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ORIGINAL RESEARCH

Resveratrol and Renal Biomarkers in Type 2 Diabetes: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Aim: This study aimed to systematically evaluate the effects of resveratrol (RSV) supplementation on renal injury-related indicators in patients with type 2 diabetes mellitus (T2DM).

Data Synthesis: This systematic review and meta-analysis included 12 randomized controlled trials (RCTs) with a total of 636 participants with type 2 diabetes. The analysis was conducted exclusively on RCTs to ensure the highest quality of evidence. The pooled results demonstrated no significant changes in blood urea nitrogen (WMD: –0.01; 95% CI: –0.66 to 0.63; P = 0.97) or serum creatinine (SMD: 0.05; 95% CI: –0.13 to 0.23; P = 0.56). Subgroup analyses revealed no significant differences regardless of RSV dose or intervention duration. In contrast, RSV supplementation resulted in a modest reduction in serum uric acid of −0.42 mg/dL (WMD: –0.42; 95% CI: –0.65 to –0.18; P = 0.0005), with low heterogeneity among the included studies (I^2 = 0%).

Conclusion: This systematic review and meta-analysis provides updated evidence that RSV significantly reduces serum UA levels in patients with T2DM, despite having no significant effects on BUN and SCr. This specific urate-lowering effect suggests a potential role for RSV in managing hyperuricemia, a common comorbidity in T2DM that contributes to renal and cardiovascular risk.

Systematic Review Registration: PROSPERO CRD420251033457.

Keywords: resveratrol, type 2 diabetes, uric acid, blood urea nitrogen, serum creatinine, meta-analysis

Introduction

Concomitant with the persistent rise in the prevalence of diabetes, the incidence of diabetic kidney disease (DKD)—a prevalent complication of diabetes—is also increasing. According to data from the International Diabetes Federation (IDF) collected in 2021, approximately 573 million adults worldwide have been diagnosed with diabetes, with around one-third of these individuals progressing to DKD.[1] Within China's diabetic population, the prevalence of DKD ranges from 21.1% to 46.6%.[2] Previous clinical approaches to managing DKD have included optimal glycemic and blood pressure control, improving microcirculation, inhibiting RASS activation, and traditional Chinese medicine treatments. However, despite the implementation of these interventions, the progression to end-stage renal disease (ESRD) has not been meaningfully delayed. Consequently, there is an urgent need for effective therapeutic strategies to control the advancement of DKD.

Resveratrol (RSV) is a non-flavonoid polyphenolic compound that is derived from grapes, nuts, berries, and red wine. As a naturally occurring antioxidant, it has been demonstrated to possess anti-inflammatory,[3] hypoglycemic,[4] hypotensive effects,[5] and the capacity to ameliorate atherosclerosis.[6] Its use as a therapeutic approach is frequently recommended for various conditions, including cancer, coronary heart disease, neurodegenerative disorders, and diabetes. According to the findings of fundamental research, RSV has been demonstrated to improve renal damage in DKD through multiple

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in vitro and in vivo mechanisms, while also delaying its progression.[7,8] However, clinical studies, particularly randomized controlled trials (RCTs), have yielded conflicting evidence regarding RSV's impact on renal function in diabetic patients. To evaluate renal function and injury in clinical settings, specific serum biomarkers are routinely used. In this analysis, we focused on blood urea nitrogen (BUN) and serum creatinine (SCr) as they are the most widely accepted and fundamental indicators for glomerular filtration rate (GFR) and renal functional capacity.[9] Changes in these parameters provide a direct assessment of renal excretory function. Furthermore, we included serum uric acid (UA) as a key outcome, given the established role of hyperuricemia as an independent risk factor for the development and progression of DKD.[10] Elevated UA levels contribute to renal inflammation, endothelial dysfunction, and oxidative stress, thereby accelerating renal damage.[11] Therefore, investigating the effect of RSV on this triad of biomarkers—BUN and SCr for functional assessment and UA for risk stratification—can provide a comprehensive perspective on its potential for renal protection in T2DM. The postulated renal benefits of RSV are supported by preclinical evidence highlighting its ability to activate key cellular pathways, including the antioxidant Nrf2 signaling,[12] the energy sensor SIRT1/AMPK axis,[13] and the inhibition of the pro-fibrotic TGF-β pathway,[14] which collectively combat oxidative stress, inflammation, and fibrosis in the diabetic kidney. This paper therefore reviews existing RCT data on RSV's effects on renal parameters in type 2 diabetes mellitus (T2DM) patients, conducting a comprehensive statistical analysis of these studies. The text incorporates newly published research from recent years, aiming to provide additional objective data supporting the clinical application of RSV in diabetes-related renal injury management.

Method

This work was reported in accordance with PRISMA guidelines.

The inclusion criteria for this systematic review were developed following the PRISMA guidelines[15] and the PICOS model, as follows: Population (P): patients with T2DM; Intervention (I): RSV supplementation; Comparison (C): control or placebo; Outcomes (O): renal function-related indicators; Study design (S): randomized controlled trials (RCTs). The study agreement has been registered in the Prospero platform (No. CRD420251033457).

Search Strategy

From the database's inception until May 2025, systematic searches were conducted in PubMed, Embase, Web of Science, Cochrane Library, VIP Database, CNKI Database, and Wangfang Database. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text terms, using the Boolean operators "AND" and "OR" to connect key concepts. The following search string represents the strategy used in PubMed and was adapted for other databases: ("resveratrol" OR "trans-resveratrol") AND ("diabetes mellitus" OR "diabetic nephropathy" OR "type 2 diabetes" OR "diabetic kidney disease") AND ("serum creatinine" OR "uric acid" OR "urea" OR "urine protein" OR "blood urea nitrogen" OR "renal function"). A comprehensive list of relevant literature was obtained through the implementation of various search methods, including synonym searches, subject term searches, free-text searches, and title/abstract searches. The resolution of discrepancies was achieved through the medium of expert panel discussions. Precise term searches, retrieval of term sets, and identification of derived terms were achieved using quotation marks, parentheses, and asterisks. No restrictions were imposed on the publication date or language. Furthermore, a manual search was conducted of the reference lists of all retrieved articles.

Selection Criteria

Two researchers (M.N., Y.Y.) conducted an initial screening to identify studies that met the inclusion criteria. This was followed by a detailed assessment of the full texts of potentially eligible studies by the same researchers. Any discrepancies were resolved through consultation with the corresponding author (G.W.).

The following criteria were used to determine the eligibility of trials for consideration: (a) randomized controlled trials (parallel or crossover design); (b) participants aged ≥18 years; (c) population consisting of individuals with T2DM mellitus; (d) comparison of RSV versus placebo; (e) inclusion of at least one renal function-related outcome measure (including urea, serum creatinine, uric acid, urinary microalbumin, urine albumin-to-creatinine ratio, or 24-hour urine protein quantification). The following criteria are to be met by studies for them to be considered: The inclusion of RSV in

a compound formulation with other active ingredients is the first criterion. Secondly, studies lacking a separate control group are to be excluded. The third criterion is that interventions that use grapes or grape products as the RSV source are to be excluded. The fourth criterion is that clinical studies with insufficient observation duration—less than one week—are to be excluded. Finally, studies involving pregnant or lactating women are to be excluded.

