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Effect of resveratrol on metabolic syndrome components: A systematic review and meta-analysis

Sedigheh Asgary[1] · Raheleh Karimi[2,3] · Saeideh Momtaz[4,5] · Rozita Naseri[6] · Mohammad Hosein Farzaei[7]

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Abstract

We summarized 16 controlled studies and evaluated the correlation of resveratrol supplementation with metabolic parameters such as the body weight, waist circumference (WC), systolic blood pressure (sbp), HDL, total cholesterol, triglyceride and glucose levels. This meta-analysis was carried out to determine the association between the resveratrol intake with metabolic parameters in metabolic syndrome patients. PubMed, Scopus, Cochrane and Google Scholar were searched from inception to December 2018 using relevant keywords. All articles were independently reviewed by two authors using predetermined selection criteria. We have selected the studies that investigated the effects of resveratrol on metabolic parameters. Of 16 studies, 10 were performed on human subjects, and in 6 studies animal models were used. Standard mean difference (SMD) with 95% confidence interval were determined using Der Simonian and Laird random-effects modeling, when there was a significant heterogeneity between studies. Funnel plot and Egger's test were conducted to examine the risk of publication bias. Pooled effect sizes in human studies indicated a significant impact of resveratrol supplementation on glucose level [−1.73 (−2.99, −0.47); $p = 0.007$)] and WC [−1.73 (−2.79, −0.67); $p = 0.001$] compared with the control group. Also combining the results of studies on rat samples ($n = 6$), indicated significant effect of resveratrol on decreasing weight [−22.95 (−44.74, −1.17); $p = 0.04$], TGs [−6.76 (−11.10, −2.42); $p = 0.001$], sbp [−7.30 (−12.48, −2.13); $p = 0.006$], and it can influence significantly on increasing HDL level (4.75 (1.87, 7.63); $p = 0.001$). However, resveratrol was not significantly effective on total cholesterol in both samples. The results of subgroup analysis of human studies showed that resveratrol has significant effect on metabolic parameters (glucose level and WC) at the dosage of > 500 mg and with long-term interventions ≥ 10 weeks. Administration of resveratrol can meaningfully reduce the BW, WC, TGs, and glucose level, also it can increase HDL, but not total cholesterol.

Keywords Resveratrol · Metabolic syndrome · Meta-analysis · Metabolism

✉ Mohammad Hosein Farzaei
mh.farzaei@gmail.com

1 Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

2 Epidemiology and Biostatistics Department, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

3 Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

4 Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran

5 Toxicology and Diseases Group, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

6 Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

7 Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

Abbreviations

BW	body weight
WC	waist circumference
sbp	systolic blood pressure
HDL	high density lipoprotein
TGs	triglyceride
SMD	standard mean difference
UCP	uncoupling protein
SIRT1	sirtuin-1
PGC-1α	proliferator-activatedreceptor-gamma-coactivator1-α
C/EBPα	CCAAT-enhancer-binding protein
PPAR	peroxisome proliferator-activated receptors
Nrf2	transcription factor nuclear factor-E2-related factor-2
RCT	randomized controlled trial
BMI	body mass index

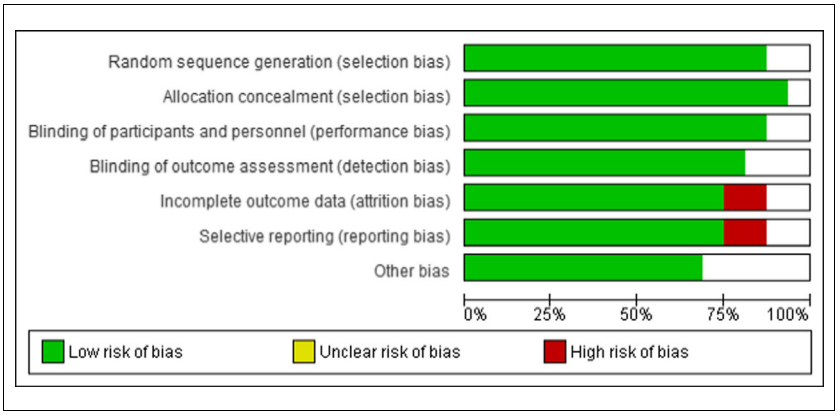

Fig. 1 Risk of bias table to assessing quality of the included studies: low risk of bias (green color), unclear risk of bias (blank), and high risk of bias (red color)

AMPK adenosine monophosphate (AMP)-activated protein kinasee
TNF-α tumor necrosis factor-alpha

1 Introduction

Metabolic syndrome refers to a set of clinically cardiovascular risk factors including obesity, insulin resistance, glucose intolerance, dyslipidemia, non-alcoholic fatty liver disease and hypertension [1]. The prevalence of the disease has an unrestrained upward trend worldwide, mainly as a consequence of insulin resistance and visceral obesity [2]. Metabolic syndrome emerges major concerns towards public health, contributing to cardiovascular and neurodegenerative diseases, cancer, and many other socioeconomic complications. In addition to the lifestyle and dietary patterns, as the key participants; genetic vulnerability, medical reasons and social determinants play significant role in progression of metabolic syndrome [3, 4]. A complex network of neural and humoral

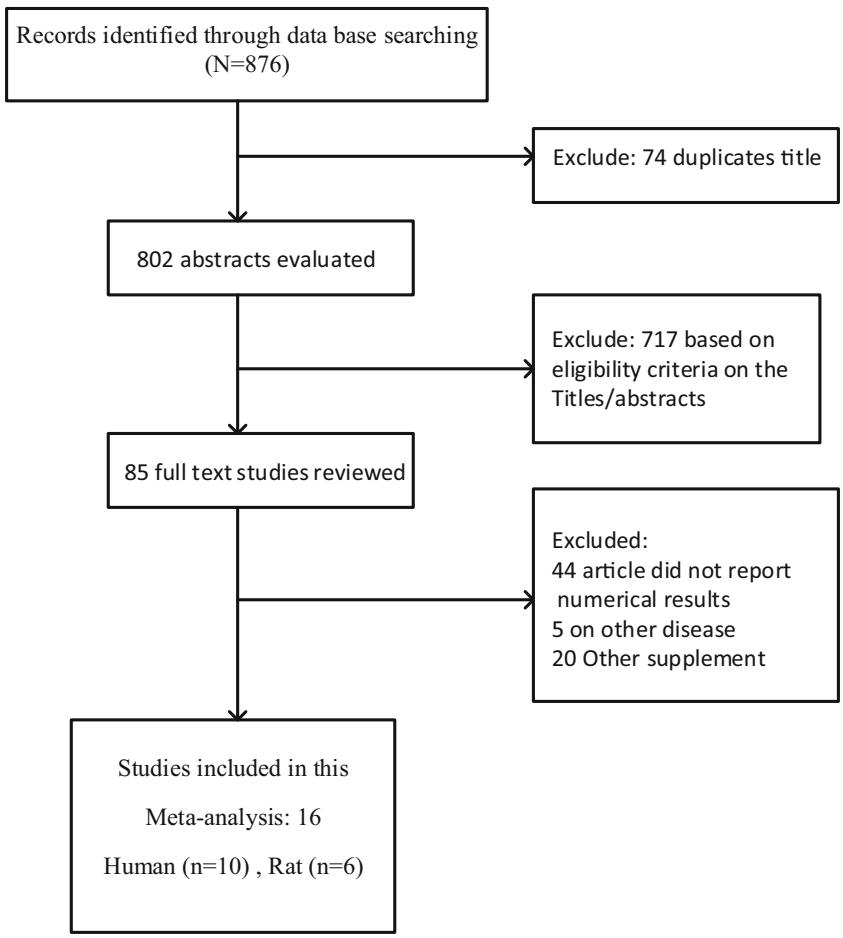

Fig. 2 Flow chart showing the process of study selection. Key words: "metabolic syndrome", "abdominal obesity", "metabolic profile", "Resveratol"

