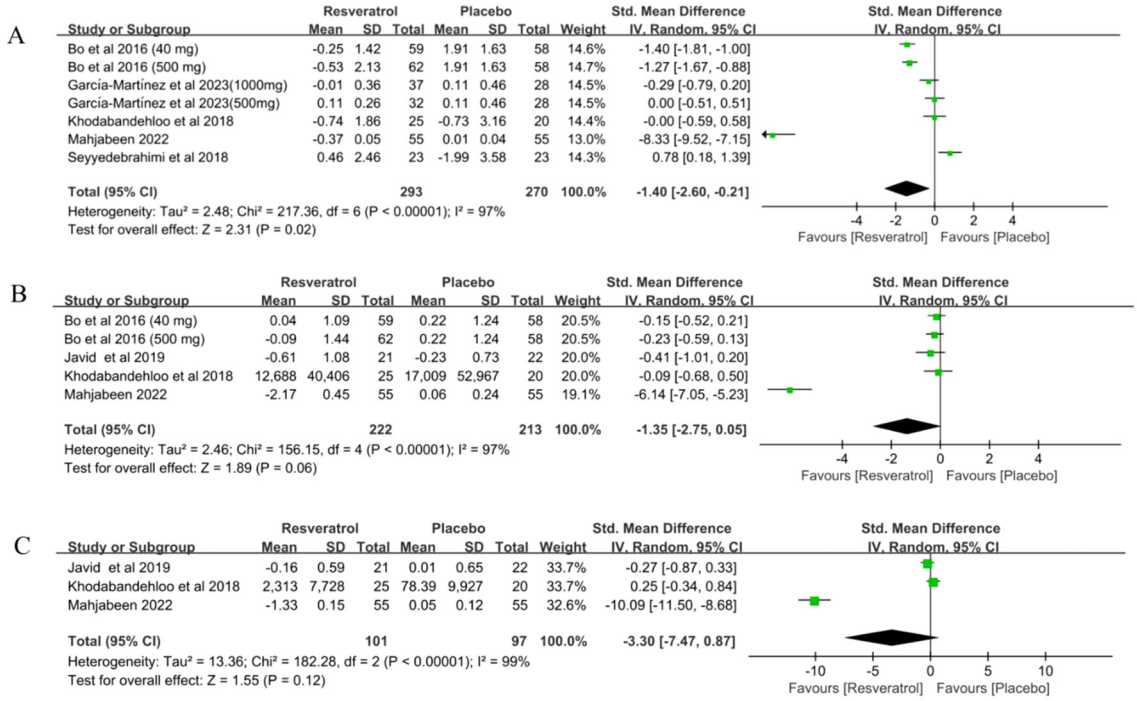

FIGURE 3
Forest plot for effect of resveratrol supplementation on biomarkers of inflammation **(A)** C-reactive protein, **(B)** interleukin-6 and **(C)** tumor necrosis factor α in type-2 diabetes mellitus patients.

Discussion

This meta-analysis is the most comprehensive data available on the effects of resveratrol supplementation on inflammation and oxidative stress in patients with T2DM. Many previous meta-analyses have confirmed that resveratrol can improve insulin resistance in T2DM patients, reduce fasting blood glucose and insulin levels, improve cardiometabolic parameters, and improve blood lipids (29, 40–43). Resveratrol is a polyphenol compound found naturally in grape skins, red wine and other foods, and is widely studied and believed to have anti-inflammatory and antioxidant effects (44). DM is a common chronic metabolic disease, often accompanied by inflammation and oxidative stress (45). In studies conducted in animal models of T2DM, resveratrol has been shown to have antioxidant, anti-inflammatory and even hypoglycemic effects (33).

This meta-analysis evaluated the overall effect of resveratrol on inflammation and oxidative stress in patients with T2DM by summarizing the results of six RTCs, involving 533 participants. In this meta-analysis, we found that resveratrol supplementation had a modest effect on inflammation and oxidative stress levels in patients with T2DM, particularly in reducing CRP levels, LPO levels, 8-isoprostanes levels, and OSS. At the same time, we observed that resveratrol supplementation increased GPx levels and Cat levels, further confirming its antioxidant effects. However, no significant differences were observed on some measures, such as IL-6, TNF-α, SOD, TAC, and MDA levels. Although our meta-analysis found no significant differences observed on certain markers of inflammation and oxidative stress, such as IL-6, TNF-α, SOD, TAC, and MDA levels. However, when we performed sensitivity analysis, we found that these outcomes were statistically significant. Due to the small number of studies included in this meta-analysis and the limited sample size, no significant differences in these outcomes were observed. The evidence quality of the relevant outcome indicators of the included literatures in this study is very low, which may affect the reliability of the research conclusions.