Data Extraction

The data extraction process was conducted independently by two researchers (S.L.W., Y.F.). The following details were specifically collected: the first author's name, the year of publication, the study location, the study design, the sample size per group, the dosage and duration of administration of RSV, the participants' age, gender, and health status. Furthermore, mean values, standard deviations, or change values for target outcome measures were extracted for both the RSV group and the control group before and after treatment. In instances where necessary, the data were converted to mean ± standard deviation format using the recommended formula.[16] The conversion of all outcome measure units was executed in a uniform manner. In instances where multiple papers derived from the same study were identified, the publication encompassing the most extensive participant cohort or the longest follow-up duration was selected for analysis. In the event that the reported data proves insufficient for inclusion, the required information will be formally requested via Email correspondence with the corresponding author. All serum creatinine values were converted to mg/dL, and uric acid values to mg/dL, where necessary, using standard conversion factors.

Assessment of Bias Risk

Two researchers (M.N. and Y.Y.) employed the Cochrane Collaboration's assessment tool[17] to evaluate the methodological quality of the included randomized controlled trials across five domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. The final assessment was conducted in accordance with the recommendations outlined in the Cochrane Handbook. Studies were considered to be of good quality if all assessed domains were found to be at low risk of bias. Conversely, studies were deemed to be of poor quality if two or more domains were determined to be at high risk of bias. Finally, studies were classified as having an unclear risk of bias if two or more domains were deemed to be at unclear risk of bias.

Certainty of Evidence

The quality of the evidence was assessed by two independent researchers (G.W., M.N.) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.[18] Randomized controlled trials (RCTs) have been shown to yield high-quality evidence initially; however, the final quality may be subject to downgrading due to limitations inherent in the study design, inconsistent findings, the presence of publication bias, and other factors. The results of this assessment are summarized in the Summary of Findings table (Table 1).

Data Analysis

The statistical analyses of the included studies' data were conducted using RevMan 5.4 software. All results were reported as means with corresponding variances; thus, weighted mean differences (WMD) with 95% confidence intervals

Table 1 Summary of Findings and GRADE Evidence Profile

BUN	324 (6 RCTs)	WMD: −0.01 (−0.66 to 0.63)	⊕⊕⊕◯ MODERATE	Downgraded one level for imprecision (wide confidence intervals crossing the line of no effect).
SCr	466 (10 RCTs)	SMD: 0.05 (−0.13 to 0.23)	⊕⊕⊕⊕ HIGH	No serious risk of bias, inconsistency, indirectness, imprecision, or publication bias were detected.
UA	411 (6 RCTs)	WMD: −0.42 (−0.65 to −0.18)	⊕⊕⊕⊕ HIGH	No serious risk of bias, inconsistency, indirectness, imprecision, or publication bias were detected.

Notes: GRADE Working Group grades of evidence: High certainty (⊕⊕⊕⊕): We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty (⊕⊕⊕◯): We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

were used as effect measures. The choice between a fixed-effect model and a random-effects model was determined a priori based on the level of statistical heterogeneity. A fixed-effect model was employed when negligible heterogeneity was present ($I^2 < 50\%$). In cases where substantial heterogeneity was observed ($I^2 \geq 50\%$), a random-effects model was used to provide a more conservative estimate, as it accounts for variability both within and between studies. In instances where $I^2 \geq 50\%$, the heterogeneity was addressed via the implementation of random-effects models or subgroup analyses. The WMD, calculated using the inverse variance method, served as the effect measure for units obtained through identical measurement methods or identical interventions. Sensitivity analyses were conducted by excluding trials identified as outliers based on effect size in the primary analysis. In instances where more than ten trials were included, the presence of publication bias was assessed using the Begg's funnel plot and the Egger's regression symmetry test. The statistical significance between studies was determined by establishing a P-value less than 0.05.

Results

An overview of the certainty of evidence for the primary outcomes, based on the GRADE framework, is presented in Table 1. The following sections detail the study selection, characteristics, and meta-analysis results.

Search and Selecting Included Studies

Pursuant to the search strategy, an initial search across seven databases yielded 1663 relevant publications. Following the exclusion of duplicates across databases, 441 publications remained for further analysis. Following a thorough examination of the abstracts, studies involving animal research, cellular studies, reviews, and non-randomized controlled trials (non-RCTs) were excluded, resulting in the retention of 22 articles. Following a thorough examination of the extant literature, 10 articles were excluded from the analysis. The primary reasons for exclusion were the absence of the requisite outcome measures for this particular analysis, inadequate study design, or insufficient research quality. Following a thorough examination of the available literature, a total of 12 studies were deemed to meet the established criteria and were thus incorporated into the subsequent meta-analysis. As illustrated in Figure 1, the process of literature search and study selection was meticulous.

Study Characteristics

A total of twelve eligible studies were identified, with four originating from Iran, two from India and one each from Mexico, Brazil, the Netherlands, Italy, Singapore, and Spain. The patient population in this study ranged in age from 45 to 75 years, with RSV doses ranging from 8 to 1000 mg/day and observation periods spanning from 45 days to 48 weeks, as outlined in Table 2.

Risk of Bias of Included Studies

Following a thorough evaluation, seven out of twelve studies were classified as high quality (Batista-Jorge et al, 2020; Khodabandehloo et al, 2018; Sattarinezhad et al, 2018; Timmers et al, 2016; Tomé-Carneiro et al, 2013, García-Martínez et al, 2023, Bo et al, 2016). A total of three studies (Bhatt et al, 2013, Movahed et al, 2013, Bhatt et al, 2012) had allocation bias. Another one studies (Goh et al, 2014) had problems with the implementation of blinding, and one study (Seyyedebrahimi et al, 2018) had bias in the blinding of outcome assessment. As illustrated in Figure 2, the methodological quality assessment results for the included studies are presented.

Meta-Analysis

Blood urea nitrogen (BUN): A total of six studies, involving 324 participants, have examined the effect of RSV on blood BUN levels in individuals with T2DM. These studies, which are listed below, were conducted by García-Martínez et al, Batista-Jorge et al, Seyyedebrahimi et al, Khodabandehloo et al, Bhattr et al, and appeared in 2023, 2020, 2018, 2018, and 2013/2012, respectively. The pooled analysis revealed no substantial effect of RSV on BUN levels in individuals with T2DM, exhibiting minimal heterogeneity between studies (WMD: −0.01; 95% CI: −0.66 to 0.63; $P = 0.97$; $I^2 = 0\%$; Figure 3).

