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REVIEW



Resveratrol supplementation and type 2 diabetes: a systematic review and meta-analysis

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ABSTRACT

This study aimed to review the literature on studies that evaluated resveratrol's effects supplementation on parameters of diabetes in humans. We conducted an online search in the following databases: Pubmed, Lilacs, Scielo, Scopus, Web of Science, Embase, and Cochrane. It included experimental studies that investigated the effects of resveratrol supplementation for diabetes treatment or prevention and its relationship with fasting blood glucose, insulin resistance, and glycated hemoglobin. Observational, non-human studies and non-randomized clinical trials were excluded. We conducted a meta-analysis to evaluate the effects of resveratrol supplementation on fasting blood glucose, insulin resistance, and glycated hemoglobin. Thirty studies were included in the review. Almost 60% demonstrated at least one significant effect of the resveratrol supplementation related to diabetes. In the meta-analysis, there was a significant effect on the reduction of insulin resistance [SMD: -0.34; CI 95%: -0.64, -0.04; $p = 0.01$; $I^2 = 70\%$] and glycated hemoglobin [SMD: -0.64; CI 95%: -1.22, -0.07; $p = 0.01$; $I^2 = 90\%$]. For fasting blood glucose, the results were significant only for individuals with diabetes [SMD: -0.85; CI 95%: -1.49, -0.21; $p = 0.01$; $I^2 = 90\%$]. This systematic review with meta-analysis demonstrated that resveratrol supplementation has protective effects on diabetes parameters.

KEYWORDS

Fasting blood glucose;
glycated hemoglobin;
insulin resistance;
resveratrols

Introduction

Diabetes is a silent disease that is associated with inappropriate eating habits and lifestyle. A study estimated that by 2045 more than 11% of the world population would be diagnosed with diabetes. This number represents more than 700 million people with this disease (Saad et al. 2019). In Brazil, 10% of the population has diabetes. The prevalence is higher in women, people over 30 years old, individuals with low education, and overweight and obese subjects. (Malta et al. 2019). A report from the Center for Disease Control and Prevention in the United States showed that, from the 34.2 million adults with diabetes, 15% were smokers, 80% were overweight, and 38% were physically inactive (CDC 2020).

Diabetes prevention is financially cheaper than treatment. It is estimated that more than \$2.2 trillion will be spent by 2030 to treat diabetes. Also, diabetes is an important risk factor for mortality since it is associated with years of life lost (Wright et al. 2017). Despite this, compared to the past, individuals with diabetes today live longer with the disease (Muschik et al. 2017). This fact is related to the continuous treatment for this problem, which increases the costs (Gregg et al. 2014). Moreover, new cases of diabetes have increased significantly among young Americans (CDC 2020). This fact

confirms the importance of preventing diabetes from the first years of life.

The treatment of diabetes consists of lifestyle changes and drug treatment. However, some individuals can develop some side effects with drug treatment, such as gastrointestinal discomfort, anorexia, nausea, abdominal discomfort, diarrhea, and reducing the intestinal absorption of vitamin B12 (Marín-Penalver et al. 2016).

Resveratrol may appear as a substance capable of helping in the treatment or prevention of diabetes. Resveratrol is a polyphenol that was first identified in 1940 in a Japanese article made from the root of a poisonous medicinal plant (TAKAOKA and M. 1940). Later in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine (Nonomura, Kanagawa, and Makimoto 1963). Studies have shown that resveratrol has health-promoting properties and antioxidant, anti-inflammatory, cardioprotective, anti-diabetes, anticancer, chemopreventive, and neuroprotective characteristics (Timmers et al. 2011; Catalgo et al. 2012).

A previous meta-analysis that included only individuals with diabetes showed benefits from resveratrol supplementation on diabetes parameters like fasting blood glucose and insulin resistance (Zhu et al. 2017). Another meta-analysis has found improvements of resveratrol supplementation on glucose control, insulin sensitivity, and glycated hemoglobin

in individuals with type 2 diabetes. However, this last meta-analysis included only two studies in the analysis for individuals with diabetes (Liu et al. 2014). So far, there is no evidence about resveratrol's effects on the general population and individuals at risk of developing type 2 diabetes. Considering the inconclusive results on the effects of resveratrol in the treatment or prevention of diabetes and the lack of evidence on the general population, the present study aimed to review the literature on studies that evaluated resveratrol's effects supplementation on parameters of diabetes in humans.

Methods

We conducted a systematic review and meta-analysis following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009). It was also prospectively registered in the International Prospective Registry for Systematic Reviews (PROSPERO) and approved under the protocol number CRD42021224389.

Inclusion criteria

We included randomized clinical trials with humans that evaluated the effects of resveratrol supplementation, compared to placebo, in type 2 diabetes treatment or prevention. We also included studies that evaluated other pathologies, as long as they included at least one parameter related to diabetes, such as insulin resistance levels, fasting blood glucose, or glycated hemoglobin.

Exclusion criteria

We excluded observational studies, studies with animals or in vitro, and non-randomized clinical trials.

Search strategy

We utilized the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework to determine articles' eligibility. Between November and December 2020, we conducted the searches in the following databases: Pubmed, Lilacs, Scielo, Scopus, Web of Science, Embase, and Cochrane. No date or language restrictions were applied. We utilized two groups of keywords to find the articles using the Medical Subject Headings (MeSH). In the first group used to search 'resveratrol,' we used: "resveratrol," and "resveratrols." In the second, terms for type 2 diabetes were used: "diabetes mellitus," "Type 2 Diabetes," "T2DM," "insulin resistance," "fasting blood glucose," and "glycated hemoglobin." Between the groups, we used the Boolean operators "OR" and "AND," respectively.

Study selection

The selection of titles, abstracts, and full texts was conducted by two reviewers (FMD and LMF), according to inclusion and exclusion criteria established. We resolved the disagreements by consensus. Finally, the references of the included studies were reviewed for possible additional articles.

Risk of bias

We utilized the Cochrane tool to assess the risk of bias (Higgins et al. 2011). Two reviewers independently assessed the risk of bias (FMD and LMF), and the authors solved disagreements by consensus. The scale items refer to questions about 1- random sequence generation (selection bias); 2- allocation concealment (selection bias); 3- blinding of patients and personnel (performance bias); 4- blinding of outcome assessment (detection bias); 5- incomplete outcome data (attrition bias); 6- selective reporting (reporting bias); 7- other bias, (other potential bias, not included in the domains described above). For the last, we considered high risk the studies that combined resveratrol with other substances. Thus, studies that administered a combined supplementation using resveratrol were classified as high risk when it was impossible to detect specific resveratrol results.

Meta-analysis

We included in the quantitative analysis studies that provided mean with standard deviation (SD) – before and after the intervention – on glycated hemoglobin (HbA1c), fasting blood glucose, and insulin resistance (HOMA-IR). We assessed the standard deviation of the mean change using the equation: $SD\ change = \sqrt{[(SD_{baseline}^2 + SD_{final}^2) - (2 \times R \times SD_{baseline} \times SD_{final})]}$, for studies with no information (Borenstein et al. 2009). Results are presented as the standardized mean difference (SMD) and 95% confidence intervals (95% CI). The Higgins I² statistic was calculated to estimate the heterogeneity between studies. Heterogeneity was statistically significant if $I^2 > 50\%$ and $p\text{-value} < 0.05$ (Higgins et al. 2003). The authors applied the DerSimonian and Laird random-effects model to pool the SMDs. Meta-analysis was performed on RStudio and RevMan softwares. The level of significance was set at 5%. Fasting blood glucose in mmol/l was converted to mg/dl. Glycated hemoglobin (HbA1c) was analyzed in % and insulin resistance in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Subgroup analyses included studies stratified by intervention time (up to 8 weeks; > 8 weeks). Also, we performed sensitivity analyses according to the Handbook for Systematic Reviews of Interventions of Cochrane software (Higgins and Green 2011). We excluded the studies that combined resveratrol with other substances and those that are not double-blind.

