REVIEW

Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus—systematic review and meta-analysis

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The red wine polyphenol, resveratrol, is highly effective in treating type 2 diabetes mellitus (T2DM) in animal models, but there is no consensus regarding its efficacy in humans. We conducted a systematic review, which included searches in nine scholarly databases and six clinical trial registries, and identified randomized controlled clinical trials whereby resveratrol was used as an adjunct to pharmaceutical interventions in T2DM. Meta-analysis on clinical parameters was performed for available data. Of 764 articles originally identified, data from six unique datasets, examining a total of 196 T2DM patients (104 resveratrol, 92 control/placebo) ultimately met inclusion criteria. Statistically significant ($p < 0.05$) positive effects, indicating that resveratrol supplementation was more effective than placebo/control, were identified for systolic blood pressure, hemoglobin A1c, and creatinine, but not for fasting glucose, homeostatic model assessment of insulin resistance, diastolic blood pressure, insulin, triglycerides, LDL, or HDL cholesterol. No major adverse events were reported and side effects of resveratrol were not different than placebo/control. Though limitations in sample size and treatment duration preclude definitive changes in clinical practice, significant improvements in multiple cardiometabolic biomarkers and an excellent safety profile support resveratrol as a leading candidate as an adjunct to pharmacological management of T2DM.

Keywords:
Cardiometabolic / French paradox / Nutraceutical / SIRT1 / Sirtuin

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1 Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic diseases in Western society and is projected to continue to have a major economic impact on healthcare worldwide [1]. As such, there is considerable need for safe interventions, which can enhance management of diabetes and address the multisystemic nature of the disease in a cost-effective manner [2]. Nutrient sensing pathways, including AMP-activated protein kinase (AMPK) and the sirtuin family of transcription factors (e.g., SIRT1), have emerged as key targets for novel interventions for type 2 diabetes and metabolic general dysfunction [3–5]. These pathways are activated by exercise and caloric restriction, both of which are associated with decreased risk of type 2 diabetes and other metabolic diseases [6] and are targeted by antidiabetes agents, including metformin [7,8]. Resveratrol, a polyphenol found in red wine, is a potent SIRT1 activator [9] (albeit indirectly through AMPK activation [10]) and has since received widespread attention from the scientific community and mainstream media for its potential to combat a number of pathological processes associated with diet and inactivity, including type 2 diabetes and its associated comorbidities [11,12].

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Abbreviations: **AMPK**, AMP-activated protein kinase; **HbA1c**, hemoglobin A1c; **$HOMA_{IR}$**, homeostatic model assessment of insulin resistance; **T2DM**, type 2 diabetes mellitus

Numerous studies have demonstrated resveratrol can prevent, attenuate, or reverse type 2 diabetes related dysfunction across multiple organ systems in multiple animal models, including swine [13] and nonhuman primates [14, 15], through targeting a complex array of signaling pathways. Animal models also suggest that resveratrol can synergistically enhance the effects of current type 2 diabetes interventions [16]. These promising findings have led to human clinical trials that have identified metabolic benefits of resveratrol treatment in obese individuals, patients with chronic disease (e.g., type 2 diabetes, cardiovascular disease, etc.), and healthy individuals [17]. Despite these encouraging findings, there is little incentive for clinicians to withhold knowingly effective treatment for type 2 diabetes for a promising, yet still investigational, nutraceutical. Rather than viewing resveratrol as an alternative to pharmaceutical products, there is value in exploring whether resveratrol can enhance the efficacy of established treatment protocols. Indeed, this has been explored in a few human clinical trials. However, differences in study methodology and numerous confounding factors sometimes produce conflicting findings, which creates obstacles in translating research into clinical practice [18].

Although medical/scientific and mainstream literature often use a combination of basic science and human data to support the potential for resveratrol in management of type 2 diabetes, data from human clinical trials have not yet been collectively evaluated. As such, there is not yet sufficient synthesis regarding efficacy and risks for clinicians to make evidence-based decisions regarding the use of resveratrol in management of type 2 diabetes. Thus, we performed a systematic review and meta-analysis of all human clinical trials, which examined the response of multiple clinical biomarkers to resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes. The results of this study will provide clinicians with an unbiased consensus of the current human clinical trial data, which can be directly applied to practice, while also highlighting directions for future clinical research.

2 Materials and methods

2.1 Search strategy and selection criteria

We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [19]. The analysis was registered at PROSPERO (2013:CRD42013003652). We used five procedures to attempt to retrieve all published research regarding the effects of resveratrol treatment on diabetic adults. To minimize the effects of publication bias, we made a concerted effort to locate more obscure journals and to obtain the details of studies whose initial presentations made it impossible to calculate effect sizes [20]. First, we conducted computer-based searches in AHFS Consumer Medication Information; CINAHL; Consumer Health Complete; Dissertation Abstracts, Health Source; PEDro; MEDLINE; Science Reference Center; and SPORTDiscus. The Boolean search terms used were as follows: resveratrol or red wine or polygonum or knotweed and diabetes or diabetic. This generic search strategy was designed to identify all studies investigating resveratrol or resveratrol-containing substances in relation to type 2 diabetes. Second, we manually searched the reference sections of all identified articles and review articles. Third, we searched clinical trials registries to identify any studies that were completed but not yet published, and contacted the principle investigators of these studies to determine publication status. Clinical trial registries searched were as follows: ClinicalTrials.gov, NIH.gov, ANZCTR, CRTI, IRCT, and ICTRP. Fourth, we searched the conference abstracts from the Resveratrol and Health Conferences (2010, 2012). Finally, we searched google.com for news stories relating resveratrol to type 2 diabetes, and for any studies identified, the original reference was sought. No restrictions were applied to the original searches. All searches were conducted through May 1, 2014.