Table 1 Summery of characteristic of studies included in the meta-analysis

Author	Study type	population	Mean age(y)	Mean doze Resveratrol	Duration	Results
Van der made SM, et al. (2015) [32]	RCT (human)	Resveratrol = 45 Placebo = 45	61 ± 7	150 mg	4 weeks	Cholesterol, HDL, TGs, sbp, Glucose
Villar M, et al. (2014) [33]	RCT (human)	Resveratrol = 11 Placebo = 10	39.8 ± 5.4	500 mg	12 weeks	Weight, WC, Cholesterol, HDL, TGs, sbp
Anton SD, et al. (2014) [34]	RCT (human)	Resveratrol = 10 Placebo = 10	73 ± 7	300 mg 1000 mg	12 weeks	Weight, WC, Glucose, sbp
Chachay VS, et al. (2014) [35]	RCT (human)	Resveratrol = 10 Placebo = 10	48.15 ± 11.7	3000 mg	8 weeks	weight
Fujitaka, et al. (2011) [36]	RCT (human)	Resveratrol = 17 Placebo = 17	45.16	100 mg	9 weeks	Weight, WC, TGs, HDL
Chen S, et al. (2014) [37]	RCT (human)	Resveratrol = 30 Placebo = 30	55.8	300 mg	3 weeks	Weight, WC, Glucose, Cholesterol, HDL
Asghari S, et al. (2017) [38]	RCT (human)	Resveratrol = 30 Placebo = 30	20–60	600 mg	12 weeks	Weight, WC, TGs, HDL, Cholesterol
Kjær ThN, et al. (2017) [39]	RCT (human)	Resveratrol = 21 Placebo = 24	49.5	1000 mg 150 mg	16 weeks	Weight, TGs
Martínez-Abundis E, et al. (2016) [40]	RCT (human)	Resveratrol = 12 Placebo = 12	Na	500 mg	12 weeks	Weight, WC
Timmers S, et al. (2011) [41]	RCT (human)	Resveratrol = 11 Placebo = 11	20–60	150 mg	4 weeks	TGs
Rivera L, et al. (2013) [42]	Preclinical study (rat)	Resveratrol = 7 Placebo = 7	–	10 mg	8 weeks	Weight, TGs, Cholesterol
Peredo-Escarcege (2016) [43]	Preclinical study (rat)	Resveratrol = 12 Placebo = 12	–	19 mg 95 mg	3 weeks	Weight, Glucose, sbp, TGs, Cholesterol, HDL
Baek, et al. (2013) [44]	Preclinical study (rat)	Resveratrol = 16 Placebo = 16	–	100 mg	4 weeks 8 weeks 12 weeks	TGs, HDL, Cholesterol, Glucose
Sutrat, et al. (2008) [45]	Preclinical study (rat)	Resveratrol = 9 Placebo = 9	–	21 mg	6 weeks	TGs, HDL, Cholesterol, Glucose
Robich MP, et al. (2010) [46]	Preclinical study (rat)	Resveratrol = 7 Placebo = 7	–	100 mg	7 weeks	Cholesterol, Glucose, sbp
Benrick A, et al. (2013) [47]	Preclinical study (rat)	Resveratrol = 10 Placebo = 9	–	400 mg	5–6 weeks	HDL, Cholesterol, Glucose

communications were attributed to the pathophysiological mechanisms involved in the development and maintenance of the disease [5]. A number of clinical criteria were launched in order to determine the metabolic syndrome profile of an individual, including WC (population and/or country cut-off), increased TGs (≥ 150 mg/dl or in treatment), reduced HDL-cholesterol (<40 mg/dl in men, <50 mg/dl in women or in treatment), hypertension (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg, or in treatment) and glucose impairment (elevated fasting glucose, > 100 mg/dl or in treatment for hyperglycemia) [6]. Metabolic syndrome is a clinically heterogeneous disease. This was mainly correlated with the impact of the syndrome on the glucose, fat and protein metabolism, cellular growth and differentiation, and the endothelial function. Up to date, energy restriction and physical activity are accounted as the main possibilities to manage the syndrome, however, due to the abortive outcomes; utilization of active biomolecules can be a complementary option to maintain the major risk factors under control. The metabolic effects of polyphenol compounds have been comprehensively investigated and were found promising in the majority of studies [7–10].

Resveratrol (3,5,4′-trihydroxystilbene), a natural non-flavonoid polyphenol belonging to the stilbenes derivative, is frequently accessible in a variety of edible fruits, including nuts, berries, grapes skin, and many others. In spite of the resveratrol abundance in food resources, its concentration is considerably low [11], yet it is efficiently absorbed upon oral administration [12]. There is a wealth of *in vitro* and *in vivo* studies, revealing the effectiveness of resveratrol in metabolic syndrome, particularly obesity and diabetes complications. A number of clinical trials indicated that resveratrol has beneficial effects on these conditions, although there are several disagreements regarding this notion.

In case of obesity, resveratrol modifies energy balance and the body fat accumulation through down-regulating the adipocyte specific transcription factors, enzymes and the genes involved in mitochondrial function [13]. In white adipose tissue,