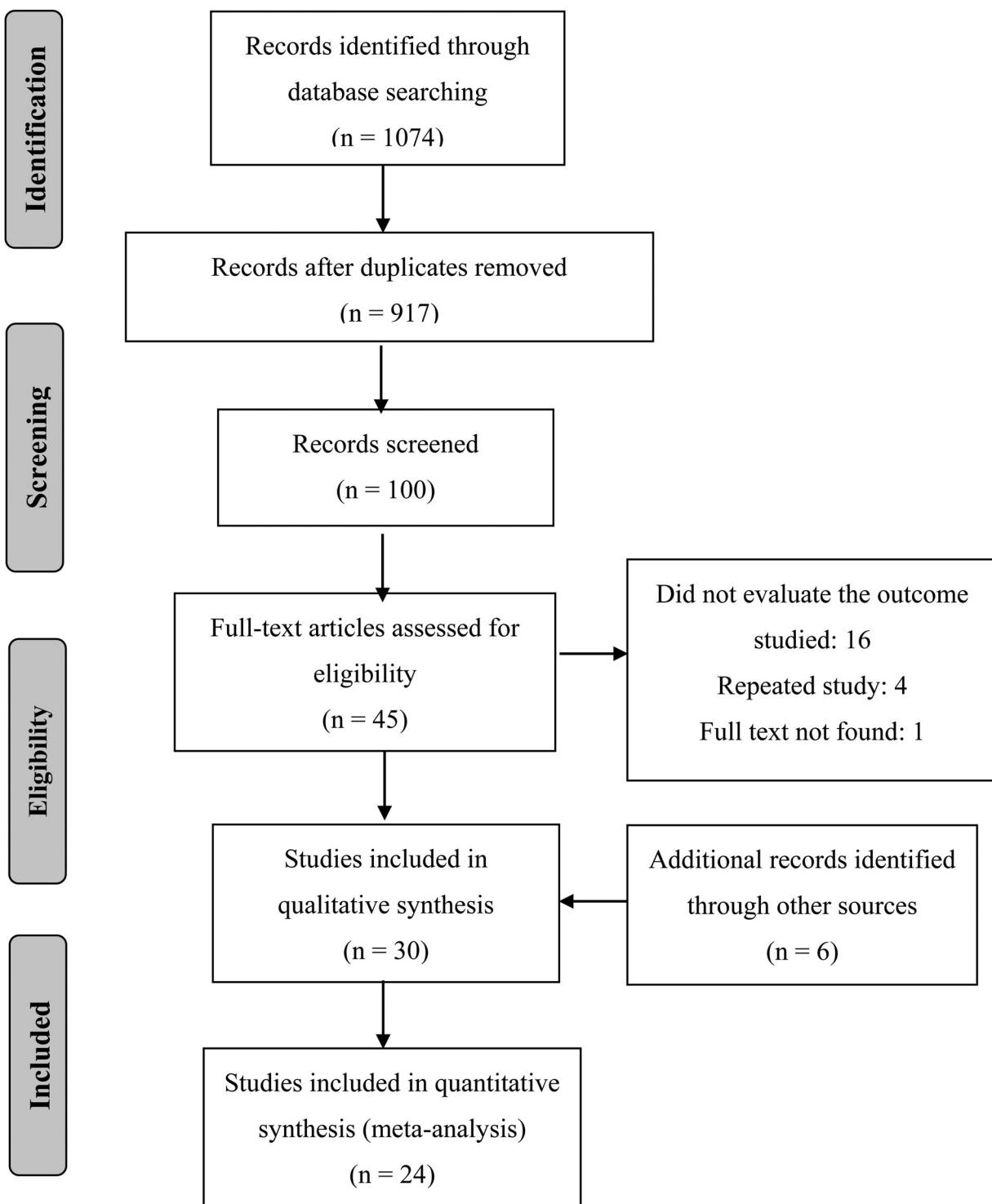


Figure 1. Flowchart of the selection of studies presented in the review.

Results

Studies characteristics

Figure 1 shows the study selection flowchart. From all databases, we find 917 unique articles, of which we selected 100 for reading abstracts. After reading the abstracts, we selected 45 articles for full reading, of which 24 were included in the review. Also, we selected six more articles from other sources, totaling 30 studies included in this review. The main reasons for exclusion at the last stage were: did not evaluate

the outcome studied ($n = 16$), repeated study (with the same sample) ($n = 4$), and the full text was not found ($n = 1$).

Of the 30 studies, 16 were published between 2016 and 2020 (Arzola-Paniagua et al. 2016; Banaszewska et al. 2016; Bo et al. 2016; Thazhath et al. 2016; Zare Javid et al. 2017; Kjaer et al. 2017; Köbe et al. 2017; Pollack et al. 2017; Kantartzis et al. 2018; Khodabandehloo et al. 2018; Sattarinezhad et al. 2019; Seyyedebrahimi et al. 2018; Abdollahi et al. 2019; Hoseini et al. 2019; de Ligt et al. 2020; Thaung Zaw, Howe, and Wong 2020). Eleven studies were

carried out in Asia (Bhatt, Thomas, and Nanjan 2012; Movahed et al. 2013; Faghihzadeh et al. 2014; Goh et al. 2014; Chen et al. 2015; Zare Javid et al. 2017; Khodabandehloo et al. 2018; Sattarinezhad et al. 2019; Seyyedebrahimi et al. 2018; Abdollahi et al. 2019; Hoseini et al. 2019), 11 in Europe (Banaszewska et al. 2016; Brasnyó et al. 2011; Yoshino et al. 2012; Poulsen et al. 2013; Witte et al. 2014; Timmers et al. 2011; Bo et al. 2016; Köbe et al. 2017; Kjaer et al. 2017; Van Der Made, Plat, and Mensink 2015; de Ligt et al. 2020), five in America (Anton et al. 2014; Méndez-del Villar et al. 2014; Arzola-Paniagua et al. 2016; Pollack et al. 2017; Kantartzis et al. 2018), and three in Oceania (Chachay et al. 2014; Thazhath et al. 2016; Thaung Zaw, Howe, and Wong 2020). Also, 29 studies were randomized double-blind (Brasnyó et al. 2011; Timmers et al. 2011; Yoshino et al. 2012; Movahed et al. 2013; Poulsen et al. 2013; Anton et al. 2014; Chachay et al. 2014; Faghihzadeh et al. 2014; Goh et al. 2014; Méndez-del Villar et al. 2014; Witte et al. 2014; Chen et al. 2015; Van Der Made, Plat, and Mensink 2015; Arzola-Paniagua et al. 2016; Banaszewska et al. 2016; Bo et al. 2016; Thazhath et al. 2016; Zare Javid et al. 2017; Köbe et al. 2017; Pollack et al. 2017; Kantartzis et al. 2018; Khodabandehloo et al. 2018; Sattarinezhad et al. 2019; Seyyedebrahimi et al. 2018; Abdollahi et al. 2019; Hoseini et al. 2019; de Ligt et al. 2020; Thaung Zaw, Howe, and Wong 2020; Kjaer et al. 2017), while one was just randomized (Bhatt, Thomas, and Nanjan 2012). Nineteen studies had 50 participants or less. The smallest sample size was ten individuals (Goh et al. 2014), and the highest 179 (Bo et al. 2016). Five studies were conducted only with men (Timmers et al. 2011; Poulsen et al. 2013; Chachay et al. 2014; Goh et al. 2014; Kjaer et al. 2017), three with women (Yoshino et al. 2012; Banaszewska et al. 2016; Thaung Zaw, Howe, and Wong 2020), and 22 with both genders.