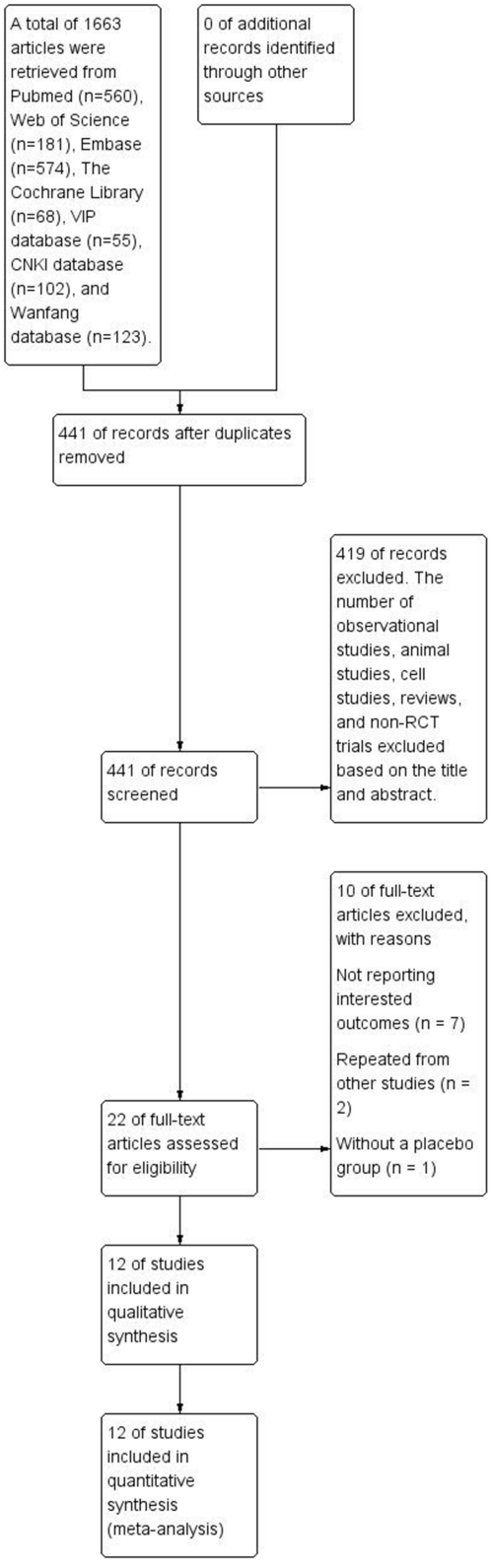

Figure 1 Flow diagram of the study selection process.
Notes: This diagram illustrates the process of identifying, screening, and including studies in the systematic review and meta-analysis, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Abbreviation: RCTs, randomized controlled trials.

Table 2 Baseline Characteristics of Included Studies

Authors (Ref)	Time	Country	Sample Size		Age(y)		Intervention		Study Design
			Control	Intervention	Control	Intervention	Control	Intervention	
García-Martínez[19]	2023	Mexico	28	32	64 ± 5	63 ± 7	Placebo	500mg/d, 24weeks	Double-blind, randomized, pacebo-controlled, parallel trial
García-Martínez[19]	2023	Mexico	28	37	64 ± 5	66 ± 6	Placebo	1000mg/d, 24weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Batista-Jorg[20]	2020	Brazil	9	13	NA	NA	Placebo	250mg/d, 12weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Seyyedebrahimi[21]	2018	Iran	23	23	58.72 ± 6.06	54.96 ± 6.37	Placebo	800mg/d, 8weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Sattarinezhad[22]	2018	Iran	30	30	55.7± 10.8		Placebo	500mg/d, 12weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Khodabandehloo[23]	2018	Iran	20	25	61.10 ± 5.61	56.48 ± 6.72	Placebo	800mg/d, 8weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Timmers[24]	2016	Nether-lands	17	17	64 (59.19–67.28)		Placebo	150mg/d, 4weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Bo[25]	2016	Italy	58	59	65.4±8.8	64.9±8.6	Placebo	40mg/d, 24weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Bo[25]	2016	Italy	58	62	65.4±8.8	65.0±7.6	Placebo	500mg/d, 24weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Goh[26]	2014	Singapore	5	5	56.8 ± 5.3	55.8 ± 7.3	Placebo	500mg/d, 12weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Tomé-Carneiro[27]	2013	Spain	9	13	57 ± 10	63 ± 12	Placebo	8mg/d, 48weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Movahed[28]	2013	Iran	31	33	51.81 ± 6.99	52.45 ± 6.18	Placebo	1000mg/d, 45day	Double-blind, randomized, pacebo-controlled, parallel trial
Bhatt[29]	2013	India	29	28	57.75± 8.71	56.67±8.91	Placebo	250mg/d, 24weeks	Double-blind, randomized, pacebo-controlled, parallel trial
Bhatt[30]	2012	India	29	28	57.75 ± 8.71	56.67 ± 8.91	Placebo	250mg/d, 12weeks	Double-blind, randomized, pacebo-controlled, parallel trial

Notes: Some studies (García-Martínez et al, 2023; Bo et al, 2016) contained multiple intervention arms testing different doses of resveratrol. Each arm is presented as a separate row and was analyzed independently in the meta-analysis against a shared control group to avoid double-counting.

Subgroup analysis revealed that different RSV doses had no effect on BUN levels in T2DM patients: low-dose group (WMD: −0.06; 95% CI: −0.72 to 0.60; P = 0.86; I^2 = 0%), high-dose group (WMD: 1.08; 95% CI: −2.06 to 4.21; P = 0.50; I^2 = 0%) Figure 4. Furthermore, in the subgroups with intervention duration less than 24 weeks (WMD: −0.00; 95% CI: −0.81 to 0.81; P = 1.0; I^2 = 0%) and those with intervention duration of 24 weeks or more (WMD: −0.03; 95% CI: −1.09 to 1.02; P = 0.95; I^2 = 0%), RSV did not have a significant effect on BUN levels Figure 5.