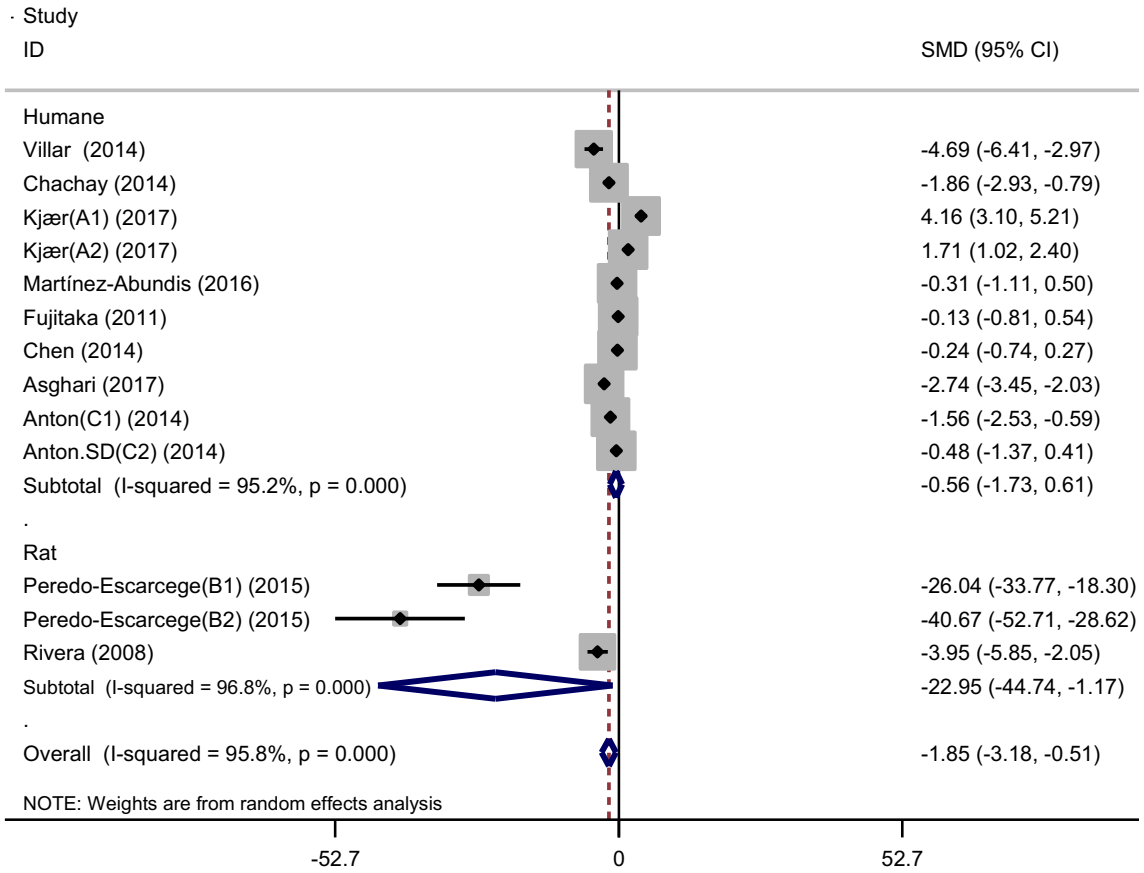

Fig. 3 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on total weight. (A1: 1000 mg , A2: 150 mg; B1:19 mg, B2:95 mg; C1: 300 mg, C2:1000 mg)

resveratrol reduces adipogenesis and/or effects on *de novo* lipogenesis through increased triacylglycerol metabolism [14], while in brown adipose tissue, the compound expands the capacity of adaptive thermogenesis [15]. Resveratrol reduces the adipose tissue fatty acid uptake mediated by the lipoprotein lipase [16], also in the liver and skeletal muscle increases the lipid oxidation [17]. In part, the body-fat lowering effect of resveratrol was correlated with enhanced uncoupling protein (UCP) expression in rats thermogenic tissues; including the interscapular brown adipose tissue and skeletal muscle; indicating its potential to increase the overall energy consumption in the body. In addition, the administration of resveratrol enhanced the gene expression of mitochondrial-transcription-factor-A, mitochondrial-protein-cytochrome-C-oxidase subunit-2, SIRT1, PPARβ/δ, and proliferator-activatedreceptor-gamma-coactivator1-α (PGC-1a) [15]. Suppression of C/EBPα and PPARγ by resveratrol, was introduced as the key molecular event responsible for its anti-adipogenic effect [18–20]. C/EBPα and PPARγ belong to the adipogenesis-inducing regulators, which are able to activate the adipogenic genes throughout the process of adipogenesis [21]. Resveratrol was shown to inhibit the proliferation and adipogenic differentiation in human preadipocytes via up-regulation of SIRT1 [22], in contrast, the compound increased TNF-α-related apoptosis-inducing ligand -induced apoptosis of human adipocytes in an SIRT1 independent manner [23].

In case of diabetes, resveratrol was found to have pleiotropic action in both animal and human investigations, as potently improves the glucose homeostasis and insulin secretion, modulates the insulin resistance, and protects pancreatic beta cells; majorly through elevating the expression/activity of AMPK and SIRT1 in various tissues of diabetic subjects, which in concurrent with its anti-oxidant and anti-inflammatory properties, make it a favorable approach to treat diabetes [24].

Given the role of oxidative stress and inflammation in the pathogenesis of hypertension, long-term administration of resveratrol attenuated oxidative stress biomarkers and renal interstitial inflammation by activating the transcription factor Nrf2 expression, thereby, improved hypertension. Concomitantly, resveratrol ameliorated the vascular nitric oxide production, endothelial dysfunction and arteriolar remodeling [25, 26]. Together, resveratrol exhibited multiple appropriate effects on metabolic syndromes and symptoms, thus in this context, the objective of this study was to provide a meta-analysis of published human/animal studies that assessed the effects of resveratrol on the clinical icons related to the metabolic complications.

2 Materials and methods

2.1 Search strategy

A systematic search of the online databases Google Scholar, PubMed, Scopus, Evidence-based medicine/clinical trials, and Cochrane library since 2000 up to the end of November 2018 without any restrictions was conducted. The search terms (MESH or non-MESH) were included ("Resveratrol") and ("metabolic syndrome" or "metabolic parameters" or "body weight" or "waist circumference" or "cholesterol" or "triglyceride" or "systolic blood pressure" or "HDL" or "abdominal obesity"). All eligible studies were reviewed, and their bibliographies were checked for other relevant publications.

2.2 Data extraction

The selection of studies for this meta-analysis was limited to the randomized clinical trial articles with participants diagnosed by metabolic syndrome, those received resveratrol. Metabolic outcomes such as BW, WC, sbp, HDL, TGs, glucose and cholesterol levels were considered as criteria. Studies were excluded, if resveratrol was used in combination with other supplements.

2.3 Quality assessment

To assess the quality of the included studies, we used the risk of bias table according to Cochrane quality assessment tool for RCTs [27]. In this table, the bias of each study, in particular, the design-related bias was evaluated in seven criteria; random sequence generation, allocation concealment, blinding of participants and personnel (for human studies), blinding of outcome assessment (for human studies), incomplete outcome data, selective reporting and other probable sources of biases. The grade/level of the quality of each study was judged as low risk, high risk or unknown risk of bias. Out of 16 studies, only 2 studies had selective reporting bias and 2 studies showed attrition bias. In general, all studies were out of bias. The table was designed according to the Review Manager 5.3 (Fig. 1).