Table 1 shows the main characteristics and results of the included studies. Of the 30 studies, 12 were carried with individuals with type 2 diabetes (Brasnyó et al. 2011; Bhatt, Thomas, and Nanjan 2012; Movahed et al. 2013; Goh et al. 2014; Bo et al. 2016; Thazhath et al. 2016; Zare Javid et al. 2017; Khodabandehloo et al. 2018; Sattarinezhad et al. 2019; Seyyedebrahimi et al. 2018; Abdollahi et al. 2019; Hoseini et al. 2019). All studies were with adults or older adults. Intervention time ranged from four (Brasnyó et al. 2011) to 96 weeks (Thaung Zaw, Howe, and Wong 2020; Yoshino et al. 2012). Resveratrol doses ranged from 10 mg (Brasnyó et al. 2011) to 3 grams per day (Goh et al. 2014; Chachay et al. 2014). Three studies used resveratrol combined with other substances, such as oral hypoglycemic (Bhatt, Thomas, and Nanjan 2012), orlistat (Arzola-Paniagua et al. 2016), and losartan (Sattarinezhad et al. 2019).

Eighteen studies (60%) found at least one protective effect of resveratrol supplementation in at least one parameter related to diabetes (Brasnyó et al. 2011; Timmers et al. 2011; Bhatt, Thomas, and Nanjan 2012; Movahed et al. 2013; Anton et al. 2014; Méndez-del Villar et al. 2014; Witte et al. 2014; Chen et al. 2015; Van Der Made, Plat, and Mensink 2015; Banaszewska et al. 2016; Zare Javid et al. 2017; Köbe

et al. 2017; Khodabandehloo et al. 2018; Sattarinezhad et al. 2019; Abdollahi et al. 2019; Hoseini et al. 2019; de Ligt et al. 2020; Thaung Zaw, Howe, and Wong 2020). From the five studies conducted only with men, only one found significant effects from resveratrol supplementation on diabetes parameters (Timmers et al. 2011). From three studies with women, two showed significant results (Banaszewska et al. 2016; Thaung Zaw, Howe, and Wong 2020). Of the 12 studies with individuals with type 2 diabetes, eight showed benefits from resveratrol supplementation (Brasnyó et al. 2011; Bhatt, Thomas, and Nanjan 2012; Movahed et al. 2013; Zare Javid et al. 2017; Khodabandehloo et al. 2018; Sattarinezhad et al. 2019; Abdollahi et al. 2019; Hoseini et al. 2019).

Risk of bias

The assessment of the risk of bias in each study can be found in Figure 2. Around 15% were classified as unclear or high risk because the authors did not provide enough data to analyze some of the design's essential items. Item 5 (attrition bias) had the highest number of studies classified as unclear or high risk of bias, in which we classified 12 of the 30 studies as unclear or high risk (Timmers et al. 2011; Yoshino et al. 2012; Poulsen et al. 2013; Anton et al. 2014; Chachay et al. 2014; Goh et al. 2014; Méndez-del Villar et al. 2014; Arzola-Paniagua et al. 2016; Kjaer et al. 2017; Pollack et al. 2017; Khodabandehloo et al. 2018; Kantartzis et al. 2018). The second item with the highest number of studies classified as unclear or high risk of bias ($n=7$) was item 1 and 2 (Brasnyó et al. 2011; Witte et al. 2014; Zare Javid et al. 2017; Pollack et al. 2017; Kantartzis et al. 2018; de Ligt et al. 2020; Thaung Zaw, Howe, and Wong 2020). The item with the lowest number of studies with a high or unclear risk of bias was item 6 (reporting bias) with no study. Only 11 studies (37%) had no item classified as unclear or high risk of bias (Movahed et al. 2013; Chen et al. 2015; Van Der Made, Plat, and Mensink 2015; Faghihzadeh et al. 2014; Banaszewska et al. 2016; Bo et al. 2016; Thazhath et al. 2016; Köbe et al. 2017; Seyyedebrahimi et al. 2018; Abdollahi et al. 2019; Hoseini et al. 2019).

Meta-analysis

Figure 3 shows the results from meta-analysis for fasting blood glucose for the overall population and stratified by intervention length. The analysis included 502 individuals in the group that received resveratrol and 509 in the group that received placebo. Results showed that resveratrol supplementation had no significant effect on fasting blood glucose compared to placebo [SMD: -0.28 ; CI95%: -0.73 , 0.17 ; $p = 0.01$; $I^2 = 91\%$]. In the subgroup analysis, we also not found significant effects in the studies with a duration of up to eight weeks [SMD: -0.12 ; 95% CI: -0.72 , 0.48 ; $p = 0.01$; $I^2 = 87\%$]. The same occurred for the group with intervention longer than eight weeks [SMD: -0.43 ; 95% CI: -1.09 , 0.23 ; $p = 0.01$; $I^2 = 93\%$].

Results of resveratrol supplementation on insulin resistance (HOMA-IR) for the overall population and stratified

Table 1. Detailed description of each study included in the systematic review.