Resveratrol can reduce inflammation in T2DM patients in a variety of ways. The inflammatory response in T2DM patients is closely associated with hyperglycemia, leading to insulin resistance and impaired islet beta cell function (46, 47). Studies have shown that resveratrol can inhibit the activation of NF-κB signaling pathway and reduce the release of inflammatory factors such as TNF-α and IL-6, thereby reducing inflammatory response and improving insulin sensitivity, thus helping to control blood sugar levels in T2DM patients (35). In addition, resveratrol can inhibit inflammation by regulating toll-like receptor signaling pathways and cytokine signaling pathways associated with inflammation (48). Secondly, resveratrol can also reduce oxidative stress in T2DM patients through antioxidant effects (46). The hyperglycemic state of T2DM patients leads to excessive production of free radicals in the body, which exceeds the clearance capacity of the antioxidant system, thus triggering oxidative stress response and impairs cell structure and function (49, 50). Studies have shown that resveratrol can increase the activity of antioxidant enzymes and reduce the level of oxidative stress indicators such as MDA, thereby reducing the damage caused by oxidative stress (48). These effects are mediated by several intracellular signaling pathways, including nuclear factor κB

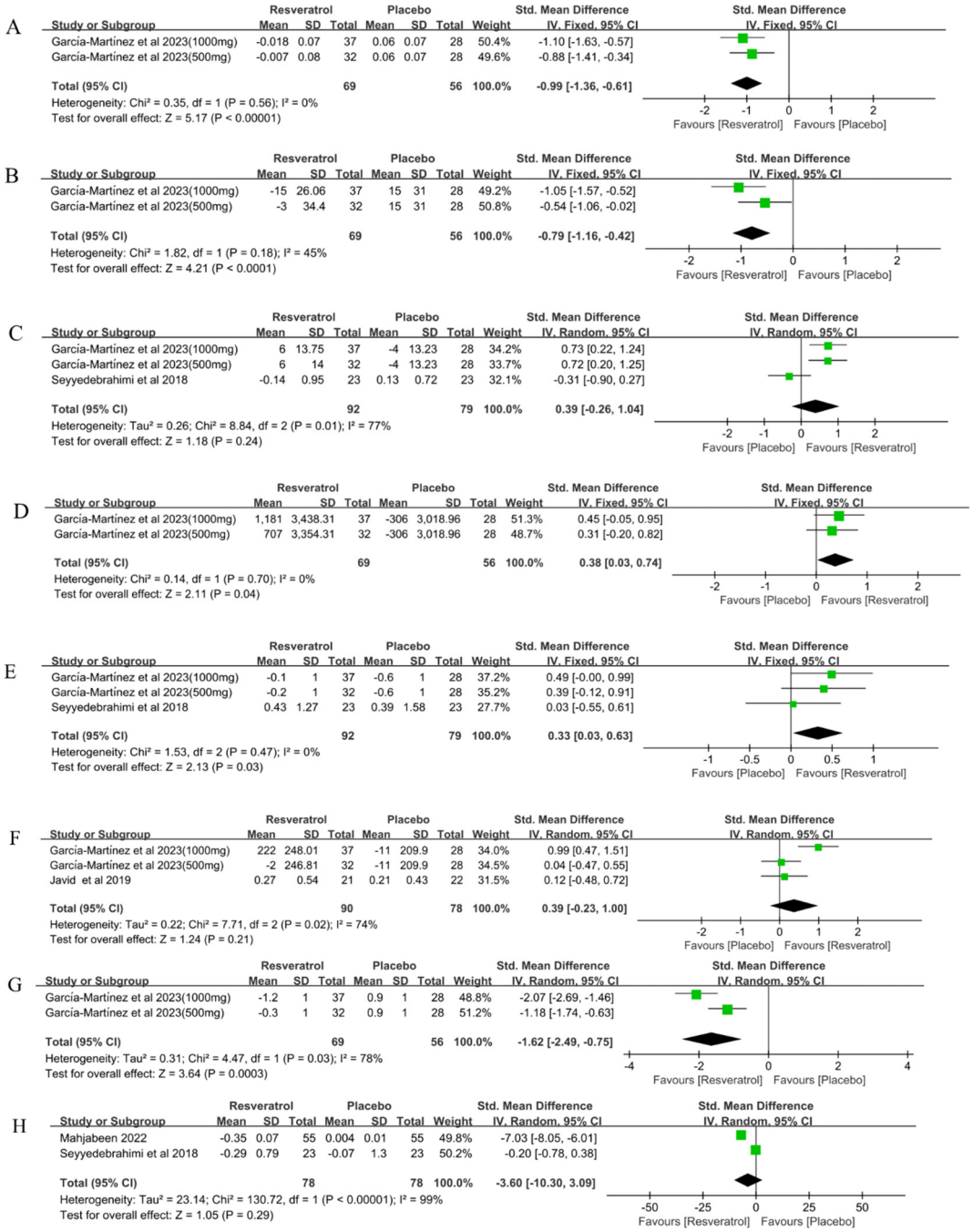

FIGURE 4
Forest plot for effect of resveratrol supplementation on oxidative stress **(A)** lipid peroxide, **(B)** 8-isoprostanes, **(C)** superoxide dismutase, **(D)** glutathione peroxidase, **(E)** catalase, **(F)** total antioxidant capacity, **(G)** oxidative stress score and **(H)** malondialdehyde in type-2 diabetes mellitus patients.

TABLE 3 Subgroup analysis.

Outcomes	Dose	No. of studies	Heterogeneity		SMD(95%CI)	*P* Value
			I2	P		
C-reactive protein	< 500 mg	2	99.2%	< 0.0001	-4.88(-11.72, 1.96)	0.162