Serum creatinine (SCr): A total of 10 studies, involving 466 participants, evaluated the effect of resveratrol on SCr levels in patients with type 2 diabetes (García-Martínez et al, 2023; Batista-Jorge et al, 2020; Khodabandehloo et al, 2018; Sattarinezhad et al, 2018; Timmers et al, 2016; Goh et al, 2014; Tomé-Carneiro et al, 2013; Movahed et al, 2013; Bhatt et al, 2013; Bhatt et al, 2012). The pooled meta-analysis demonstrated no significant effect of resveratrol

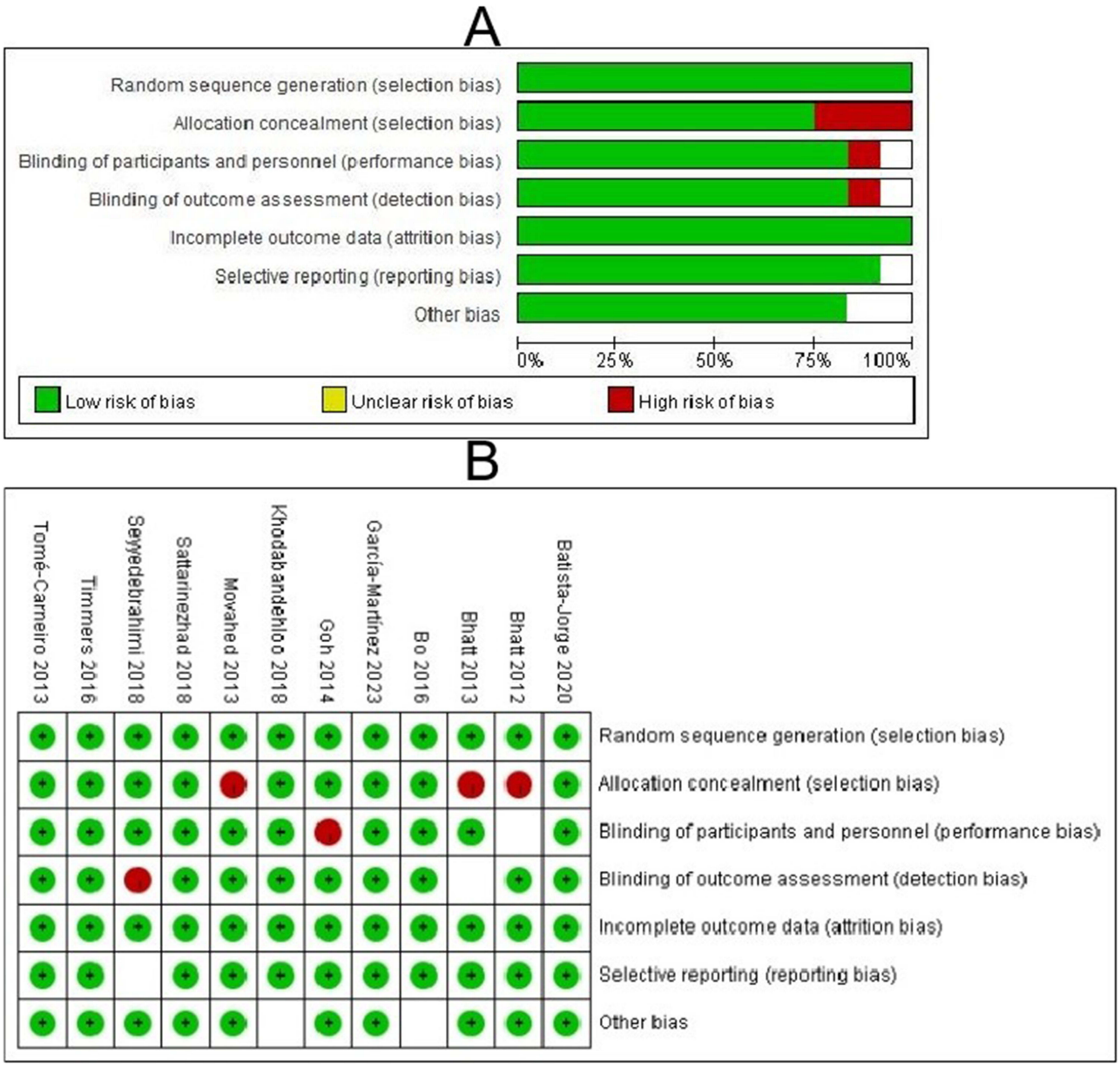

Figure 2 Assessment of the risk of bias for the included studies.
Notes: (**A**) Risk of bias graph: presents the review authors' judgements for each risk of bias item as percentages across all included studies. (**B**) Risk of bias summary: blank presents the review authors' judgements for each risk of bias item across all included studies. + indicates low risk of bias; blank indicates unclear risk of bias; − indicates high risk of bias.

supplementation on SCr levels (SMD: 0.05; 95% CI: −0.13 to 0.23; P = 0.56), with low heterogeneity among the included studies (I^2 = 23%) Figure 6.

Subgroup analyses were conducted based on dosage and intervention duration. Regarding dosage, no significant alterations in SCr levels were observed with low-dose RSV (SMD: 0.12; 95% CI: −0.43 to 0.68; P = 0.66), medium-dose RSV (SMD: 0.05; 95% CI: −0.19 to 0.29; P = 0.67), or high-dose RSV (SMD = 0.03; 95% CI: −0.27 to 0.33; P = 0.84) Figure 7. Similarly, when stratified by intervention duration, resveratrol did not exert a significant effect in studies shorter than 24 weeks (SMD = 0.19; 95% CI: −0.04 to 0.43; P = 0.10) or in those lasting 24 weeks or longer (SMD = −0.15; 95% CI: −0.43 to 0.13; P = 0.29) Figure 8.

Uric acid (UA): A total of six studies (encompassing 411 participants) examined the effect of RSV on uric acid levels in individuals with T2DM (García-Martínez et al, 2023; Batista-Jorge et al, 2020; Khodabandehloo et al, 2018;

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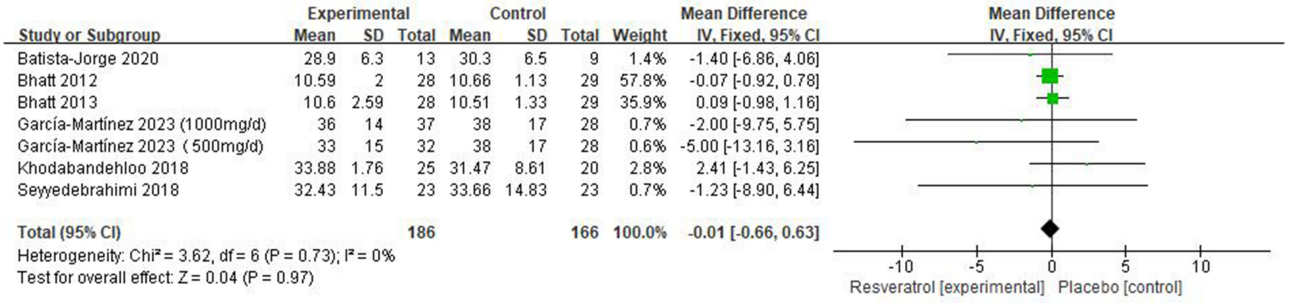

Figure 3 Forest plot showing the effect of resveratrol (RSV) supplementation on blood urea nitrogen (BUN) levels in patients with type 2 diabetes mellitus (T2DM).
Notes: The squares represent the point estimate of the WMD for each individual study, with the horizontal lines extending to the 95% CI. The size of the square corresponds to the study's weight in the meta-analysis. The diamond at the bottom represents the pooled WMD and its 95% CI. The vertical line of unity (WMD = 0) indicates no effect.
Abbreviations: WMD, weighted mean difference; CI, confidence interval.