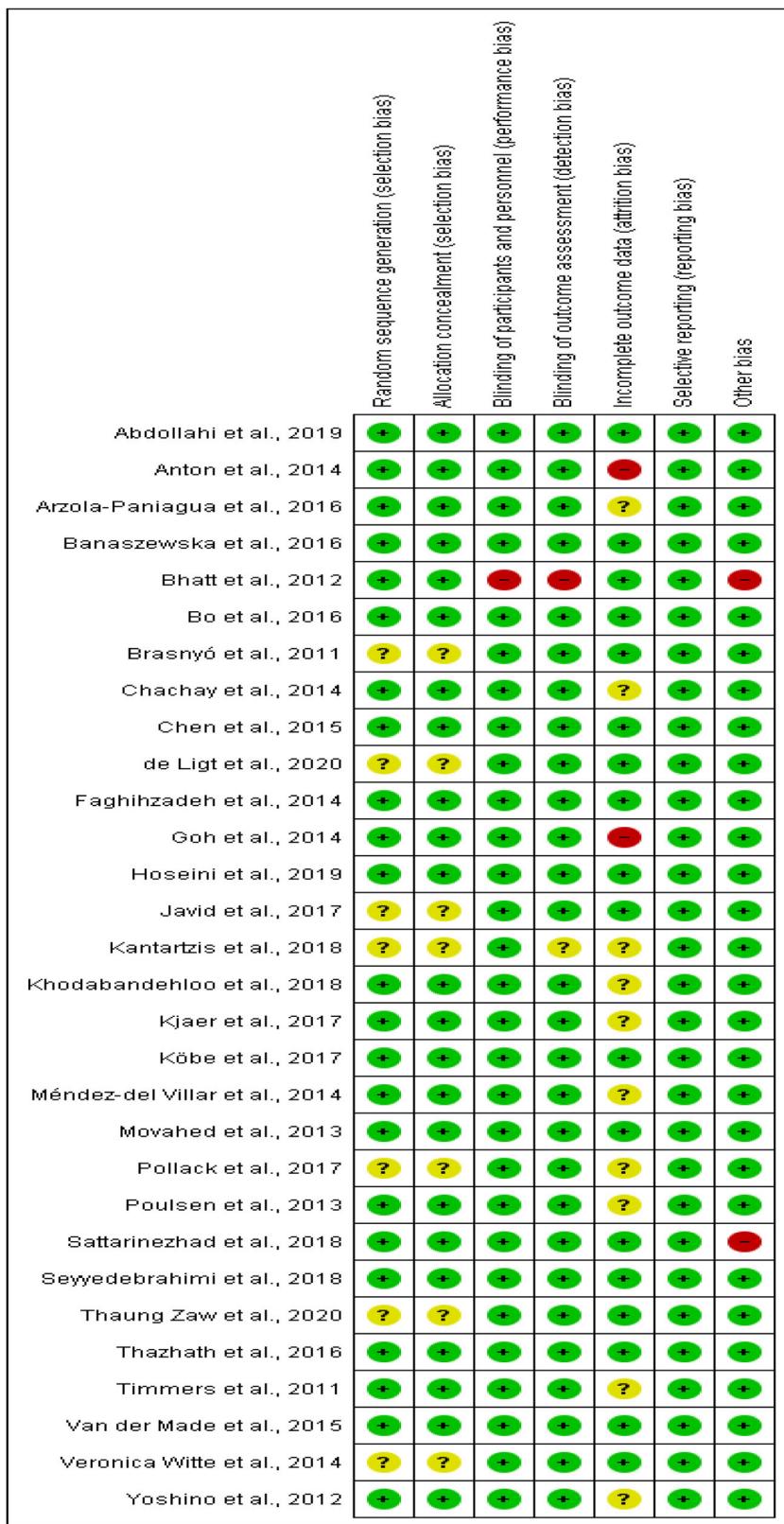
Identification	Location	Sample	Age	Duration in weeks	Study design	Resveratrol doses	Main results
Brasnyó et al. 2011	Hungary	19 individuals with type 2 diabetes	Mean age of 58 years in the intervention group and 53 in the control	4	Randomized double blind	10 mg daily or placebo	The group that ingested resveratrol had an improvement in insulin resistance
Timmers et al. 2011	Switzerland	11 obese men	Mean age 52 years between the groups	4	Randomized double blind	150 mg daily or placebo	Those in the intervention group showed benefits on glucose and insulin resistance
Bhatt, Thomas, and Nanjan 2012	India	57 individuals with type 2 diabetes	Mean age of 57 years in the intervention group and 58 in the control	12	Randomized	250 mg daily + oral hypoglycemic or oral hypoglycemic	Improvement in fasting blood glucose and glycated hemoglobin
Yoshino et al. 2012	Switzerland	29 eutrophic or overweight women	Mean age of 58 years in the intervention group and 59 in the control	12	Randomized double blind	75 mg daily or placebo	No differences in diabetes parameters between groups
Movahed et al. 2013	Iran	64 individuals with type 2 diabetes	Mean age of 52 years between the groups	6	Randomized double blind	1 g daily or placebo	Resveratrol had an antidiabetic effect compared to placebo
Poulsen et al., 2013	Denmark	24 obese men	Mean age of 44 years in the intervention group and 31 in the control	4	Randomized double blind	500 mg daily or placebo	No differences in diabetes parameters between groups
Anton et al. 2014	United States	32 overweight elderly	Mean age 73 years	13	Randomized double blind	300 mg, 1 g daily or placebo	Glucose remained stable in the intervention group, while in the control group, there was a significant increase
Chachay et al. 2014	Australia	20 overweight or obese men	Mean age of 48 years in the intervention group and 47 in the control	8	Randomized double blind	3 g of daily or placebo	No differences in diabetes parameters between groups
Faghizaddéh et al. 2014	Iran	50 individuals with nonalcoholic fatty liver disease	Mean age of 44 years in the intervention group and 46 in the control	12	Randomized double blind	500 mg daily or placebo	No differences in diabetes parameters between groups
Goh et al. 2014	Singapore	10 men with type 2 diabetes	Mean age of 56 years between the groups	12	Randomized double blind	3 g daily or placebo	No differences in diabetes parameters between groups
Méndez-del Villar et al. 2014	Mexico	24 individuals with metabolic syndrome	Mean age of 40 years between the groups	12	Randomized double blind	500 mg daily or placebo	Improvement in insulin sensitivity in the group that ingested resveratrol
Witte et al., 2014	Germany	46 older adults with overweight	Mean age of 65 years in the intervention group and 64 in the control	26	Randomized double blind	200 mg daily or placebo	No differences in fasting blood glucose but a significant reduction in glycated hemoglobin in the intervention group

(continued)

Table 1. Continued.

Identification	Location	Sample	Age	Duration in weeks	Study design	Resveratrol doses	Main results
Chen et al. 2015	China	60 individuals with nonalcoholic fatty liver disease	Mean age of 44 years between the groups	12	Randomized double blind	300 mg daily or placebo	Resveratrol showed benefits on diabetes parameters like insulin resistance and fasting blood glucose
Van Der Made, Plat, and Mensink 2015	Netherlands	45 individuals with overweight or mild obesity	Mean age 61 years between the groups	4	Randomized double blind	150 mg daily or placebo	Significant reduction in glucose in the group that ingested resveratrol
Arzola-Paniagua et al. 2016	Mexico	84 individuals with obesity	Mean age of 39 years between the groups	28	Randomized double blind	4 groups: orlistat, 100 mg resveratrol, orlistate + 120 mg resveratrol or placebo	No differences in diabetes parameters between groups
Banaszewska et al. 2016	Poland	34 women with polycystic ovary syndrome	Mean age of 27 years between the groups	12	Randomized double blind	1500 mg daily or placebo	Resveratrol showed benefits on diabetes parameters like insulin sensitivity
Bo et al. 2016	Italy	179 individuals with type 2 diabetes	Mean age of 65 years between the groups	26	Randomized double blind	40 mg, 500 mg daily or placebo	No differences in diabetes parameters between groups
Thazhath et al., 2016	Australia	28 individuals with type 2 diabetes	Mean age of 67 years between the groups	5	Randomized double blind	500 mg resveratrol twice daily or placebo	No differences in diabetes parameters between groups
Zare Javid et al. 2017	Iran	43 individuals with type 2 diabetes	Mean age of 49 years in the intervention group and 51 in the control	4	Randomized double blind	480 mg daily or placebo	Improvement in insulin resistance in the intervention group
Kjaer et al. 2017	Denmark	74 men with metabolic syndrome	Mean age of 49 years in the low dose group, 51 in the high dose and 47 in the placebo	16	Randomized double blind	150 mg, 1 g daily or placebo	No differences in diabetes parameters between groups
Köbe et al. 2017	Germany	40 individuals with mild cognitive impairment	Mean age of 65 years in the intervention group and 69 in the control	26	Randomized double blind	200 mg daily or placebo	Significant reduction on glycated hemoglobin on those that ingested resveratrol
Pollack et al. 2017	United States	30 individuals with glucose intolerance	Mean age of 67 years between the groups	6	Randomized double blind	2 g daily or placebo	No differences in diabetes parameters between groups
Kantartzis et al. 2018	Germany	105 overweight and obese individuals with insulin resistance	Ages between 18 and 70 years	12	Randomized double blind	150 mg daily or placebo	No differences in diabetes parameters between groups
Khodabandehloo et al. 2018	Iran	45 individuals with type 2 diabetes	Mean age of 56 years in the intervention group and 61 in the control	8	Randomized double blind	800 mg daily or placebo	Significant reduction in fasting blood glucose in the group that ingested resveratrol
Sattarinezhad et al. 2019	Iran		Mean age of 57 years in the intervention	12	Randomized double blind		Significant reduction in diabetes parameters