	≥ 500mg	5	89.7%	< 0.0001	-0.18(-0.88, 0.53)	0.626
Interleukin-6	< 500 mg	3	99%	< 0.0001	-2.20(-5.12, 0.71)	0.140
	≥ 500mg	2	0	0.7	-0.19(-0.50, 0.12)	0.220

SMD, Standard mean difference; CI, Confidence interval

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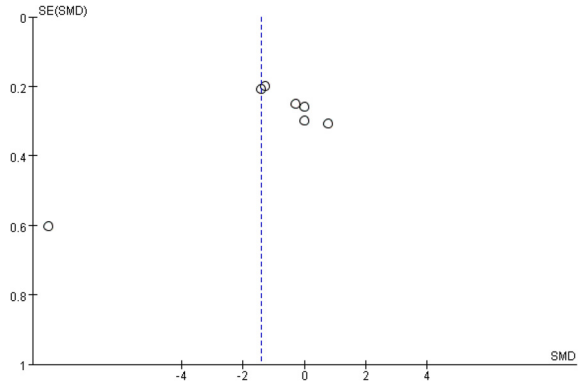

FIGURE 5
Funnel diagram of C-reactive protein.

inhibitor kinase/nuclear factor (NF) κB inhibitor/NF-κB pathway, adenosine phosphate kinase pathway, phosphatidylinositol-3 kinase/protein kinase B/endothelial nitric oxide synthase, etc (35, 46, 51). Resveratrol can improve insulin resistance by upregulating miRNA mmu-miR-363-3p through PI3K-Akt pathway and prevent pancreatic β cell damage and dysfunction (52, 53). Resveratrol can restore pancreatic β cells by inhibiting p38/p16MAPK pathway through SIRT1-dependent pathway, thus effectively improving ethanol-induced diabetes (54, 55). Resveratrol activates SIRT-1/NF-κB signaling pathway to reduce cellular inflammation and oxidative stress (56, 57). The anti-inflammatory effect of Resveratrol is mainly achieved by reducing cellular inflammation and oxidative stress by regulating STAT1 and SIRT1 signaling pathways. Studies have shown that Resveratrol inhibits the expression of COX-2 and iNOS by blocking the activation of NF-κB (58). In addition, Resveratrol can regulate the expression of NF-κB/Nrf 2 after H2O2 treatment (59). Therefore, part of the efficacy of Resveratrol, including anti-inflammatory antioxidant effects, may be mediated by the NF-κB/Nrf-2 pathway. In general, resveratrol can reduce the level of inflammation and oxidative stress in T2DM patients by inhibiting the release of inflammatory factors and enhancing antioxidant capacity, thus playing a certain role in improving the condition of DM. Future studies can further explore the potential mechanism of resveratrol in the treatment of diabetes and provide more references and guidance for clinical treatment.