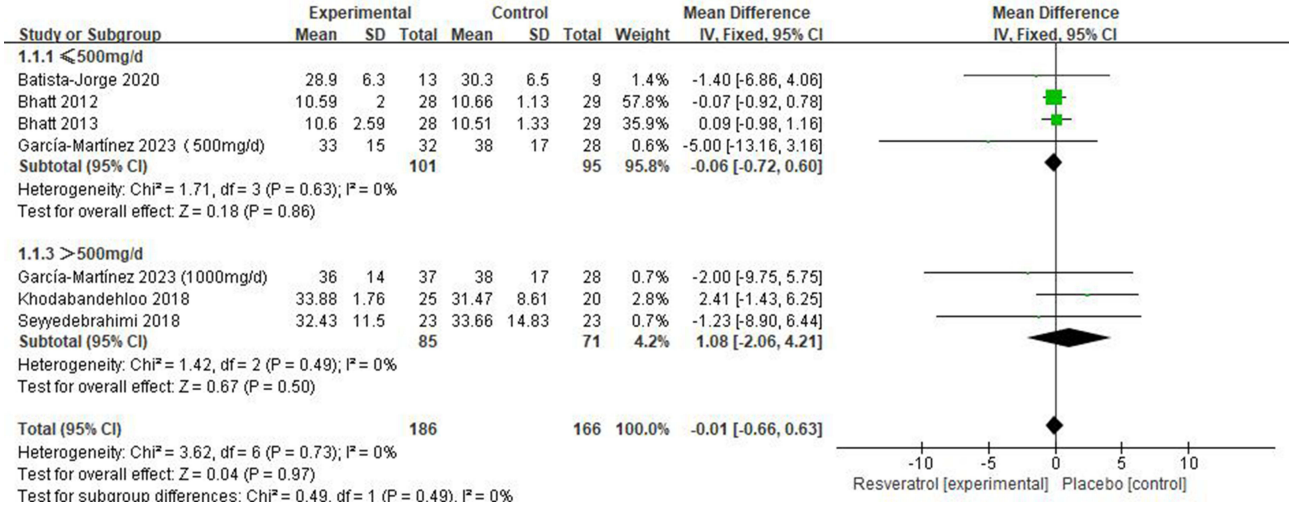

Figure 4 Forest plot of subgroup analysis showing the effect of different resveratrol (RSV) doses on blood urea nitrogen (BUN) levels.
Notes: Subgroups are defined by RSV dosage (eg, low dose, high dose). The squares represent the point estimate of the WMD for each individual study, with the horizontal lines extending to the 95% CI. The diamond for each subgroup represents the pooled WMD and its 95% CI for that dose category. Bolded values: Represent the pooled weighted mean difference (WMD) and its 95% confidence interval for that dose subgroup (eg, low-dose group, high-dose group). Significance: Used to determine whether resveratrol has a statistically significant effect on BUN at that dose level. If the confidence interval does not cross 0, it indicates a significant effect at that dose.

Seyyedebrahimi et al, 2018; Bo et al, 2016; Tomé-Carneiro et al, 2013). The pooled analysis demonstrated that, compared with the placebo group, RSV significantly reduced serum UA levels in T2DM patients, with low heterogeneity between studies (WMD: −0.42; 95% CI: −0.65 to −0.18; P = 0.0005; I^2 = 0%) Figure 9.

Discussion

The present study was conducted with the objective of conducting a systematic review and meta-analysis to comprehensively evaluate the effects of RSV on renal injury-related indicators in patients with T2DM. The pooled analysis revealed that RSV supplementation had no significant effect on BUN or SCr levels in T2DM patients compared with placebo. To gain further insight, subgroup analyses were conducted based on intervention duration and dosage. The findings of the study demonstrated that RSV exerted no substantial influence on BUN and SCr levels across a range of intervention dosages or durations. The absence of a significant effect on BUN and SCr, while perhaps initially perceived as a negative finding, offers critical interpretive value. It suggests that in the relatively short duration and early-stage patient populations characteristic of the included RCTs, RSV's primary renal benefit may not be captured by these conventional markers of glomerular function. Instead, our findings support a paradigm where RSV's initial role lies in mitigating key

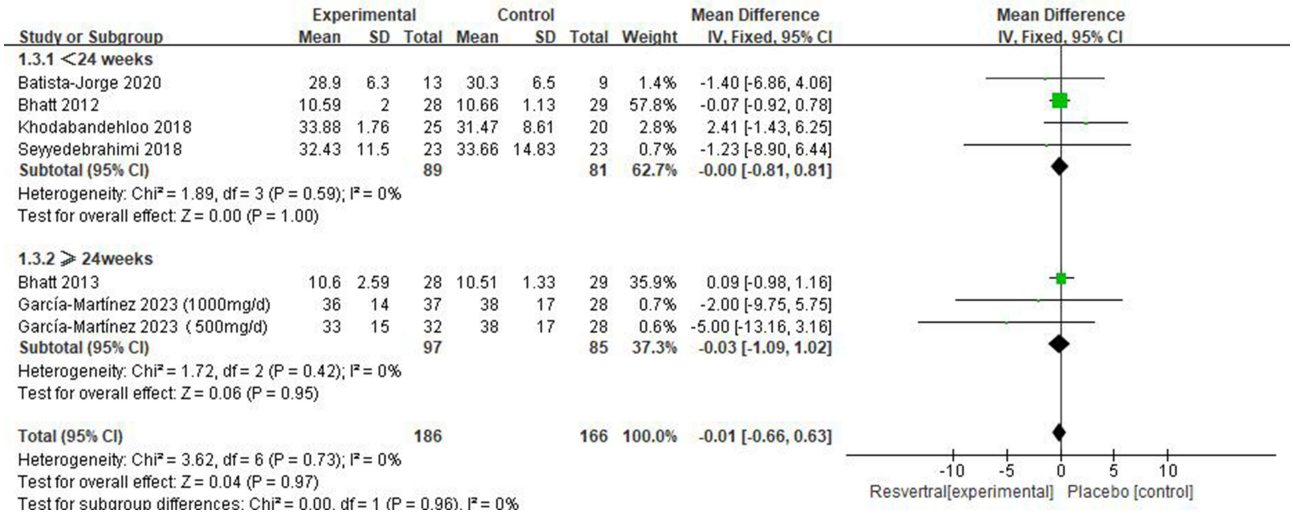

Figure 5 Forest plot of subgroup analysis showing the effect of resveratrol (RSV) on blood urea nitrogen (BUN) levels at different intervention durations.
Notes: Subgroups are defined by intervention duration (eg, <24 weeks, ≥24 weeks). The squares represent the point estimate of the WMD for each individual study, with the horizontal lines extending to the 95% CI. The diamond for each subgroup represents the pooled WMD and its 95% CI for that duration category. Bolded values: Represent the pooled WMD and its 95% confidence interval for that duration subgroup (eg, <24 weeks, ≥24 weeks). Significance: Used to determine whether resveratrol has a significant effect on BUN across different intervention durations.