Seyyedebrahimi et al. 2018	Iran	60 individuals with type 2 diabetes and albuminuria 46 individuals with type 2 diabetes	group and 56 in the control Mean age of 55 years in the intervention group and 59 in the control Mean age of 50 years between the groups	Randomized double blind	500mg daily + losartan or placebo + losartan 800mg daily or placebo	like fast blood glucose and insulin resistance No differences in diabetes parameters between groups
Abdollahi et al. 2019	Iran	71 overweight individuals with type 2 diabetes	Mean age of 61 years in the intervention group and 63 in the control Mean age of 61 years in the intervention group and 62 in the control	Randomized double blind	1g daily or placebo	Significative reduction in fasting blood glucose in the group that ingested resveratrol
Hoseini et al. 2019	Iran	56 individuals with type 2 diabetes and cardiovascular disease 41 overweight individuals	Mean age of 61 years in the intervention group and 63 in the control Mean age of 61 years in the intervention group and 62 in the control	Randomized double blind	500mg daily or placebo	Significant effect in glycemic control in the intervention group
de Ligt et al. 2020	Netherlands	125 postmenopausal women	Mean age of 65 years between the groups	Randomized double blind	150mg daily or placebo	There was no improvement in insulin sensitivity, but there was a significant reduction in hemoglobin in the group that ingested resveratrol
Thaung Zaw, Howe, and Wong 2020	Australia			Randomized double blind	75 mg daily or placebo	Improvement in insulin resistance in the group that ingested resveratrol

**Figure 2.** Cochrane risk of bias toll results for included studies.

by duration of intervention are shown in **Figure 4**. The analysis included 308 individuals in the intervention group and 304 in the control group. Results showed that there was a significant reduction in insulin resistance in individuals who ingested resveratrol [SMD: -0.34; CI95%: -0.64, -0.04;

$p=0.01$; $I^2 = 70\%$]. Studies with a duration of up to eight weeks also remained statistically significant [SMD: -0.42; 95% CI: -0.79, -0.04; $p=0.01$; $I^2 = 67\%$]. For studies longer than eight weeks, the results were not significant [SMD: -0.22; 95% CI: -0.77, 0.34; $p=0.01$; $I^2 = 78\%$].

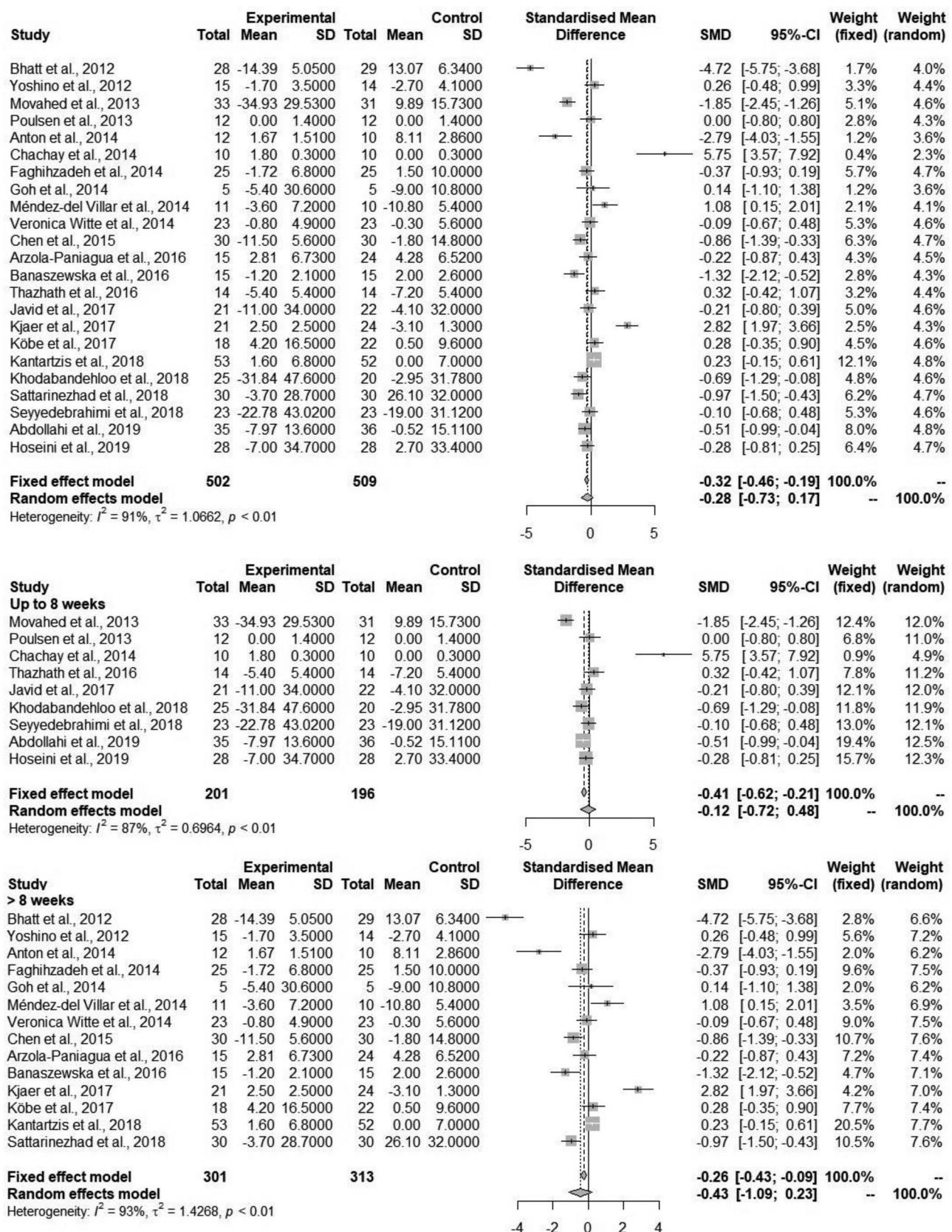
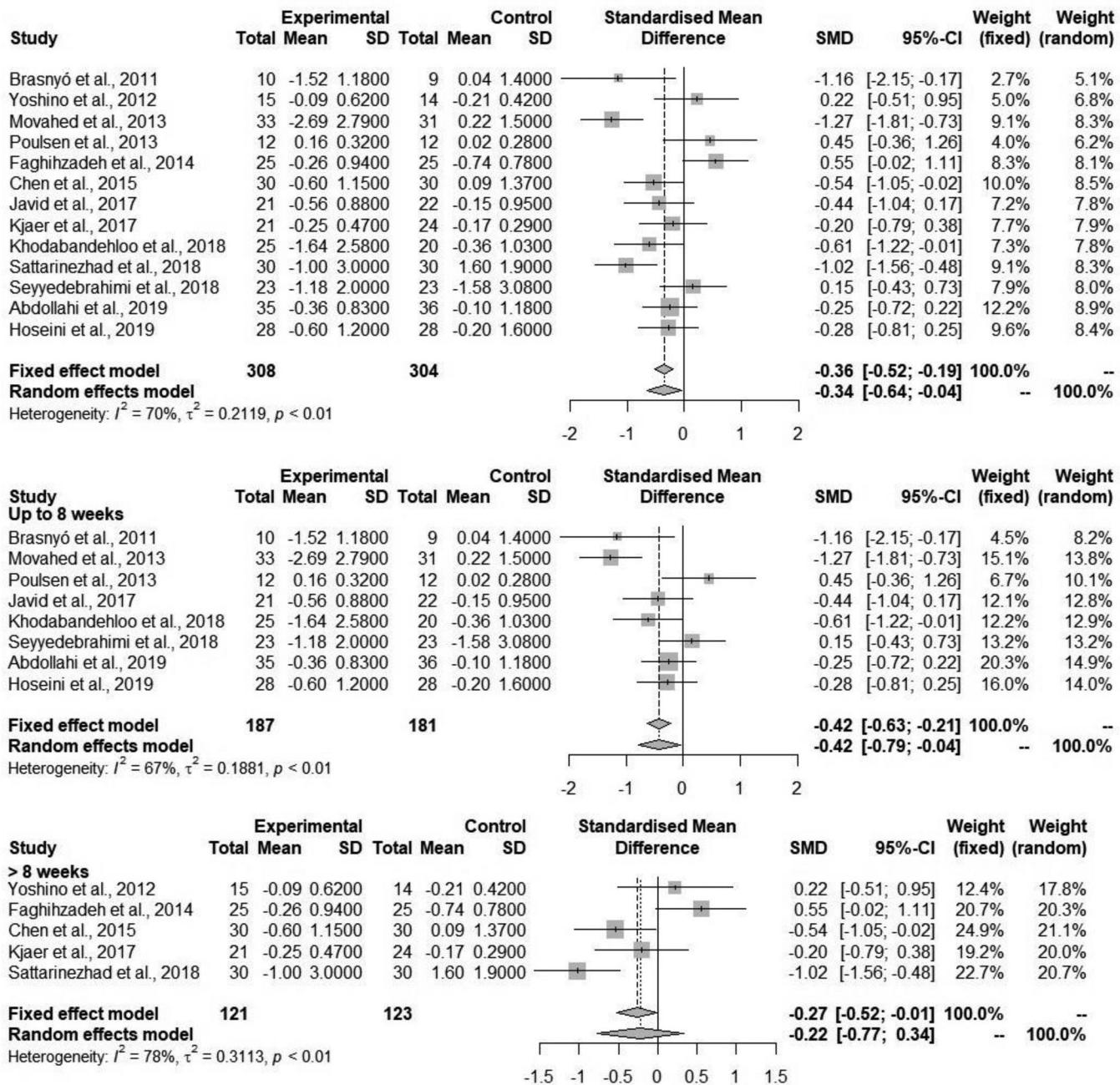