Titles of all identified citations were independently screened to identify studies that potentially met the inclusion criteria. The abstracts of relevant studies were then reviewed, and full-text articles were retrieved for further screening and review as necessary. Two authors (HH, JMS) independently confirmed the eligibility of studies and collated the data from the qualifying studies. HAH and JMS extracted the data for the meta-analysis, which were double checked by one another. Study quality was assessed by HAH and JAS by the Jadad score [21], and JMS served as a tie-breaking vote as necessary. To qualify for inclusion, studies had to be randomized controlled trials comparing interventions that differed only in resveratrol condition, which were done in adults with type 2 diabetes (>18 years old). If other interventions were given, they had to be the same in all treatment groups. Only articles that were published in English language peer-reviewed journals were included.

2.2 Data extraction

Data were collected onto a prepiloted data extraction form that included the following: (1) study characteristics, including authors, publication year, sample size, study design, study duration, dose, type of intervention; (2) population information (e.g., age, gender); and (3) clinical outcome data commonly used in monitoring outcomes in type 2 diabetes clinical trials [22]: hemoglobin A1c (HbA1c), fasting plasma glucose, insulin, creatinine, homeostatic model assessment of insulin resistance ($HOMA_{IR}$), LDL and HDL, triglycerides, as well as systolic and diastolic blood pressure. When results for a given variable were reported in multiple units between different studies, all data were converted to identical units. If outcomes were reported multiple times in different stages of trials, only values representing the baseline to final assessment were included in our meta-analysis.

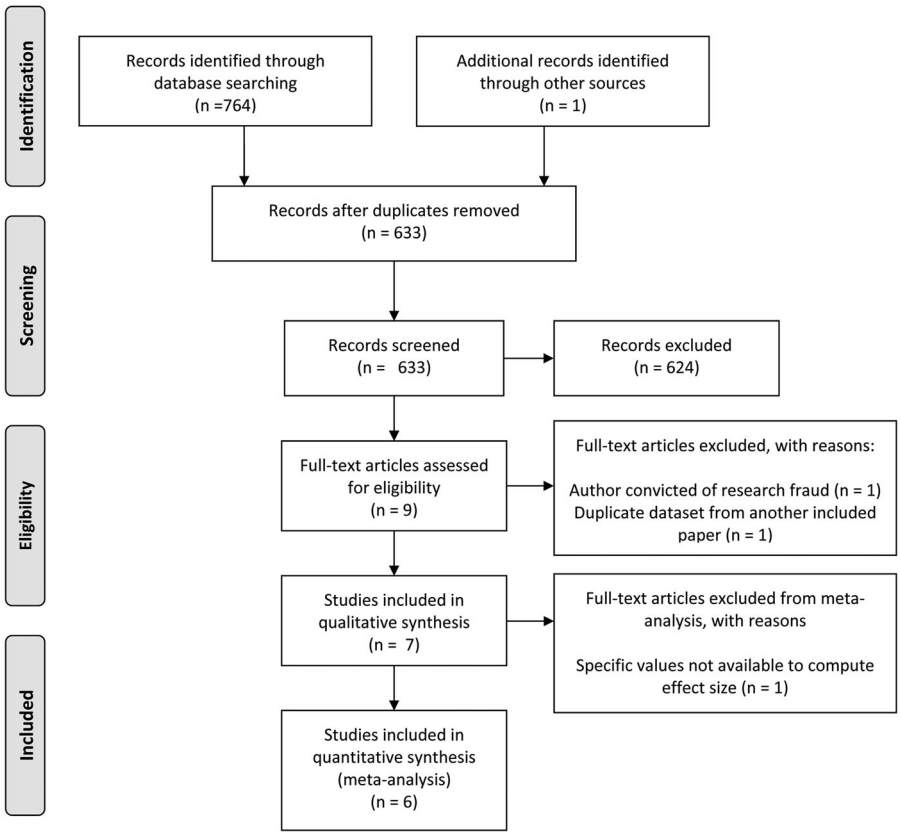

Figure 1. PRISMA flow diagram of search results.