2.4 Statistical method

Studies were summarized based on several characteristics including the publication information, sample size, and the

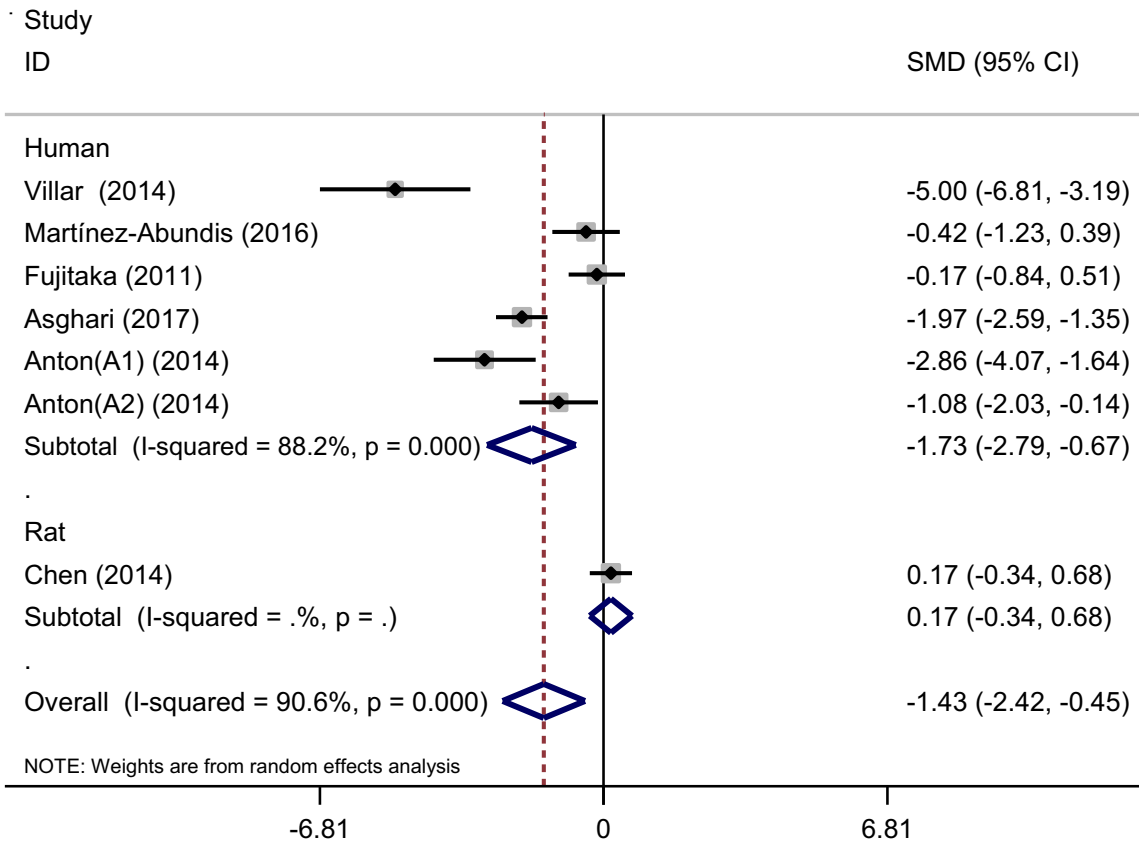

Fig. 4 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on waist circumference. (A1: 300 mg, A2:1000 mg)

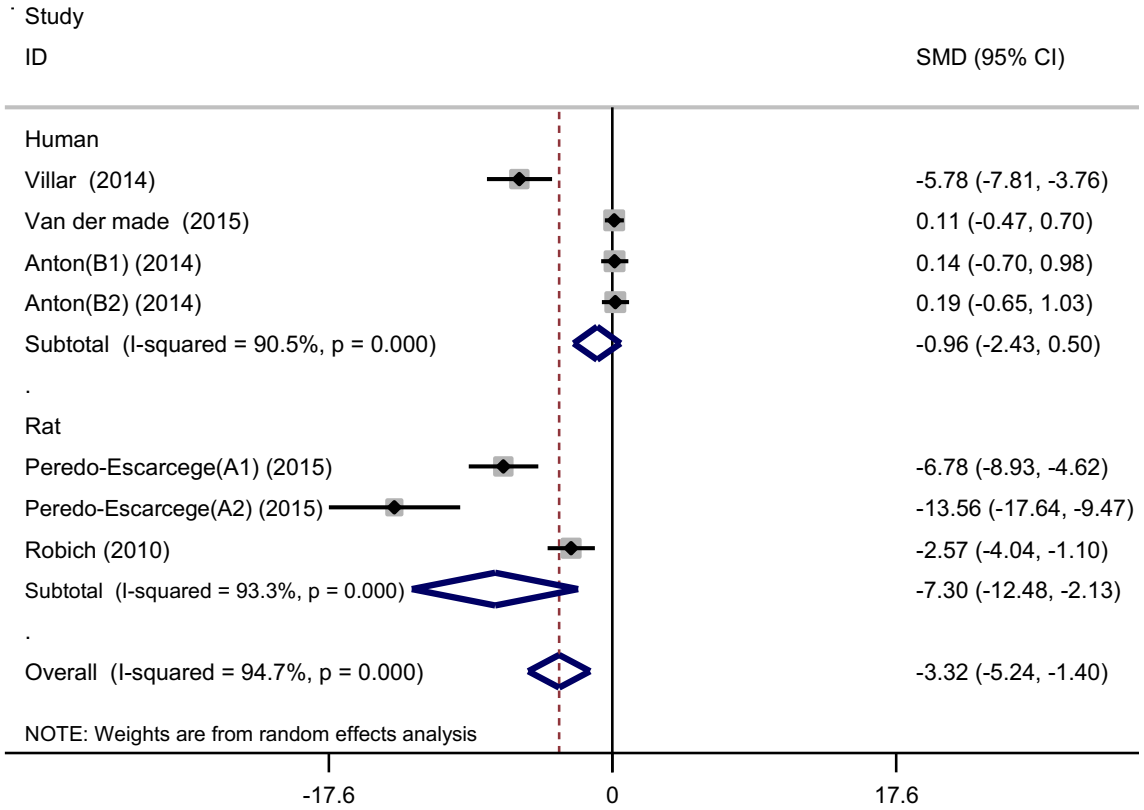

Fig. 5 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on systolic blood pressure. (A1: 19 mg; A2: 95 mg, B1: 300 mg, B2:1000 mg)

outcome measurements in each group (resveratrol and placebo). In each study, the mean of metabolic syndrome-related items was reported prior and after the intervention, thus, the mean difference was calculated for each outcome in both groups (resveratrol and placebo). Finally, the SMD and 95% CI were reported to show the difference in mean of the intervention and the placebo groups. The Z-test was used to check the significance of SMD. *P*-values less than 0.05 were statistically considered significant.

I^2statistic and Chi-square test were used to assess the heterogeneity between randomized controlled trials (RCTs). For I^2 statistic, values above 50%, and for the chi-square test, P-values <0.05 indicated the high degree of heterogeneity [28]. The heterogeneity calculated using the random-effect models of Der Simonian and Laird. Otherwise, we used the fixed-effect model using the method of inverse variance. To investigate the source of heterogeneity, the subgroup analysis was considered separately in each subgroup and performed according to the dosage, duration of the treatment and the mean age. Once the results differed between the subgroups, the variable was known as the root of heterogeneity among studies [29]. Sensitivity was measured to assess the stability of the results, to see whether the low-quality RCTs would influence the overall efficacy of resveratrol to reduce the disease. The publication bias was investigated by both graphical (funnel plots) and tests methods (Egger's regression test and the Begg) [30]. To confirm the publication bias, the trim and fill methods were used to modify the outcomes [31].