Figure 3. Resveratrol effects on fasting blood glucose total and stratified by length of intervention.

Figure 5 shows the results for glycated hemoglobin (HbA1c) for the overall population and stratified by intervention time. The analysis included 299 individuals in the intervention group and 297 in the control group. Compared

to placebo, resveratrol showed a significant reduction in glycated hemoglobin [SMD: -0.64 ; CI95%: -1.22 , -0.07 ; $p = 0.01$; $I^2 = 90\%$]. In the subgroup analysis, resveratrol had no significant effect compared to placebo among

**Figure 4.** Resveratrol effects on insulin resistance (HOMA-IR) total and stratified by length of intervention.

individuals from studies with a length of intervention up to eight weeks [SMD: -0.02 ; 95% CI: -0.52 , 0.49 ; $p = 0.01$; $I^2 = 76\%$]. However, in studies with a duration of more than eight weeks, the results were significant [SMD: -1.43 ; 95% CI: -2.53 , -0.34 ; $p = 0.01$; $I^2 = 94\%$].

Figure 6 shows the analysis for studies conducted with individuals with diabetes, for fasting blood glucose, glycated hemoglobin, and insulin resistance (HOMA-IR). Compared to placebo, resveratrol showed a significant reduction in fasting blood glucose [SMD: -0.85 ; CI95%: -1.49 , -0.21 ; $p = 0.01$; $I^2 = 90\%$] and insulin resistance [SMD: -0.58 ; 95% CI: -0.92 , -0.23 ; $p = 0.01$; $I^2 = 64\%$]. However, for glycated hemoglobin, the results were negligible [SMD: -0.84 ; 95% CI: -1.73 , 0.05 ; $p = 0.01$; $I^2 = 93\%$]. Figure 7 shows the sensitivity analysis excluding studies that utilized resveratrol with

other substances and those that are not double-blind. Compared to placebo, resveratrol showed a significant reduction in insulin resistance [SMD: -0.34 ; CI95%: -0.64 , -0.04 ; $p = 0.01$; $I^2 = 70\%$]. However, for fasting blood glucose and glycated hemoglobin, the results were negligible.

Discussion

To the best of our knowledge, this is the most recent systematic review and meta-analysis from randomized clinical trials about the effects of resveratrol supplementation on parameters of diabetes, like fasting blood glucose and hemoglobin glycated. From 2017 to 2014, the previous meta-analysis included only nine and eleven studies in the