2.3 Statistical analysis

We pooled data with a random effect meta-analysis with weighted mean differences and 95% confidence intervals (CIs) reported. We extracted the means and SDs for the baseline and posttreatment for both groups when available. When not available, we extracted the change scores (baseline—postintervention scores) for both groups. To assess heterogeneity and inconsistency in results of individual studies, we used Cochran's Q statistic and the I^2 statistic ($I^2 > 50\%$ was used as a threshold indicating significant heterogeneity across studies [23]). We used Hedges and Olkin's [24] procedures to correct for sample-size biases. To derive effect sizes for within-subject studies, one needs the correlation between posttreatment and baseline measures. Unfortunately, it is rare to find reported values of r when the primary research studies do not investigate relations between measures, and none of the studies in this synthesis reported r. Thus, we used a conservative value of $r = 0{\cdot}50$. Positive effect sizes in this meta-analysis represent an improvement in the outcome (i.e., resveratrol supplementation resulted in improvements in the outcome compared to the control group), which was interpreted as a decrease for each variable, except for HDL. Publication bias was assessed with the fail safe N and funnel plots. All tests were two-tailed and $p < 0.05$ was deemed statistically significant. We analyzed the data with comprehensive meta-analysis (version 2).

3 Results

A summary of the search results is found in Fig. 1. The search revealed nine published randomized clinical trials that met inclusion criteria for the study. A search of multiple clinical study, and data from this study were not published (as confirmed through contact with the study's principle investigator). One publication was excluded from further review, due to the principal investigator's work being retracted due to research misconduct [25]. A review of two of the published articles revealed that they came from the same study, and used identical baseline data, with Bhatt et al. [26] reporting 3-month posttreatment results and Kumar et al. [27] reporting 6-month posttreatment results, and thus, only Kumar et al. were analyzed. Thus, unique datasets from seven publications were analyzed, with Jadad scores ranging from 1 to 5 (Table 1). Trials ranged from 4 wk to 12 months duration. The number of participants ranged from 10 to 214 adults with type 2 diabetes, and the dose of resveratrol ranged from 10 to 5000 mg/day. A summary of the key details of these studies is found in Table 1 and a summary of results for the biomarkers of interest is found in Table 2. A summary of all registered clinical trials is found in Supporting Information Table 1.

We could not include Elliott et al. [28] in the meta-analysis because the data are only reported on a subsample, with unspecified N, and results are presented as figures, rather than

data tables with specific values. The study sponsor was contacted to obtain detailed summary data; however, this inquiry was not addressed at the time of manuscript submission (3 months following original inquiry). However, it should be noted that participants in that study were drug naïve, which contrasts all other included studies, in which patients were treated with resveratrol as an adjunct to their existing pharmacological therapy. Additionally, we computed effect size with and without the Tome-Carneiro et al. [29], since that trial used a mixture of resveratrol and grape polyphenol extract, rather than resveratrol itself. Exclusion of Tome-Carneiro et al. [29] did not change the significance of the results.

A total of 196 patients with type 2 diabetes (104 resveratrol, 92 placebo) were included in the meta-analysis. Table 3 displays the effect size information for the outcomes. Significant positive effect sizes were evidenced for HbA1c creatinine and systolic blood pressure (Fig. 2), indicating that resveratrol supplementation resulted in significant improvements compared to the control condition for the respective outcomes. Nonsignificant effect sizes were found for $HOMA_{IR}$, glucose insulin, diastolic blood pressure, cholesterol, and triglycerides (Supporting Information Fig. 1). The small values for the *Nfs* indicated that more research is needed before firm conclusions can be made regarding the efficacy of resveratrol supplementation. The range of heterogeneity among the effect sizes was large (range = 0–81).

Of the five datasets included in the meta-analysis, all except for Kumar et al. [27] provided information regarding adverse events. A total of three adverse events in the resveratrol treatment and one adverse event in the control group were observed, and all were mild.

4 Discussion

The primary purpose of this systematic review and meta-analysis was to evaluate the effects of resveratrol treatment on clinically relevant metabolic biomarkers in patients with type 2 diabetes already undergoing pharmaceutical interventions. While animal models have provided a strong case for resveratrol as a component of management for type 2 diabetes, only seven acceptable human clinical trials have examined the effects of resveratrol treatment in diabetic adults. Meta-analysis of the six clinical trials with sufficient data revealed statistically significant moderate positive effects of resveratrol treatment as an adjunct to pharmacological management of type 2 diabetes for HbA1c, creatinine, and systolic blood pressure. The very low incidence of adverse effects does not appear to be greater with resveratrol treatment compared to placebo. Given the short duration of clinical trials to date, long-term effects of resveratrol treatment are currently unknown and it remains to be determined how safe this nutritional supplement is for long-term use. Likewise, a number of current pharmacological agents used in type 2 diabetes management carry a risk of side effects and lack long-term safety data [2].