3 Results

3.1 Search result

First, two reviewers independently searched databases Google Scholar, PubMed, Scopus, Evidence-based medicine/clinical trials, and Cochrane library for relevant English papers since 2000 up to the end of November 2018; thus 876 articles were extracted. Excluding duplicates, undesired titles and abstracts; only 16 articles were selected for meta-analysis. At the end, a third researcher approved the selection to ensure the accuracy of the data (Fig. 2).

3.2 Study characteristics

The basic characteristics of all included studies summarized in Table 1. We included 10 randomized double-blind, placebo-controlled clinical trials in human and 6 controlled preclinical studies in rat which were published between years 2008 and 2017. Participants were aged between 20 to 75 years old (mean

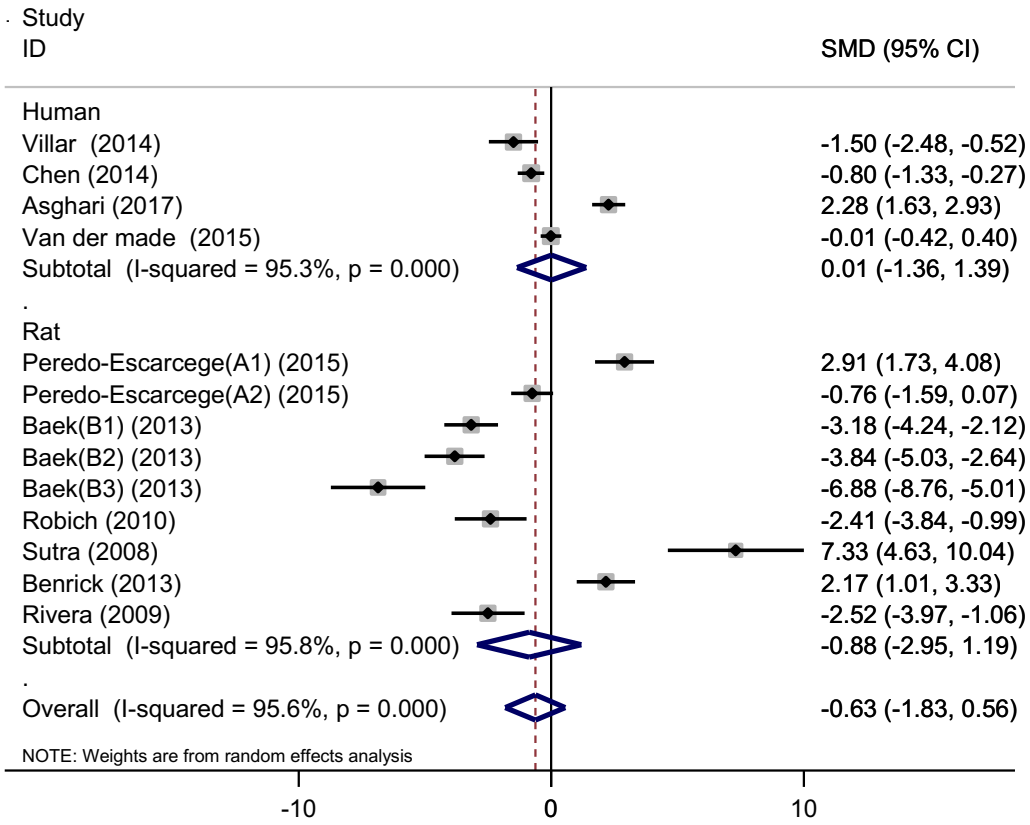

Fig. 6 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on total cholesterol. (A1: 19 mg; A2: 95 mg; B1: 4weak; B2: 8weak; B3: 12weak)

age = 50.27), and the dosage of resveratrol ranged from 100 to 3000 mg/day for human and 10 to 400 mg/day for animal samples. In human studies sample size in the resveratrol group was 197 cases and in the placebo group 199 patients. In rat studies for resveratrol group there were 61 cases, and 60 in the control group. The duration of studies varied from 4 weeks to 12 weeks. Out of 16 extracted studies, 10 examined the effect of resveratrol on the body weight, 6 reported data for the WC, 5 provided data on sbp, 10 studied were conducted on cholesterol changes, 9 studies reported data for TGs, 8 investigated the effect of resveratrol on glucose level, and 9 on HDL level.

3.3 Effect of resveratrol on metabolic components

Human studies: The pooled mean difference of 10 clinical trials conducted on human samples, showed that the administration of resveratrol significantly decreased glucose level [−1.73 (−2.99, −0.47); $p = 0.007$)] compared with the control group, and there were significant differences (between resveratrol and placebo groups) on WC [−1.73 (−2.79, −0.67); $p = 0.001$]. Versus Meta-analyzes on other components indicated that resveratrol consumption can reduce them in patients with metabolic syndrome, but these reductions were not statistically significant. Weight [−0.56 (−1.73, 0.61); $p = 0.347$], TGs [−1 (−2.04, 0.03); $p = 0.06$], sbp [−0.97 (−2.43, 0.50); $p = 0.196$], total cholesterol [0.01 (−1.36, 1.39); $p = 0.986$], and we did not have significant increase on HDL [0.69 (−0.46, 1.84); $p = 0.238$]. In all of these analyzes there was a significant heterogeneity between human studies ($I^2 > 80\%$). As a result, a random effect model was used to fit the models. Figures (3, 4, 5, 6, 7, 8 and 9).

Animal studies: Combining the results of studies on rat samples (n=6), (all randomized and have a control group) indicated that resveratrol can reduce significantly some components of metabolic syndrome such as weight [−22.95 (−44.74, −1.17); $p = 0.04$], TGs [−6.76 (−11.10, −2.42); $p = 0.001$], sbp [−7.30 (−12.48, −2.13); $p = 0.006$] in resveratrol sample compared with the control. And it can influence significantly on increasing HDL level (4.75 (1.87, 7.63); $p = 0.001$). However, no significant effect was observed on the reduction of glucose (Unlike human studies), ($p = 0.06$), total cholesterol (Like human studies), ($p = 0.405$), and WC ($n = 1$) [−0.17 (−0.34, 0.68); $p = 0.510$]. As a result of heterogeneity between result of studies ($I^2 > 80\%$), a random effect model was used to fit the models. Figures (3, 4, 5, 6, 7, 8 and 9).