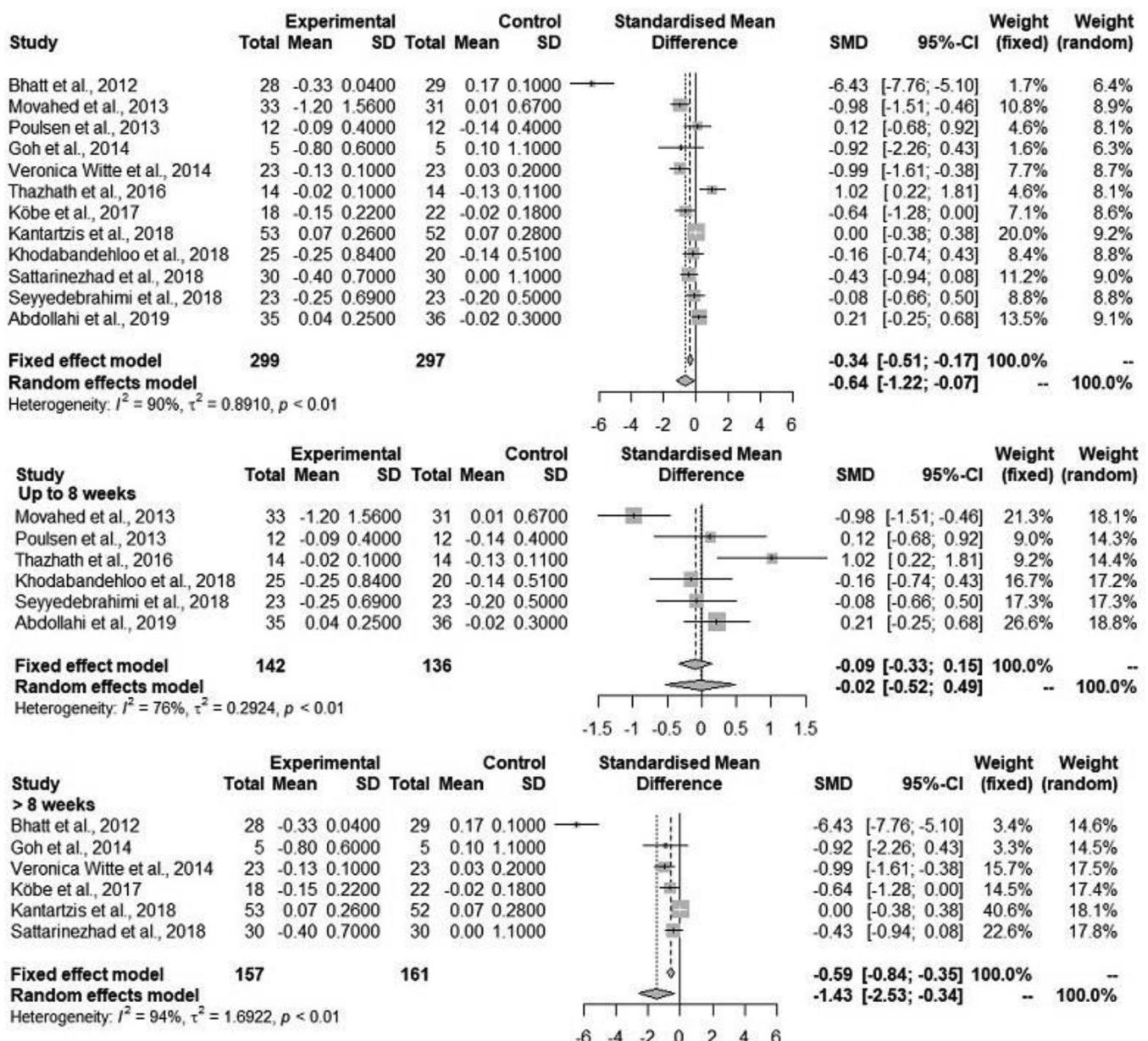


Figure 5. Resveratrol effects on glyated hemoglobin (HbA1c) total and stratified by length of intervention.

quantitative analysis (Zhu et al. 2017; Liu et al. 2014). Our analysis included 24 studies, more than double the other studies. From the 30 studies included in this systematic review, our results demonstrated that 60% of the studies had shown significant supplementation effects with resveratrol on diabetes parameters, like fasting blood glucose, insulin resistance, and glyated hemoglobin. Our meta-analysis results showed positive effects of resveratrol supplementation on insulin resistance and glyated hemoglobin. However, for fasting blood glucose, there are no significant results. When stratified by intervention time, the results were significant for studies with a duration of up to eight weeks on insulin resistance and studies longer than eight weeks for glyated hemoglobin. Our last analysis showed significant results for fasting blood glucose and insulin resistance when we included only the studies with diabetic individuals. One previous meta-analysis showed significant results on fasting

blood glucose and insulin resistance, but not in glyated hemoglobin (Zhu et al. 2017). Another meta-analysis showed benefits on fasting blood glucose, insulin resistance, and glyated hemoglobin (Liu et al. 2014). Our negative results for subgroup analysis in the insulin resistance may be due to the low number of studies with intervention time longer than eight weeks. Also, only six studies were included in the subgroup analysis for glyated hemoglobin, which may explain the analysis's negative results for studies with a duration of up to eight weeks.

From the 30 studies, only two showed side effects. The first reported some gastrointestinal side effects when doses of 1.5 g twice a day were administrated (Pollack et al. 2017). In another study, two individuals (one in the group that received resveratrol and the other in the control group) reported gastrointestinal effects such as mild dyspepsia (Sattarinezhad et al. 2019). A previous study investigating

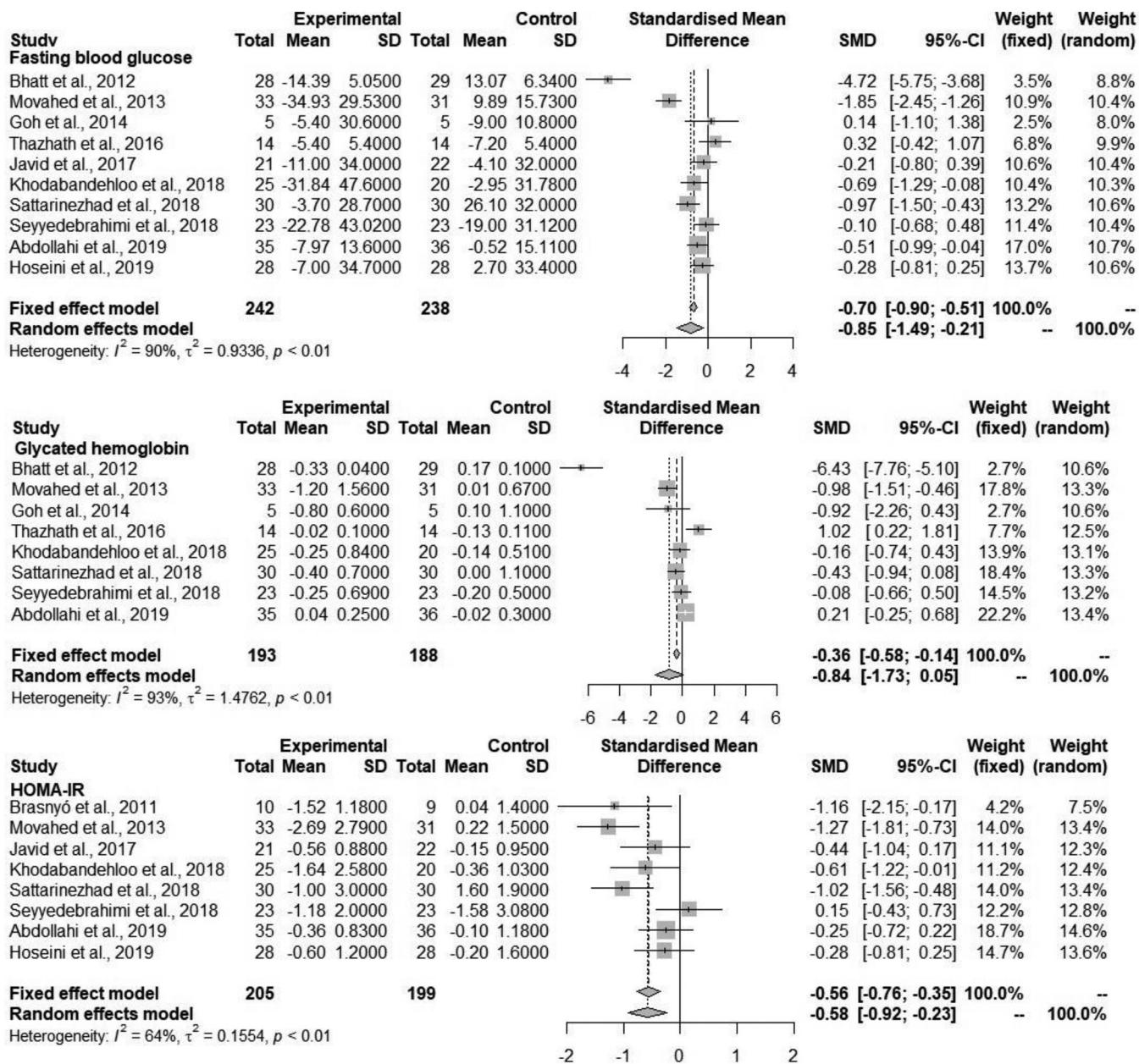


Figure 6. Resveratrol effects on fasting blood glucose, glycated hemoglobin, and insulin resistance for individuals with diabetes.

resveratrol supplementation showed gastrointestinal side effects when high doses are administrated (2.5 to 5 g daily). In doses below 2.5 g, there are no side effects reported by the participants (Brown et al. 2010). Moreover, a review that included clinical trials showed that resveratrol is safe and well-tolerated in doses of up to 5 g daily (Patel et al. 2011). A recent review of resveratrol security showed that low doses are safe, but some studies have shown some side effects with high doses (Shaito et al. 2020). The authors suggest further studies to investigate resveratrol's safety and investigate doses that are safe and effective in treating various pathologies (Shaito et al. 2020).