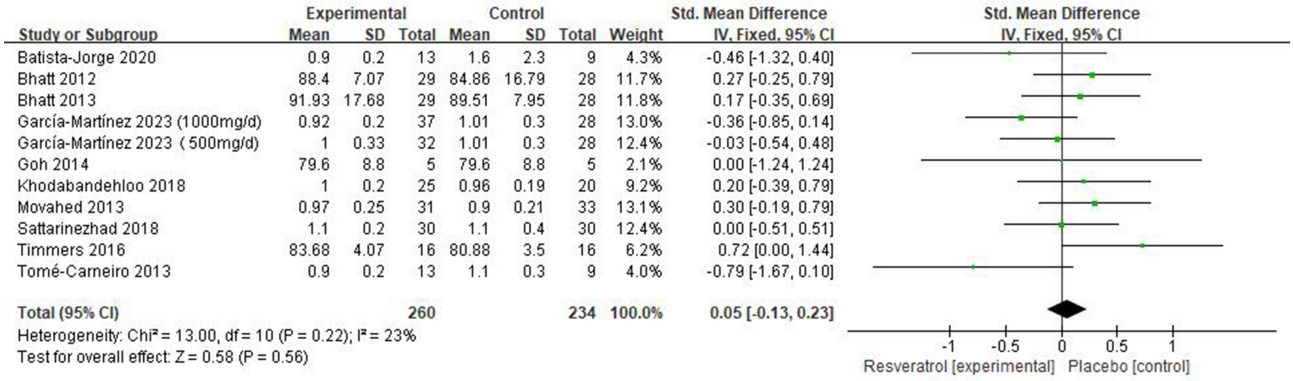

Figure 6 Forest plot showing the effect of resveratrol (RSV) supplementation on serum creatinine (SCr) levels in patients with type 2 diabetes mellitus (T2DM).
Notes: The squares represent the point estimate of the SMD for each individual study, with the horizontal lines extending to the 95% CI. The size of the square corresponds to the study's weight in the meta-analysis. The diamond at the bottom represents the pooled SMD and its 95% CI. The vertical line of unity (SMD = 0) indicates no effect. Bolded values: Represent the pooled standardized mean difference (SMD) and its 95% confidence interval for all studies. Significance: Reflects the overall effect of resveratrol on SCr. A confidence interval crossing 0 indicates no significant overall effect.
Abbreviations: SMD, standardized mean difference; CI, confidence interval.

risk factors for renal deterioration, such as hyperuricemia, oxidative stress, and inflammation, potentially delaying the onset of functional decline marked by rising BUN/SCr. Concurrently, the study demonstrated that RSV significantly reduced UA levels in T2DM patients. While our pooled results confirm that RSV supplementation does not significantly alter BUN or SCr levels in the short-to-medium term—a finding consistent with some prior reviews[31]—our robust demonstration of a serum UA reduction adds a new and important dimension to the clinical profile of RSV in T2DM management. This effect is particularly relevant given that hyperuricemia is an independent risk factor for the development and progression of DKD.[32] The present meta-analysis provides an updated and nuanced perspective on the effects of RSV on renal parameters in T2DM. Its principal novelty lies not in demonstrating a reversal of conventional renal function markers, but in uncovering a specific and significant urate-lowering effect. The study also demonstrated low heterogeneity across studies, lending high credibility to these findings.

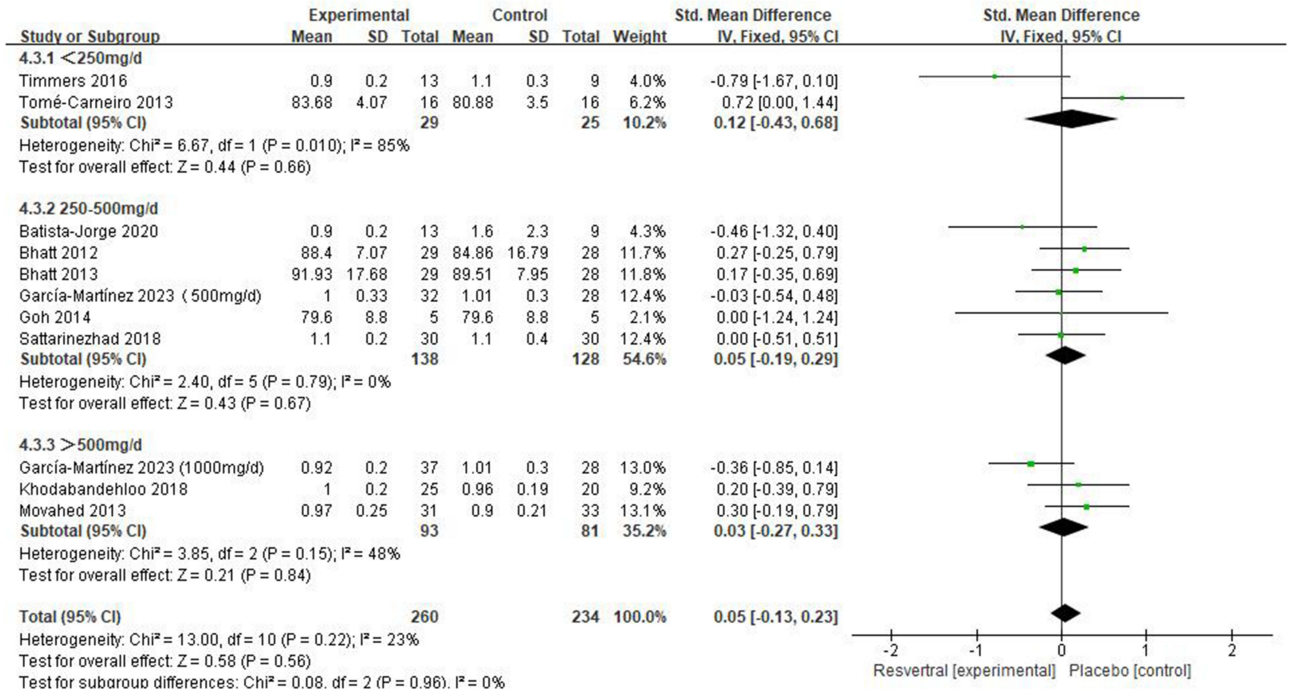

Figure 7 Forest plot of subgroup analysis showing the effect of different resveratrol (RSV) doses on serum creatinine (SCr) levels.
Notes: Subgroups are defined by RSV dosage (eg, low, medium, high dose). The squares represent the point estimate of the SMD for each individual study, with the horizontal lines extending to the 95% CI. The diamond for each subgroup represents the pooled SMD and its 95% CI for that dose category. Bolded values: Represent the pooled SMD and its 95% confidence interval for each dose subgroup (low, medium, high). Significance: Used to determine whether different doses have differential effects on SCr.