Limitation

First of all, because there were few RCT trials in this field, the sample size was insufficient, which affected the research results. Second, the dose and intervention time of resveratrol included in the study were different, which also affected the evaluation effect of this study. Third, most of the included documents come from Middle Eastern countries, which may have ethnic and regional differences. Finally, due to limitations in the number of included studies and the type of specific intervention, we did not conduct more subgroup analyses. Therefore, we suggest that readers should take these limitations into account when applying the conclusions of this study.

TABLE 4 GRADE systematic evaluation of evidence quality.

Outcomes	Quality assessment					Intervention/Control	SMD(95%CI)	Quality of evidence
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
C-reactive protein	Not serious	Serious[2]	Not serious	Not serious	Serious[4]	293/270(7 studies)	-1.40(-2.60, -0.21)	Low: ⊕⊕◯◯
Interleukin-6	Limitations[1]	Serious[2]	Not serious	Not serious	Serious[5]	222/213(5 studies)	-1.35(-2.75, 0.05)	Very low: ⊕◯◯◯
Tumor necrosis factor α	Limitations[1]	Serious[2]	Not serious	Serious[3]	Serious[5]	101/97(3 studies)	-3.30(-7.47, 0.87)	Very low: ⊕◯◯◯
Lipid peroxide	Not serious	Not serious	Not serious	Serious[3]	Serious[5]	69/56(2 studies)	-0.99(-1.36, -0.61)	Low: ⊕⊕◯◯
8- isoprostanes	Not serious	Not serious	Not serious	Serious[3]	Serious[5]	69/56(2 studies)	-0.79(-1.16, -.042)	Low: ⊕⊕◯◯
Superoxide dismutase	Not serious	Serious[2]	Not serious	Serious[3]	Serious[5]	92/97(3 studies)	0.39(-0.26, 1.04)	Very low: ⊕◯◯◯
Glutathione peroxidase	Not serious	Not serious	Not serious	Serious[3]	Serious[5]	69/56(2 studies)	0.38(0.03, 0.74)	Low: ⊕⊕◯◯
Catalase	Not serious	Not serious	Not serious	Serious[3]	Serious[5]	92/97(3 studies)	0.33(0.03, 0.63)	Low: ⊕⊕◯◯
Total antioxidantcapacity	Limitations[1]	Serious[2]	Not serious	Serious[3]	Serious[5]	90/78(3 studies)	0.39(-0.23, 1.00)	Very low: ⊕◯◯◯

(Continued)

TABLE 4 Continued

Outcomes	Quality assessment						Intervention/ Control	SMD(95%CI)	Quality of evidence
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias				
Oxidative stress score	Not serious	Serious[2]	Not serious	Serious[3]	Serious[5]		69/56(2 studies)	-1.62(-2.49, -0.75)	Very low: ⊕◯◯◯
Malondialdehyde	Not serious	Serious[2]	Not serious	Serious[3]	Serious[5]		78/78(2 studies)	-3.60(-10.30, 3.09)	Very low: ⊕⊕◯◯

[1]Some RCTs did not mention using the randomized scheme hiding or randomized grouping; [2]Significant heterogeneity;[3]The study sample size was small;[4] The funnel plot was asymmetrical; [5]The number of studies was small.

Conclusion

Resveratrol improved inflammation and oxidative stress in T2DM patients to some extent. The relevant mechanism may be related to its antioxidant and anti-inflammatory effects, which has certain guiding significance for clinical practice. However, due to the limitations of the study, more large-sample, multi-center clinical studies are needed to verify this conclusion, so as to better guide clinical practice.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

PZ: Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YJ: Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. JS: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. XZ: Conceptualization, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1463027/full#supplementary-material

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