Closer examination of the three variables that demonstrated statistically significant positive effects when collectively evaluated through meta-analysis (HbA1c, creatinine, systolic blood pressure) reveals generally consistent changes across the studies. The only exceptions to this general observation are Goh, who found no change in plasma creatinine, and Bransyo, who reported a nonsignificant small magnitude negative effect on systolic blood pressure. Aside from these two exceptions, one study reported a statistically significant improvement for HbA1c and creatine, and two studies found a statistically significant improvement for systolic blood pressure. All others reported nonsignificant improvements in resveratrol compared to the control group. For the remaining biomarkers for which improvements were not significant in the meta-analysis, the direction of effect was generally inconsistent between studies. There was a nonsignificant trend for glucose ($p = 0.069$), which was likely heavily influenced by strong statistically significant positive effects reported by Bhatt and Movahed, but offset by negative effects reported by Bashmakov and Goh. Only Movahed reported a positive effect for HDL, which was statistically significant, and with all other studies reporting nonsignificant effects for decreases in HDL. Results for all other parameters were inconsistent between studies. The wide variation in pharmacological management, resveratrol treatment, study duration, and multiple other factors may have contributed to the inconsistent results for these parameters. However, the general consistency for HbA1c, creatinine, and systolic blood pressure across studies, despite methodological differences between studies, emphasizes the value of resveratrol as an adjunct to pharmacotherapy.

The biomarkers analyzed in this meta-analysis are clinically relevant for monitoring treatment and progression of T2DM across multiple organ systems and have been used as outcome variables previously [22]. Insulin resistance, a hallmark of T2DM, is characterized by $HOMA_{IR}$, which is calculated using fasting insulin and glucose concentrations. The results of this meta-analysis revealed no consistent changes for these variables, yet it did show a significant benefit for glycosylated hemoglobin (HbA1c). This may have major clinical implications, given that large clinical trials have firmly established that a reduction in HbA1c is associated with decreased risk for multiple diabetic complications and death [30, 31]. While this finding may be met with optimism, caution is still warranted in this regard until more larger scale clinical trials examine the effects of resveratrol treatment on HbA1c. It may be somewhat surprising that a statistically significant positive effect was observed for HbA1c, but not for $HOMA_{IR}$ or glucose concentration (though a strong trend toward significance was noted for glucose, and all results for $HOMA_{IR}$ were in the same direction). Fasting glucose and insulin concentrations, and therefore $HOMA_{IR}$, represent one point in time, whereas HbA1c represents glycemic load across multiple weeks. As such, it may be speculated that resveratrol

Table 1. Descriptive summary of trials

First author (year)	Design (country)	Participants	Resveratrol (RSV) group	Control/ comparison group	Main outcome measures	Other outcome measures	Main conclusions	Adverse events	Jadad score
Bashmakov (2014) [53]	Sixty-day, placebo-controlled, examiner-blinded, parallel-group randomized controlled pilot clinical trial (Egypt)	$N = 31$ patients with diabetic foot syndrome (DO = 7) age 56.4 years	$N = 14$ (eight males) 50 mg/day RSV	$N = 10$ (seven males)	Diabetic ulcer size, foot pressure during walking	Insulin, metabolic markers, and cardiovascular risk factors	RSV promotes reduction of diabetic foot ulcers and reduces plasma fibrinogen. Significant reduction in fasting glucose in RSV group only	Information not reported	4
Bhatt[a] (2013) [26] Kumar (2013) [27]	Six-month, prospective, open-label, randomized, controlled trial (India)	$N = 57$ patients with T2DM (DO = 5) Age = 57.2 years F/M: 36/21	$N = 29$ (DO = 2) 250 mg/day RSV (Bioforte)	$N = 28$; (DO = 3)	Clinical markers of metabolic function	Biochemical markers of oxidative stress	RSV effective in improving glycemic control, and also improved biomarkers of lipid metabolism, and body mass	Information not reported	3
Brasnyo (2011) [46]	Four weeks, double-blind, randomized (Hungary)	$N = 19$ Caucasian male patients with T2DM (DO = 0) Age = 55.2 years Lipid[b] lowering medication was ceased during trial	$N = 10$ 10 mg/day (98% trans-RSV) (Agina Nutraceuticals, gelatin capsule)	$N = 9$; Placebo	Insulin resistance and oxidative status	Underlying biochemical mechanisms responsible for RSV's antidiabetic effects	RSV improved insulin sensitivity and decreased blood glucose levels, and delayed appearance of glucose peaks after a test meal	No adverse events, side effects, or drug interactions observed in either group	4

(*Continued*)