The mechanisms by which resveratrol can improve diabetes parameters are complex and are not yet fully understood. In glycemia, animal studies showed that resveratrol could have an anti-hyperglycemic effect that results from a stimulating activity in the intracellular glucose transport

(Szkudelski and Szkudelska 2011). Also, experiments with rat cells showed that resveratrol could stimulate glucose uptake in the absence of insulin (Szkudelski and Szkudelska 2011). The increase in glucose uptake induced by resveratrol may be related to increased glucose transporter's action on the cytoplasmic membrane (Vallianou, Evangelopoulos, and Kazazis 2013). The mechanisms related to improving insulin action seem to be related to the reduction of adiposity, changes in the expression of genes, and changes in some enzymes' activity (Szkudelski and Szkudelska 2011). Resveratrol may also enhance adiponectin levels, being a potential mechanism for improving insulin sensitivity (Vallianou, Evangelopoulos, and Kazazis 2013).

Our assessment of bias showed 15% of the studies as unclear risk of bias due to the lack of essential details on clinical trials' methodology. Two studies also showed high

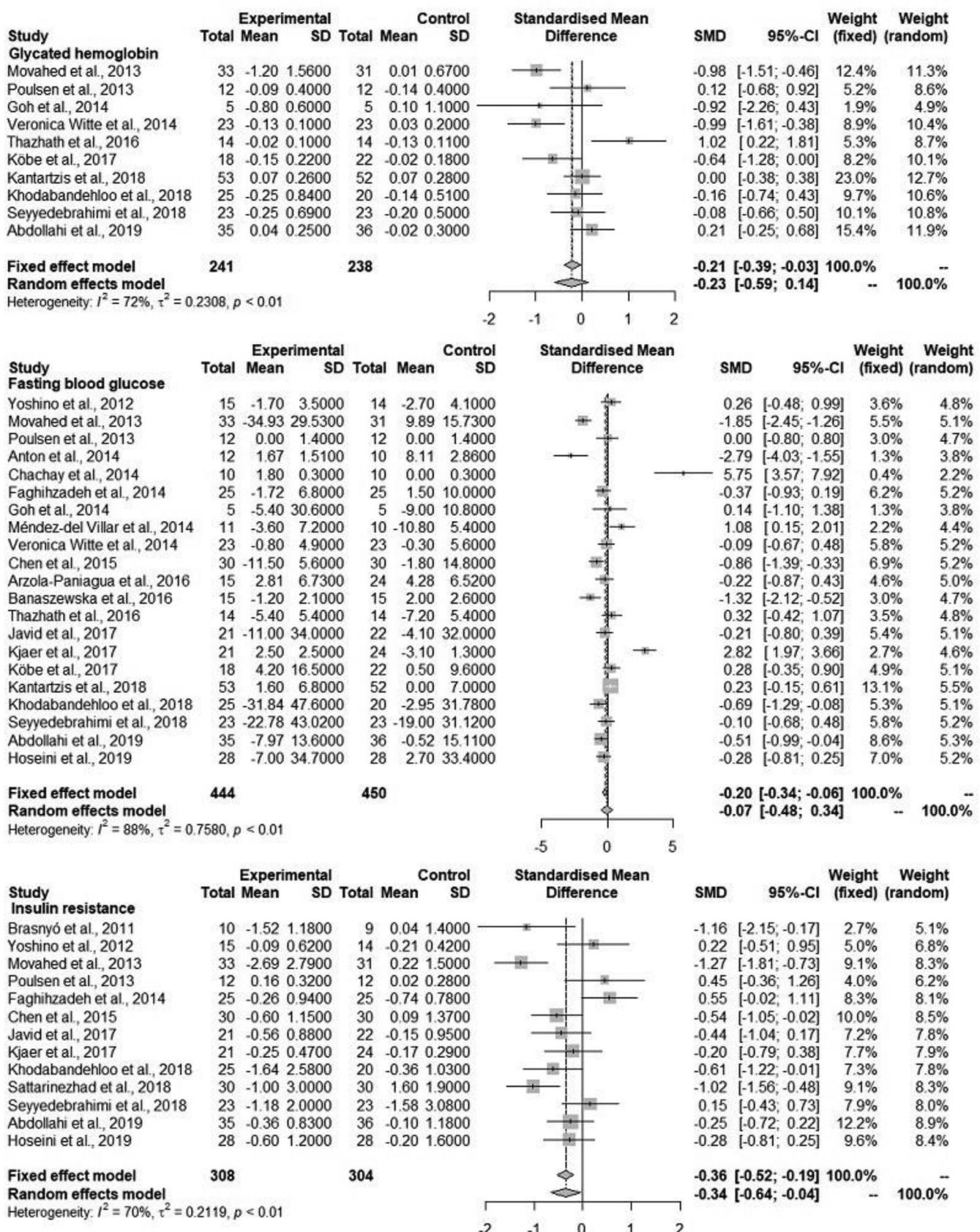


Figure 7. Sensitivity analysis without studies that combined resveratrol with other substances and those that are not double-blind.

risk in item 7 (other bias) because they combined resveratrol with other substances and showed only the combined result. Moreover, we observed a high heterogeneity between

studies. For example, one study utilized doses of 10 mg daily (Brasnyó et al. 2011), while the other two utilized 30 times bigger (3 g daily) (Goh et al. 2014; Chachay et al. 2014).

Despite this, high doses do not seem to make a difference in the results since the study used 10 mg had significant results, while the two that used 3 g did not. The largest study's intervention time was 96 weeks (Thaung Zaw, Howe, and Wong 2020), 24 times longer than studies with the shortest intervention time (Hoseini et al. 2019; Zare Javid et al. 2017; Van Der Made, Plat, and Mensink 2015; Poulsen et al. 2013; Timmers et al. 2011; Brasnyó et al. 2011). In the meta-analysis, we observed that studies longer than eight weeks performed better results in almost all analyzes. Except for insulin resistance, the studies with a duration of up to eight weeks had significant results, while those longer than eight weeks had not. Further studies should use doses of up to 2.5 grams daily and intervention time of more than eight weeks. Given the potential of resveratrol to treat or prevent diabetes, we hope that new studies will be more homogeneous and confirm the findings we found here.

This review has several strengths. First, we included a large number of databases. We also have not included restrictions for year of publication or language. Our meta-analysis included many individuals between groups, reaching more than a thousand for fasting blood glucose. Despite these positive points, we are not free from limitations. First, studies published in the gray literature were not included, such as theses and dissertations. These studies can provide null or negative results that end up not being published (Paez 2017). Another limitation is that the meta-analyses included studies with samples composed of individuals with various types of pathologies, such as diabetes, nonalcoholic fatty liver disease, metabolic syndrome, polycystic ovary syndrome, mild cognitive impairment, albuminuria, and cardiovascular disease. However, as far as we know, none of these complications can affect resveratrol results in diabetes parameters.

Our results demonstrated that resveratrol supplementation could help in treating or preventing diabetes, decreasing insulin resistance, glycated hemoglobin, and fasting blood glucose. Resveratrol supplementation may be an aid in the treatment or prevention of this pathology. Further studies with more homogeneous doses and duration over eight weeks are needed to confirm these findings and confirm resveratrol's safety.

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Declaration of interest statement

The authors declare no conflict of interest.

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