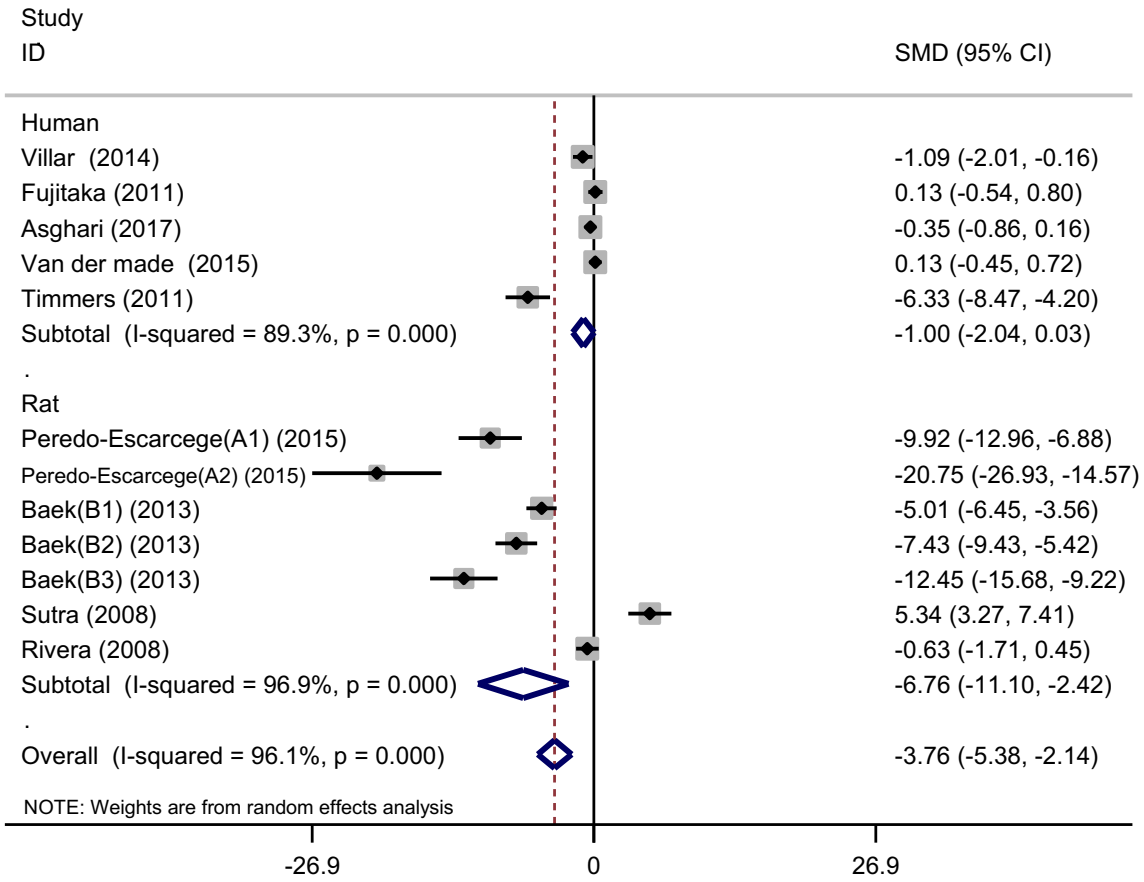

Fig. 7 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on triglyceride level. (A1: 19 mg; A2: 95 mg; B1: 4weak; B2: 8weak; B3: 12weak)

3.4 Publication Bias

The Begg and Egger's tests along with the Funnel plot model were used to assess the publication bias. Results for glucose, total cholesterol and WC did not confirm the publication bias, while the outcomes of these tests were significant for the BW, sbp, TGs level and HDL (*P*-values = 0.015, 0.000, 0.006, 0.04). Therefore, the Trim and Fill methods were used to modify the results, although the results did not change.

3.5 Subgroup analysis

To evaluate the results based on some effective variables such as resveratrol dosage and duration of the treatment (in human studies), and the study population (human or rat population), subgroup analysis was performed. According to the results (Table 2), using resveratrol at dosage of ≥ 500 mg and the period of time more than 10 weeks can significantly reduce WC. Also, resveratrol can decrease significantly glucose level in duration of > 10 weeks. While for other components the duration of resveratrol administration and dosage were not significantly effective. Regarding study population, resveratrol significantly reduced glucose level in human trials. Moreover, the intervention of resveratrol caused a significant reduction in TGs, HDL, sbp, weight and WC in animal studies.

4 Discussion

Current meta-analysis inclined to assess whether resveratrol is able to implement positive impacts on subjects diagnosed with metabolic syndrome, prior and after the treatment. This study evidently clarifies the effectiveness of resveratrol on the management of metabolic syndrome. Regarding the symptoms of metabolic syndromes, resveratrol elevated HDL cholesterol, while alleviated the amounts of the BW, WC, sbs, cholesterol, TGs and glucose; of note, only the outcome of cholesterol evaluation was not statistically significant.

The findings of other interventions are also in agreement with the outcomes of this study [33, 41]. In a recent randomized, placebo-controlled clinical trial, it was elucidated that resveratrol at concentration of 150 mg, did not improve the inflammatory status, glucose homeostasis, bp, or hepatic lipid content in middle-aged men with metabolic syndrome, whereas, at dose of 1000 mg, the polyphenol significantly increased total cholesterol, LDL

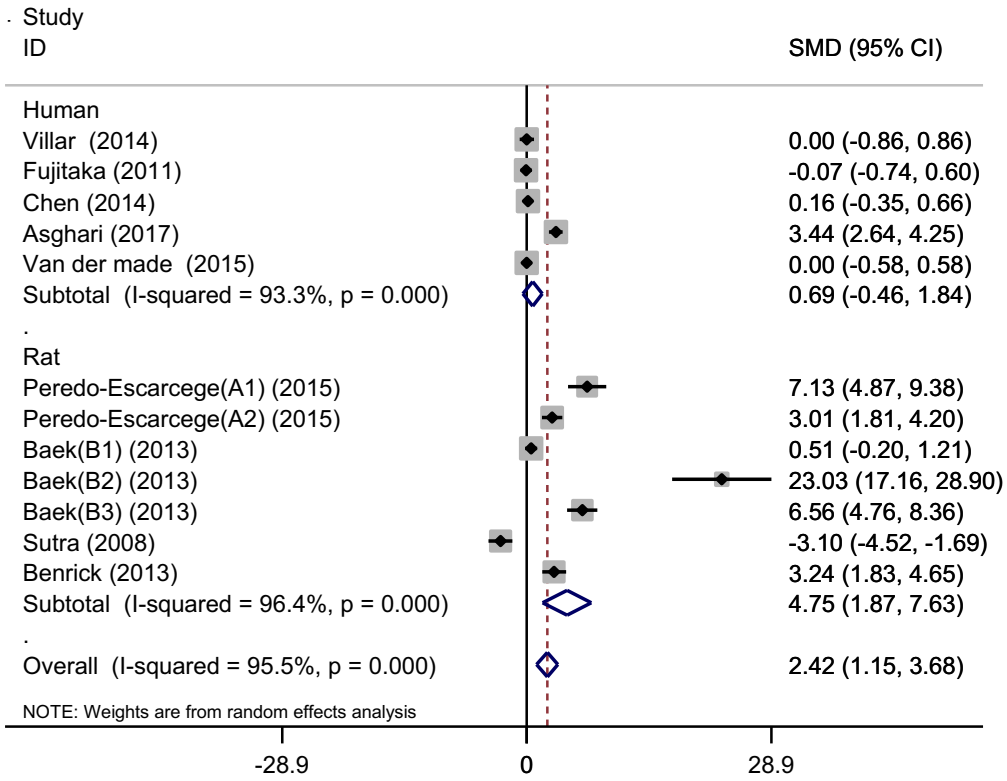

Fig. 8 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on HDL. (A1: 19 mg; A2: 95 mg, B1: 4 weak; B2: 8 weak; B3: 12weak)