Table 1. Continued

First author (year)	Design (country)	Participants	Resveratrol (RSV) group	Control/ comparison group	Main outcome measures	Other outcome measures	Main conclusions	Adverse events	Jadad score
Elliott[b] (2009) [28]	Four-week, randomized, placebo-controlled trial (unspecified)	$N = 214$ drug-naïve male patients with T2DM (age 18–62 years) from two separate trials	Trial 1: once daily of SRT501 (2.5 g) Trial 2: twice daily regimen of SRT501 (5 g/day)	Unspecified	Safety and pharmacoki-netic profile	Glycemic control (fed and postprandial glucose and insulin levels), oral glucose tolerance testing	Twenty-eight days of 5 g/day micronized RSV shows positive glucose-lowering effects in humans. Fasting insulin and HbA1c were unchanged	"Adverse events were generally mild in nature and reversible." No further information provided	1
Goh (2014) [47]	Twelve-week, randomized, double-blind, parallel group (Singapore)	$N = 10$; T2DM men (age = 56.3 years) on stable oral hypo-glycemic regimen (DO = 0)	$N = 5$; 3 g/day trans-RSV from *polygonum cuspidatum* (Mega Resveratrol, Danbury, USA; started at 500 mg/day, increased by 500 mg/day every 3-day to maximum dose of 3 g/day)	$N = 5$; placebo	Skeletal muscle SIRT1 expression and energy expenditure	AMPK, p-AMPK, GLUT4 expression levels, body mass, HbA1c, plasma lipid subfraction, adiponectin, insulin sensitivity	RSV regulates energy expenditure through increased skeletal muscle SIRT1 and AMPK expression	RSV: - Asymptomatic and mild elevation of ALT in patient with fatty liver (1) - Diarrhea and mild hypo-glycemia (1) - Mild cellulitis at biopsy site (1) *Placebo*: - Mild cellulitis at biopsy site (1)	5

(*Continued*)

Table 1. Continued

First author (year)	Design (country)	Participants	Resveratrol (RSV) group	Control/ comparison group	Main outcome measures	Other outcome measures	Main conclusions	Adverse events	Jadad score
Movahed (2013) [48]	Forty-five days, randomized placebo-controlled double-blinded (Iran)	$N = 66$; (33 females, 33 males) patients with T2DM (DO = 2; age = 52.1 years; $N = 4$ on insulin treatment)	$N = 33$; 1 g/day RSV capsules (Biotivia)	$N = 31$; placebo tablets	Blood glucose	Insulin, metabolic markers, and cardiovascular risk factors	RSV reduced blood glucose, HbA1c, insulin concentration, insulin resistant, and improved HDL cholesterol	No adverse events, side effects, or drug interactions. No changes in liver enzymes in RSV.	5
Tome-Carneiro (2013) [29]	Twelve-month randomized placebo-controlled, triple-blind (Spain)	$N = 22$; hypertensive male patients with T2DM who had stable coronary artery disease (age = 60 years)	$N = 13$; RSV-enriched grape extract (8 mg/day)	$N = 9$ Placebo Grape seed extract ($n = 13$)[c]	Molecular changes in peripheral blood mononuclear cells	Multiple clinical parameters and biochemical markers and micro-RNA's associated with metabolism and inflammation	RSV decreases expression of multiple biomarkers associated with inflammation	No adverse events, side effects, or drug interactions observed in either group	3

T2DM, type 2 diabetes; RSV, resveratrol; SRT501, micronized resveratrol formulation.
Participants: *N*, number of participant at the end of trial; DO, number of participants who dropped out before end of trial.
a) Same data. Bhatt reported 3-month data; Kumar reported 6-month data. Used the baseline and 6-month data to compute effect size.
b) Data are only reported on a subsample and the exact *N* is not reported so we cannot compute effect size.
c) Effect size data reported on resveratrol-enriched grape extract versus placebo.

Table 2. Summary of findings within each study

First author	Insulin	Glucose	$HOMA_{IR}$	HbA1c	Creatinine	Systolic blood pressure	Diastolic blood pressure	LDL	HDL
Bashmakov et al. [53]	↑							↓	↓
Brasnyo et al. [46]	↓	↓	↓			↑	↓	↑	↓
Goh et al. [47]	↑	↑	↓	↓	↔			↑*	↑
Kumar et al. [27]		↓*		↓	↓*	↓*	↓*	↓*	↓*
Movahed et al. [48]	↓*	↓*	↓*	↓*	↓	↓*	↓	↓*	↑*
Tome–Carneiro et al. [29]		↓		↓	↓	↓	↔	↑	↓

Arrows (↑ increase; ↓ decrease; ↔ no change) represent the effect of resveratrol, relative to placebo, for a given variable. Blank cells signify studies that did not report data for these variables.
*Represents a statistically significant difference at $p < 0.05$ level. All other arrows represent nonsignificant trends.

treatment provides the greatest benefits under nonfasting conditions, possibly through reducing 24-h glycemic load through altering postprandial metabolism. Further, statistical analysis of heterogeneity indicated considerable variation in the effect size for $HOMA_{IR}$, which may be reflective of different treatment protocols. However, the studies evaluated in this meta-analysis do not allow a mechanism to be elucidated and further research is needed in this realm.

T2DM is characterized by alterations in fatty acid metabolism, which ultimately results in decreased HDL and increased LDL and triglycerides. This meta-analysis found no significant changes for either of these variables. Because dyslipidemia is a well-established risk factor for diabetes and cardiovascular disease, blood lipid profile is routinely addressed by pharmacotherapy (e.g., statins). It is possible that the resveratrol treatment protocols utilized in the clinical trials analyzed were not able to further improve lipid profile beyond potential improvements already realized through previous history of pharmacotherapy. Additionally, the studies in this meta-analysis did not report measurements of lipoprotein A, which especially is atherosclerogenic and typically elevated in T2DM [32], and it should therefore be examined in future trials.