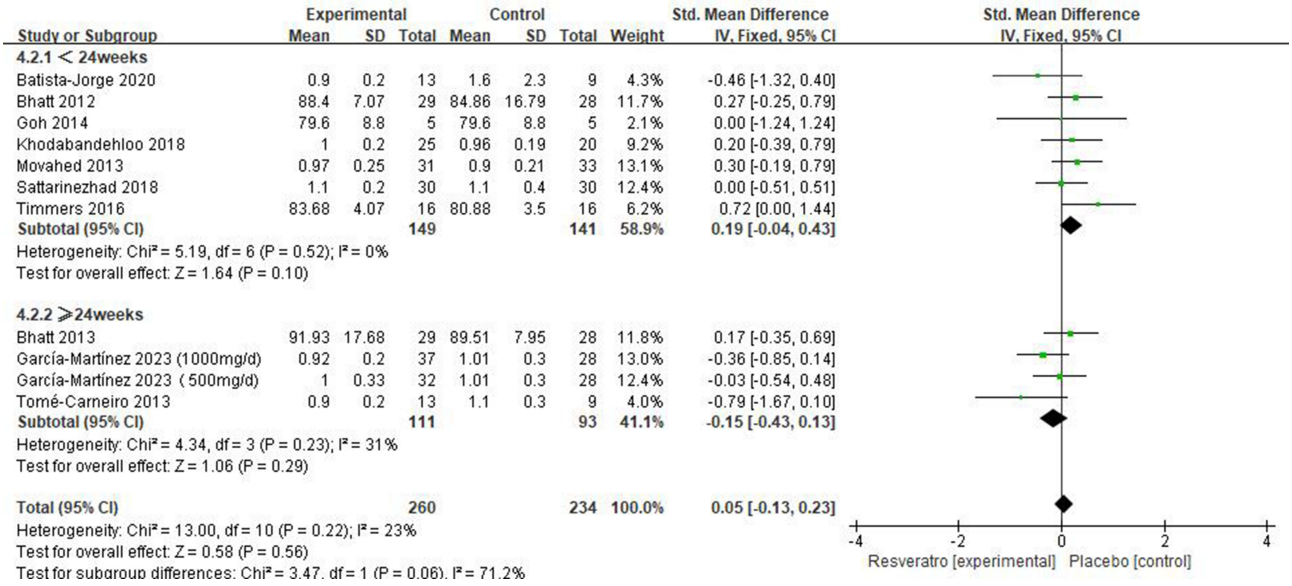

Figure 8 Forest plot of subgroup analysis showing the effect of resveratrol (RSV) on serum creatinine (SCr) levels at different intervention durations.
Notes: Subgroups are defined by intervention duration (eg, <24 weeks, ≥24 weeks). The squares represent the point estimate of the SMD for each individual study, with the horizontal lines extending to the 95% CI. The diamond for each subgroup represents the pooled SMD and its 95% CI for that duration category. Bolded values: Represent the pooled SMD and its 95% confidence interval for each duration subgroup. Significance: Used to assess whether the intervention duration influences the effect of resveratrol on SCr.

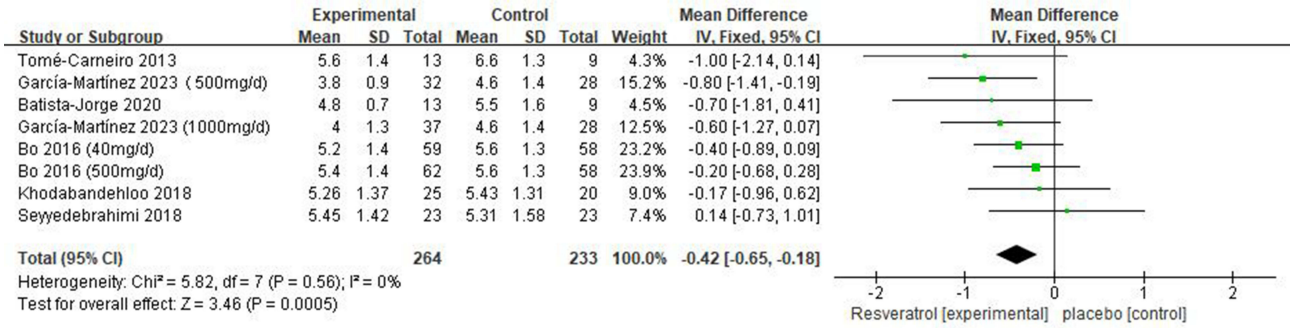

Figure 9 Forest plot showing the effect of resveratrol (RSV) supplementation on serum uric acid (UA) levels in patients with type 2 diabetes mellitus (T2DM).
Notes: The squares represent the point estimate of the WMD for each individual study, with the horizontal lines extending to the 95% CI. The size of the square corresponds to the study's weight in the meta-analysis. The diamond at the bottom represents the pooled WMD and its 95% CI. The vertical line of unity (WMD = 0) indicates no effect. Bolded values: Represent the pooled WMD and its 95% confidence interval for all studies. Significance: Reflects the overall effect of resveratrol on UA. If the confidence interval does not cross 0 (eg, a negative interval in this study), it indicates a significant reducing effect.