cholesterol, and fructosamine levels compared with the placebo. Besides, resveratrol treatment could not effect on the inflammatory gene expression of adipose and muscle tissues (i.e. *SIRT-1*, *NRF1*, *TFAM*) in striated muscle [39]. Interventional randomized controlled trial on 60 patients with non-alcoholic fatty liver disease exposed to resveratrol for 3 months (150 mg resveratrol, twice daily), showed a significant decline in insulin resistance, glucose and lipid metabolism and reduced the levels of inflammation-related cytokines such as TNF-α, cytokeratin 18, and the fibroblast growth factor 21 [37]. In accordance with our data, in 12 patients diagnosed with metabolic syndrome, the administration of resveratrol caused significant differences in BW, body mass index (BMI), fat mass, WC, the area under the curve of insulin, and insulinogenic index [33]. Resveratrol supplementation (30 days, 150 mg/day) to 11 healthy obese men significantly reduced adipocyte size and enhanced adipogenesis, mainly through suppressing Wnt and Notch signaling pathways that are implicated to adipogenesis of preadipocytes and/or multipotent precursor cells [48]. In another double-blind, randomized crossover comparison, administration of resveratrol (30, 90 and 270 mg) at weekly intervals to 19 overweight/obese patients (men and women) with untreated borderline hypertension, improved flow-mediated dilatation of the brachial artery in a dose-related manner [49]. Data from a meta-analysis study indicated that resveratrol significantly decreased the sbp level at doses ≥ 150 mg/day, while it is not beneficial on diastolic blood pressure level [50]. In case of diabetes, a meta-analysis revealed that resveratrol consumption remarkably attenuated fasting glucose, insulin, glycated hemoglobin, and insulin resistance levels in diabetic participants, however, did not affect glycemic measures in non-diabetic persons. Subgroup and sensitivity analyses specified that BMI, study design, resveratrol dosage and the study duration are not effective on fasting blood glucose and insulin concentrations in nondiabetic participants [51].

In contrast to our report, several studies have shown that this compound has no positive effect on the metabolic syndrome or the related symptoms or complications. For instance, in a randomized, placebo-controlled crossover study conducted in 45 overweight and slightly obese men and women receiving resveratrol (150 mg per day) or placebo for 4 weeks, resveratrol could not change metabolic risk factors associated with cardiovascular health including apolipoprotein A-I, apolipoprotein B100, HDL cholesterol, LDL cholesterol, triacylglycerol, glucose, insulin, plasma markers of inflammation and endothelial function (i.e. interlukine-6, TNF-α, E-selectin, thrombomodulin, P-selectin, intercellular Adhesion Molecule 1, sICAM-1, and soluble vascular cell adhesion molecule-1 [32]. A meta-analysis of 7 randomized controlled trials demonstrated that resveratrol supplementation had no

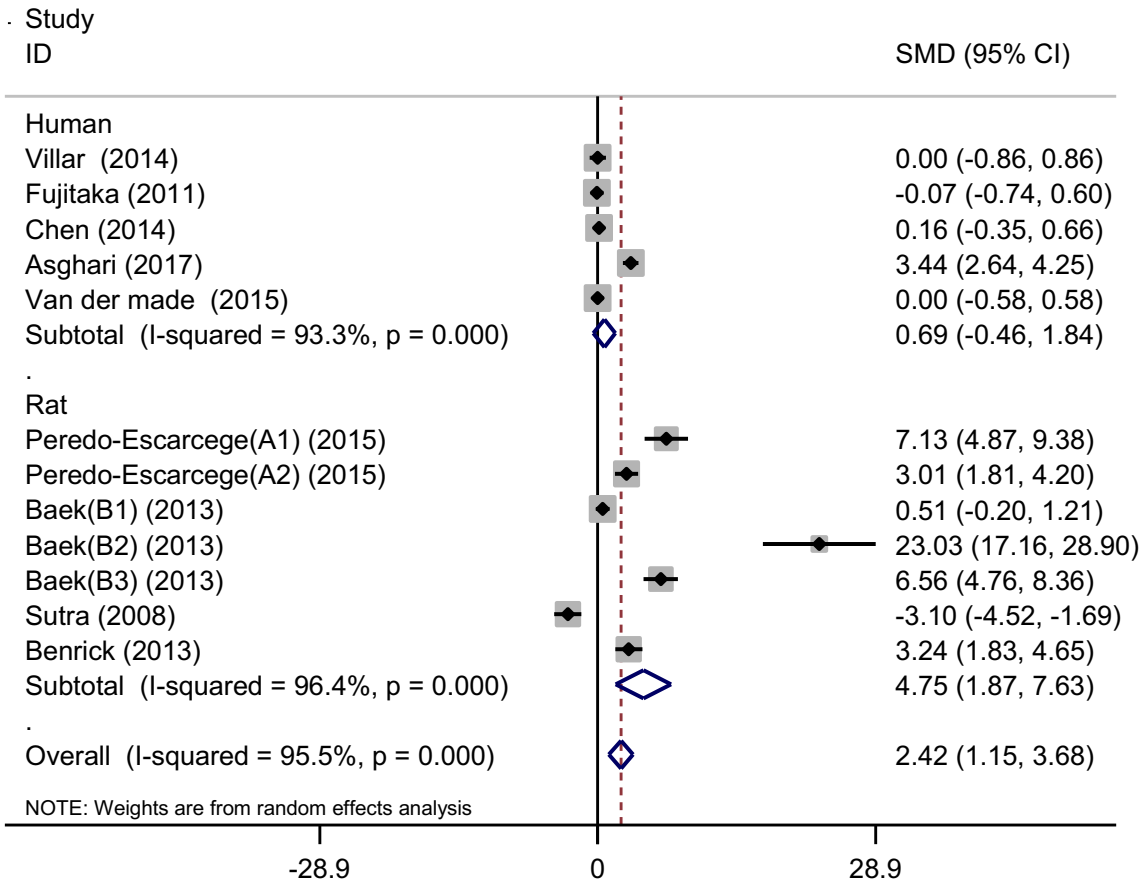

Fig. 9 Forest plot of Standardized mean difference between Resveratrol and placebo groups for the effect of resveratrol supplementation on glucose. (A1: 19 mg; A2: 95 mg, B1: 4 weak; B2: 8 weak; B3: 12weak; C1:300 mg, C2:1000 mg)

significant effect on the lipid parameters; total cholesterol, LDL, HDL, and TGs [52]. This should be noted that in metabolic syndrome subjects, cross-over and randomized controlled trials with single phenolic compound do not provide reliable data regarding the protective effects of polyphenols on cardiovascular diseases as reported *in vitro* studies.