The aforementioned metabolic changes and associated activation of inflammatory pathways contribute to the pathogenesis of atherosclerosis and further cardiovascular disease, and the consequent impaired vascular function contributes to the development of various complications, including renal disease, retinopathy, and neuropathy. Nephropathy leading to end-stage renal disease is a leading contributor to mortality in T2DM [33]. Type 2 diabetic individuals with elevated plasma creatinine, a biomarker indicative of kidney function, have a considerably greater rate of cardiovascular disease and mortality risk than those with normal creatinine levels [34]. Likewise, hypertension, elevated cholesterol, and high HbA1c are key risk factors for the development of nephropathy and atherosclerotic cardiovascular disease in type 2 diabetic patients [35, 36]. As such, resveratrol's positive effect on systolic blood pressure, HbA1c, and plasma creatinine concentration is clinically relevant. Because of the varied durations of resveratrol treatment, and treatment protocols in general, it is not known whether decreases in systolic blood pressure and plasma creatinine concentration are a result of reduced glycemic load (as suggested by improved HbA1c), or if these benefits occurred from a physiologically independent mechanism. Indeed, resveratrol has been demonstrated

Table 3. Meta-analysis results

Outcome	M ES (SE)	95% CI	*N*	*Q* statistic	The I^2	*Nfs*
HbA1c [27, 29, 47, 48]	0.43 (0.16)**	0.10–0.75	4	2.21, $p = 0.52$	0	3
Glucose [27, 29, 46–48]	0.36 (0.19)	−0.02 to 0.75	6	8.24, $p = 0.23$	39.35	2
Creatinine [27, 29, 47, 48]	0.53 (0.16)***	0.20–0.85	4	1.64, $p = 0.65$	0	4
Insulin [46–48, 53]	0.42 (0.42)	−0.42 to 1.25	4	11.89, $p = 0.008$	74.77	3
$HOMA_{IR}$ [46–48]	0.93 (0.60)	−0.25 to 2.11	3	10.56, $p = 0.005$	81.07	13
Triglyceride [29, 46–48]	0.33 (0.32)	−0.26 to 0.95	4	9.07, $p = 0.03$	66.94	0
LDL cholesterol [27, 29, 46–48, 53]	0.11 (0.30)	−0.47 to 0.70	6	17.66, $p = 0.002$	71.70	0
HDL cholesterol [27, 29, 46–48, 53]	−0.17 (0.27)	−0.72 to 0.38	6	15.87, $p = 0.007$	68.49	0
Systolic BP [27, 29, 46, 48]	0.58 (0.24)*	0.09 to 1.06	4	6.16, $p = 0.10$	51.37	9
Diastolic BP [27, 29, 46, 48]	0.30 (0.16)	−0.01 to 0.61	4	1.85, $p = 0.61$	0	0

A positive effect was considered a reduction (decrease) for each variable, except for HDL cholesterol, in which an increase was considered a positive effect.
M ES, mean effect size; SE, standard error; CI, confidence interval; *N*, number of effect sizes.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