Extensive fundamental research has elucidated the molecular mechanisms underlying RSV's renal protective effects from multiple perspectives.[33] Firstly, with regard to the mechanisms of antioxidants and anti-inflammatories, a fundamental pathological mechanism of DKD involves oxidative stress and chronic inflammation. RSV has been shown to function as a potent antioxidant, directly scavenging reactive oxygen species (ROS) and enhancing the activity of intracellular antioxidant enzymes (such as SOD and caspase-3).[34] Furthermore, a study revealed that RSV can ameliorate renal interstitial fibrosis and mitochondrial dysfunction in diabetic models by enhancing PINK1-Parkin-mediated mitophagy, thereby reducing renal tubular injury.[35] This improvement in mitochondrial function may work in concert with its known antioxidant effects and could also contribute to the observed improvement in uric acid metabolism. Secondly, regarding inflammation, RSV significantly reducing the expression of downstream inflammatory mediators such as TNF-α, IL-6, and IL-1β, thereby alleviating inflammatory infiltration and tissue damage in the kidney.[36] Notably, evidence from the gut-renal axis suggests that RSV's anti-inflammatory action may be partially mediated by its modulation of gut microbiota. It has been shown to increase the abundance of short-chain fatty acid (SCFA)-producing bacteria, which may subsequently suppress renal NLRP3 inflammasome activation and attenuate albuminuria in diabetic conditions.[37] This provides a novel systemic perspective for RSV's anti-inflammatory and renal protective effects beyond direct cellular pathways. Further elucidating the direct cellular mechanisms, a recent experimental study demonstrated that RSV attenuates renal inflammation and promotes autophagy in diabetic rats by mediating the SphK1 pathway via Sirt1.[38] This finding underscores the role of RSV in activating key cellular homeostasis pathways, linking its anti-inflammatory effects to the enhancement of autophagy, a critical process for maintaining renal cell health. With respect to anti-fibrotic action, renal fibrosis signifies a pivotal step in the progression of DKD to end-stage disease. A multitude of research studies conducted on animal subjects have demonstrated the efficacy of RSV in effectively inhibiting the classic pro-fibrotic TGF-β1/Smad3 signaling pathway.[39] Liu et al[40] conducted a dose-response meta-analysis in animal models, revealing that RSV treatment reduced urinary protein excretion rates in DKD models in a dose-dependent manner. The researchers also found that RSV treatment mitigated glomerular mesangial matrix expansion and tubulointerstitial fibrosis severity. Its mechanism also involves upregulating the expression of the inhibitory Smad protein Smad7, thereby negatively regulating TGF-β1 signaling.[41] With respect to the enhancement of metabolic and hemodynamic functions, RSV has been observed to activate AMPK and SIRT1, thereby enhancing insulin sensitivity and regulating glucose and lipid metabolism.[35] This, in turn, serves to mitigate the impact of metabolic disorders on renal function. SIRT1 activation has been shown to promote PGC-1α deacetylation, thereby enhancing mitochondrial biogenesis and function, which in turn improves energy metabolism in renal tubular epithelial cells.[42] Furthermore, RSV has been shown to exhibit endothelium-dependent vasodilatory effects, thereby improving renal microcirculation and reducing intraglomerular hypertension.[43] This study is the first meta-analysis of RCTs to confirm that RSV significantly reduces serum uric acid levels specifically in patients with type 2 diabetes. Hyperuricaemia exerts a direct deleterious effect on the kidneys by activating the renal renin-angiotensin system

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(RAS), inducing inflammation, and promoting oxidative stress. The urate-lowering mechanism of RSV may be associated with its inhibition of hepatic xanthine oxidase (XO) activity, thereby reducing uric acid production, and its regulation of renal urate transporters (such as URAT1 and GLUT9) by modulating their expression to promote urate excretion.[44] This benefit, independent of conventional renal function indicators, adds a new and important dimension to the renal protective effects of RSV.

In the field of clinical research, there is a scarcity of randomized controlled trials (RCTs) investigating the effects of RSV on renal function indicators in patients with T2DM, and the existing findings are inconsistent. Some studies have shown that RSV significantly improves BUN and SCr levels in T2DM patients, while others have reported no significant effects. Previous meta-analyses investigating the effects of resveratrol on renal parameters in diabetic populations have been limited in scope and consistency. The 2020 meta-analysis by Nyambuya et al[31] which included only five RCTs (n=388), concluded that resveratrol had no significant effect on BUN or SCr in T2DM patients and did not report on uric acid levels. More recently, Abdollahi et al[45] (2023) conducted a broader analysis across 35 RCTs in general adult populations and found that resveratrol significantly reduced SCr and BUN, though not UA. However, this analysis was not specific to T2DM, and its findings may not directly translate to this metabolically distinct population. Both earlier reviews were constrained by the limited number of available trials, variability in patient characteristics, and a lack of focus on uric acid—a key biomarker in diabetic kidney disease progression. The present study therefore seeks to provide an updated and focused synthesis of recent RCTs, with an expanded sample size and specific attention to serum uric acid, in order to clarify the role of resveratrol in renal protection among patients with T2DM. Our updated meta-analysis, which includes the latest RCTs (literature search up to 2025), re-evaluated the data and found that RSV still had no significant effect on BUN or SCr in T2DM patients, but did show a significant improvement in UA levels. The discrepancies among these meta-analyses may be attributed to differences in patient baseline characteristics—such as the presence of diabetes, systemic inflammation levels, stage of renal function, and sample size—as well as variations in RSV dosage (ranging from 8 to 1000 mg/day), bioavailability of formulations, and patient compliance. The discrepancies among these meta-analyses, including our null findings on BUN and SCr, may be further informed by preclinical evidence. A comprehensive dose–response meta-analysis of animal studies suggested that RSV's effects on key renal outcomes are dose- and time-dependent, with more pronounced benefits often requiring higher doses or longer durations than those commonly used in clinical trials.[46] This underscores a critical translational gap and may explain the lack of significant changes in conventional renal markers like BUN and SCr in our current clinical dataset. Given the multi-target renal protective mechanisms of RSV elucidated in basic research, along with the results of this clinical analysis, we recommend future research should prioritize the execution of rigorously designed, long-term, large-scale randomized controlled trials with clinical hard endpoints (eg, doubling of creatinine, ESRD, or mortality) as primary outcomes. Further exploration is warranted into the personalised application value of RSV across different stages of DKD and its efficacy when combined with novel therapies like SGLT2 inhibitors, ultimately clarifying its clinical position in populations with T2DM-related chronic kidney disease. In conclusion, this updated analysis shifts the narrative around RSV and renal health in T2DM. It moves beyond the focus on traditional function markers and provides compelling, novel evidence for its urate-lowering action. This specific effect, combined with its multi-targeted mechanistic potential, positions RSV as a promising complementary agent for managing hyperuricemia and potentially mitigating associated renal and cardiovascular risks in the T2DM population. Future long-term trials with UA as a primary endpoint are warranted to confirm this benefit and define its place in clinical practice.

Study Limitations

1. The included RCTs exhibited heterogeneity in RSV dosage, intervention duration, and patient baseline characteristics. 2. A number of studies exhibited inadequate sample sizes, and certain studies demonstrated deficient reporting of allocation concealment and blinding implementation details. These shortcomings have the potential to introduce bias. 3. The present review principally concentrated on laboratory surrogate endpoints, omitting the assessment of hard endpoints such as ESRD or cardiovascular events. 4. The study did not thoroughly examine the variability in the efficacy of RSV across patients with different baseline renal function levels.

Conclusions

This systematic review and meta-analysis provides updated evidence that RSV significantly reduces serum UA levels in patients with T2DM, despite having no significant effects on BUN and SCr.

Data Sharing Statement

Data are available upon request from the corresponding author.

Acknowledgments

This work was reported in accordance to PRISMA guidelines.

Author Contributions

Wei Gu: Conceptualization, Methodology, Validation, Writing—original draft, Funding acquisition. Na Mu: Conceptualization, Methodology, Validation, Writing—original draft. Yan Yan: Formal analysis, Writing—original draft. Liwei Shi: Validation, Formal analysis, Writing—original draft. Fan Yang: Conceptualization, Writing—review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflict of interest in the research. 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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