Altogether, resveratrol influences on multiple aspects of metabolic syndrome through its regulatory action on SIRT1 [22] and glucose metabolism [53], modification of insulin secretion and resistance [33], modulation of the adipogenesis regulator genes (i.e. C/EBPα and PPARγ) [21], up-regulation of mitochondrial energy sensing network (i.e. adenosine monophosphate (AMP)-activated protein kinase (AMPK) and PPARγ coactivator 1a (PGC-1α)) [54], decline in lipogenesis [14], and stimulation of lipolysis [55]. A comprehensive review reported that resveratrol is well tolerated for neurological disorders, cardiovascular diseases, diabetes, and obesity, however, poor bioavailability of resveratrol was introduced as the main drawback [56]. Pharmacokinetic investigations revealed that resveratrol's inadequate bioavailability is ascribed to its extensive metabolism along the gastrointestinal tract, poor aqueous solubility and low chemical stability [57]. To overcome such defects, as we explained extensively in our previous publication [58], a number of strategies might be helpful. For example, combination of resveratrol with elements able to suppress its metabolism (i.e. glucuronidation inhibitors, intestinal ABC transporters inhibitors) [59, 60], or co-administration of resveratrol with other natural compounds (i.e. phenolic compounds) may improve its bio-efficacy/availability [61, 62]. Thereby, resveratrol alone or in combination with other phytochemicals and/or the available anti-obesity and anti-diabetic therapies could target multiple molecules or molecular pathways in the adipogenesis system [63]. Orlistat and sibutramine are the most prescribed obesity treatment medications with known reverse effects such as elevated blood pressure, dry mouth, constipation, and insomnia, of which, orlistat weakens the intestinal fat absorption by inhibiting pancreatic lipase, and sibutramine is an anorectic or appetite suppressant [64]. In a clinical trial on 48 obese objects, a considerable weight loss of about 2 times was observed in orlistat-resveratrol group compared with the placebo group, none of these agents monotherapy caused a significant difference from the placebo. Other parameters including BMI, WC, fat mass, TGs, leptin, and leptin/adiponectin ratio were also reduced following orlistat-resveratrol administration [63]. Likewise, the synergistic effects of metformin, resveratrol and

Table 2 Subgroup analysis

Subgroup	No. of studies	Test of relationship		Test of heterogeneity	
		SMD (95%CI)	P- value	I^2	P- value
Glucose					
Study population					
Rat	8	-0.96 (-1.95, 0.031)	0.06	89.2%	< 0.001
Human	4	-1.73 (-2.93 , -0.76)	0.007	91.5%	< 0.001
Duration*					
> 10 week	3	-2.42 (-4.31 , -0.53)	0.01	89.5%	< 0.001
<10 week	1	-0.16 (-0.57 , 0.26)	0.462	0%	-
Mean dose*					
< 500 mg	3	-1.14 (-2.26 , -0.03)	0.04	89.4%	< 0.001
≥ 500 mg	1	-3.77 (-5.28 , -2.26)	< 0.001	0%	0.560
Sbp					
Study population					
Rat	3	-3.32 (-5.24 , -1.40)	0.006	90.5%	< 0.001
Human	4	-0.97 (-2.43 , 0.50)	0.196	93.3%	< 0.001
Duration*					
> 10 week	2	-2.75 (-8.55 , 3.05)	0.353	93.4%	< 0.001
< 10 week	2	0.14 (-0.34, 0.62)	0.574	96.3%	< 0.001
Mean dose*					
≥ 500 mg	2	-2.72 (-8.57 , 3.13)	0.361	96.5%	< 0.001
< 500 mg	2	0.12 (-0.36 , 0.60)	0.618	0%	0.964
HDL					
Study population					
Rat	7	4.75 (1.87 , 7.63)	0.001	93.3%	< 0.001
Human	5	0.69 (-0.46 , 1.84)	0.238	96.4%	< 0.001
Duration*					
> 10 week	3	1.19 (-0.88 , 3.26)	0.260	96.1%	< 0.001
< 10 week	2	-0.03 (-0.47 , 0.41)	0.895	0%	0.879
Mean dose*					
≥ 500 mg	2	1.72 (-1.65 , 5.10)	0.316	97%	< 0.001
< 500 mg	3	0.05 (-0.28 , 0.38)	0.768	0%	< 0.001
Weight					
Study population					
Rat	3	-1.85 (-3.18 , -0.52)	0.039	96.8%	< 0.001
Human	10	-0.56 (-1.73 , 0.61)	0.347	95.2%	< 0.001
Duration*					
> 10 week	7	-0.51 (-2.35 , 1.32)	0.583	96.6%	< 0.001
<10 week	3	-0.62 (-1.46 , 0.21)	0.144	95.2%	< 0.001
Mean dose*					
< 500 mg	7	-0.83 (-2.39 , 0.73)	0.299	95.8%	< 0.001
≥ 500 mg	3	0.03 (-1.73 , 1.79)	0.973	93.7%	< 0.001
TGs					
Study population					
Rat	7	-3.76 (-5.38 , -2.14)	0.002	89.3%	< 0.001
Human	5	-1 (-2.04 , 0.03)	0.06	96.9%	< 0.001
Duration*					
> 10 week	2	-0.62 (-1.30 , -0.07)	0.08	46.2%	0.173
< 10 week	3	-1.61 (-3.67, 0.45)	0.162	94.1%	< 0.001

Table 2 (continued)

Subgroup	No. of studies	Test of relationship		Test of heterogeneity	
		SMD (95%CI)	P- value	I^2	P- value
Mean dose*					
< 500 mg	2	-0.62 (-1.30 , -0.07)	0.08	46.2%	0.173
≥ 500 mg	3	-1.61 (-3.67, 0.45)	0.162	94.1%	< 0.001
WC					
Study population					
Rat	1	-1.73 (-2.79 , -0.67)	0.001	88.2%	< 0.001
Human	6	0.17 (-0.34 , 0.68)	0.510	0%	-
Mean dose*					
< 500 mg	4	-1.46 (-4.09 , 1.17)	0.277	87.6%	< 0.001
≥ 500 mg	2	-1.90 (-3.12 , -0.59)	0.005	93%	< 0.001
Duration*					
> 10 week	5	-2.08(-3.23 , -0.93)	< 0.001	85.8%	< 0.001
< 10 week	1	-0.17 (-0.84 , 0.51)	0.628	0%	-

*Subgroup on human studies

hydroxymethylbutyrate led to increased insulin sensitivity mediated by AMPK, favorable to reduce the therapeutic doses of metformin necessary to treat diabetes [65].

5 Conclusion

Herein, we can propose that dietary supplementation with resveratrol might be an adjunct to manage metabolic syndrome and its associated complications through several important dimensions, worth mentioning, the participant's sex and age, the resveratrol dosage, and the intervention duration are critical factors that have to be deliberated. However, the small sample size and the shortage of the studies duration are supposed to be the crucial limitations of this meta-analysis, yet this report offers new information in terms of the participant's age, the resveratrol dosage, and the intervention duration for future studies. Resveratrol molecule could be the scaffold structure to design synthetic derivatives with improved bioavailability; also, more studies should be conducted on males and female objects separately. Prolonged clinical trials with greater sample size will also qualify the outcomes of the related investigations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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