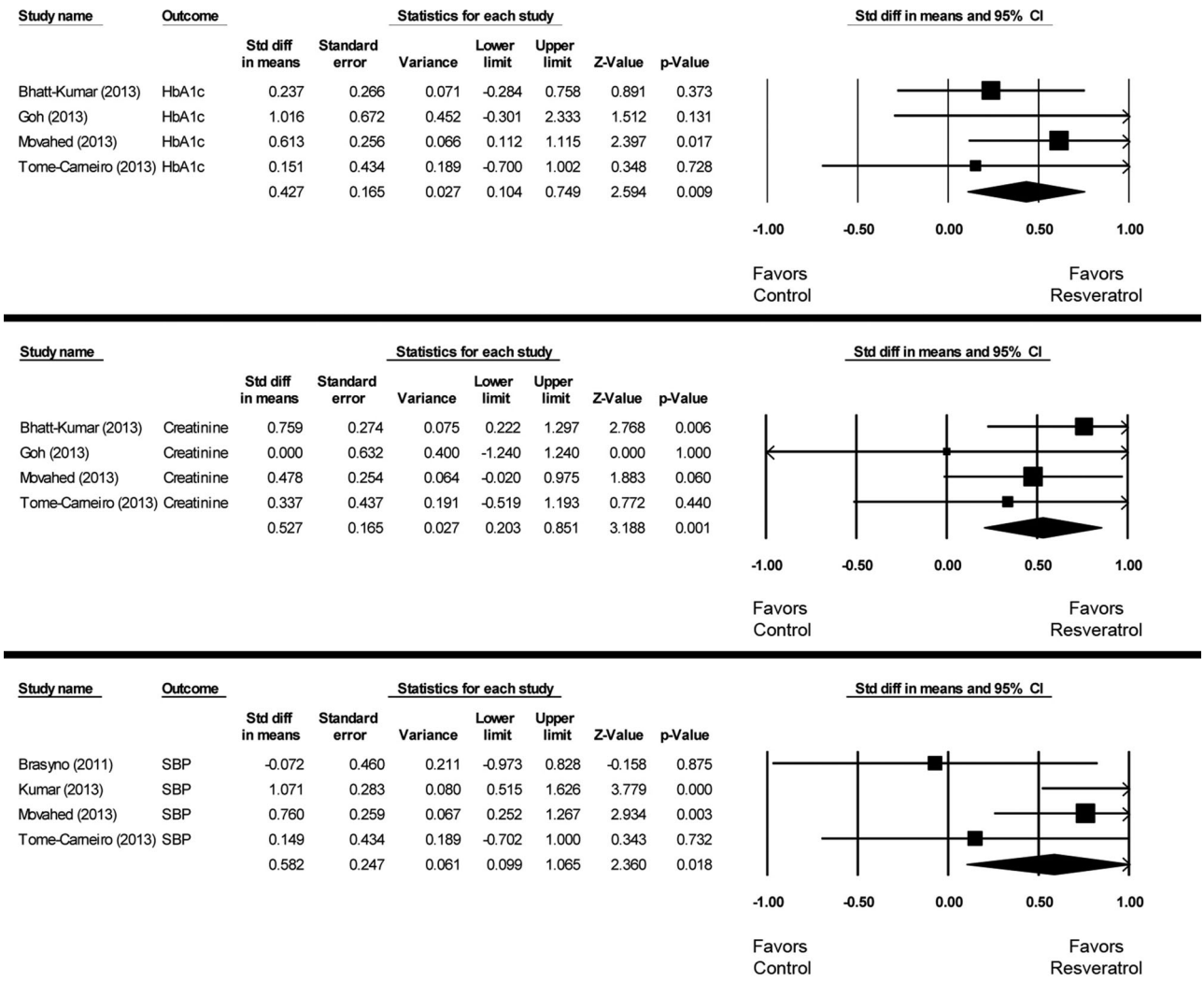

Figure 2. Forest plot for biomarkers, which had significant effects in the meta-analysis. A positive effect size represents a decrease in HbA1c (top), creatinine (middle), and systolic blood pressure (bottom).

to acutely improve vascular endothelial function [37] and blood flow [38] in humans. Nonetheless, future large-scale human clinical trials examining resveratrol treatment should attempt to better understand the relationships between these changes.

The consistently positive effects of resveratrol treatment on HbA1c, creatinine, and systolic blood pressure support the systemic benefits of resveratrol treatment. This global effect may be especially important in patient management, given the numerous factors that contribute to the pathogenesis and progression of type 2 diabetes across multiple organ systems. The added benefit of resveratrol treatment beyond pharmaceutical interventions may relate to its ability to modulate multiple signaling pathways, perhaps including some not targeted by current pharmacological interventions. Indeed, metformin and rosiglitazone have been demonstrated to have different mechanisms that ultimately activate AMPK [39]. Given the diversity of pathways modulated by resveratrol in multiple tissues, the effects of resveratrol may extend far beyond the basic biomarkers analyzed in this study. Future clinical trials should examine the effects of resveratrol treatment on comorbidities associated with type 2 diabetes (e.g., vascular dysfunction) and include standardized non-fasting clinically relevant outcome measures that challenge metabolism (e.g., oral glucose tolerance test). Indeed, some of the trials identified took this comprehensive approach, but such methodology was not universal enough to be evaluated by meta-analysis.

It is well established that resveratrol undergoes extensive metabolism before entering the systemic circulation and that

there is considerable interindividual variability in plasma bioavailability of resveratrol and its metabolites [17]. If one assumes that physiologic response is at least partially dependent on plasma concentration of resveratrol, it follows that there should be substantial interindividual variability in clinical efficacy. Thus, it is possible that summary data from each clinical trial used in the meta-analysis may reflect a combination of "responders" and "nonresponders" to resveratrol. If this is the case, some individuals may experience greater-than-expected benefit while others may experience no benefit from resveratrol treatment. Novel delivery methods for resveratrol may allow for more consistent bioavailability and also reduce the risk of gastrointestinal side effects [40, 41].

There are a number of challenges in translating animal research into human clinical practice [42], and the establishment of optimal dosage that safely maximizes therapeutic response for type 2 diabetes treatment is paramount. While one must be careful in extrapolating data from nondiabetic individuals, it is worth noting that previous studies have deemed resveratrol dosages up to 5 g/day to be safe over a 1 month period, with reversible gastrointestinal side effects being the most common complaint [43]. The potential benefit on kidney function, observed by improved plasma creatinine levels, may seem contradictory to reports from one study in which five of 24 individuals with multiple myeloma developed kidney failure after receiving 5 g/day of micronized resveratrol [44]. However, this is consistent with the 20% incidence of kidney failure in multiple myeloma [45], and it is uncertain whether the cause of this was resveratrol alone, interactions with pharmaceuticals, or a combination of other multiple factors. Further, while resveratrol treatment has sometimes been reported to slightly lower blood glucose in normoglycemic individuals, even large doses do not appear to provide any risk of hypoglycemia or other adverse events. The optimal dosage for resveratrol treatment for any clinical condition in humans is currently unknown [18]. Limited clinical trial data prevents a thorough statistical analysis of the dose–effect relationship, however, there is some evidence this may hold true in humans. For instance, Tome-Carneiro et al. [29] and Brasnyo et al. [46] used the smallest dosages of resveratrol (8 and 10 mg/day, respectively) and had some of the least dramatic results for many outcome measures. Nonetheless, considerably more research is needed to refine dosage protocols. Additionally, one must interpret the data from the included studies carefully. For instance, Kumar et al. [27] found a significant effect for fasting glucose and HbA1C, but the primary driver of this may be a result of differences in groups at baseline combined with increased values in the control group, rather than substantial improvements in the resveratrol group. This may still be regarded as a beneficial effect (i.e., resveratrol prevented progression of metabolic dysfunction), but caution is warranted.

This meta-analysis ultimately sought to broadly determine if resveratrol treatment could enhance pharmaceutical treatment of type 2 diabetes, but the magnitude of any effects is quite difficult to determine at this time. One of the primary confounding factors in the studies included in the meta-analysis is differences in resveratrol dosage between studies, with a range from $\leq$10 mg/day (Brasnyo et al. [46] and Tome-Carniero [29]) to $\geq$1000 mg/day (Goh et al. [47] and Mohaved et al. [48]). While it would be interesting to determine if a longer duration had a greater effect, the study with the longest duration (1 year, Tome-Carniero et al. [29]) had the lowest dosage, and those with the largest dosages (Goh et al. [47] and Movahed et al. [48]) were of relatively short duration ($\leq$12 wk). It is interesting to note that Movahed found more statistically significant improvements in a short period of time using a much higher dosage than Bransyo, but it is not certain whether this is due to the higher dosage or simply a greater sample size. Further, the studies identified were conducted in a diversity of locations worldwide, and it is possible that genotypic variation between different ethnic groups, as well as geocultural differences in lifestyle and dietary factors, could influence response to resveratrol. Additionally, differences in pharmaceutical management and patient status (e.g., duration of treatment before receiving resveratrol, comorbidities, etc.) between the populations studied may cause disparities in efficacy. Thus, future research examining the effects of resveratrol treatment on type 2 diabetes should be sufficiently structured, such that (1) the effects of resveratrol can be compared between different pharmaceutical management protocols, and (2) the ideal administration protocol (i.e., dosage, timing) for resveratrol can be determined within a given pharmaceutical treatment.

Although the meta-analysis identified improvements in most of the clinical outcome measures assessed, the nature of the clinical trials identified introduces some limitations to the overall study. Specifically, the seven studies included in this systematic review were single-center trials, conducted relatively short-term, used fixed resveratrol dosages, had relatively small sample sizes, had no follow-up assessments, provided limited descriptive information on participants (e.g., retinopathy/neuropathy status, socioeconomic status), and lacked moderator analyses. The small sample sizes, however, most likely precluded the examination of important moderator variables (e.g., gender, age). It is also possible that publication bias exists, however, this seems unlikely, given that all but one of the completed studies identified through the clinical trials registry search was published (and the conference abstract associated with that unpublished study reported positive results [49]).

Even if resveratrol is effective in treating diabetic patients, it must be remembered that a number of other potential interventions exist, and therefore continued exploration of comparative efficacy and tolerability are essential [50]. Future clinical trials should explore whether different dosages of resveratrol are at least equally effective as existing treatments, as explored by Elliott et al. [28], and also attempt to identify which formulations of resveratrol have the most beneficial effects on specific pharmaceutical interventions. It is possible that different dosages or resveratrol matrices may provide greater efficacy, or allow for reduced dosage of

pharmaceutical products. It must also be emphasized that, although resveratrol is often viewed as an exercise mimetic, it should not be viewed as a substitute for physical activity, which has been demonstrated to be efficacious in the management of type 2 diabetes [51].

In conclusion, the results of this meta-analysis indicate that short-term (<1 year) resveratrol treatment provides a small, but significant improvement in the status of multiple clinically relevant biomarkers (systolic blood pressure, HbA1c, and creatinine) in adults with pharmacologically managed type 2 diabetes. The incidence of side effects was very small, not different than placebo, and no major adverse events were reported. Although total sample size was limited, the consistency of findings from trials conducted in multiple countries suggests results may be generalizable to a diverse patient population. The favorable benefit-to-risk ratio does provide evidence for clinicians to incorporate resveratrol treatment into patient management, however, like many current type 2 diabetes interventions, the long-term risks and benefits of doing so are heretofore unknown. There are not yet sufficient data to determine the optimal dosage of resveratrol or if clinical improvements in metabolic biomarkers from adjunct resveratrol treatment are consistently accompanied by changes in the comorbidities associated with type 2 diabetes. It is essential that widespread changes in clinical management are employed only with sufficient safety and efficacy data [52]. Given the physiological benefits identified through this meta-analysis, there is reasonable incentive for pursuit of resveratrol interventions as an adjunct to standard pharmaceutical management in type 2 diabetes through larger, long-duration clinical trials with additional outcome measures.

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