Resveratrol Effects on Metabolic Syndrome Features: A Systematic Review and Meta-Analysis

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Abstract: Resveratrol is a natural polyphenol with important anti-inflammatory and antioxidant properties for treating cardiometabolic disorders. Therefore, the present meta-analysis aimed to review and investigate the oral resveratrol supplementation effects on metabolic syndrome (MetS) components. The bibliographic search was carried out in 2023 in the following databases: PubMed, Web of Science, and Scopus. Studies that investigated the oral resveratrol effects on the MetS parameters were included. Statistical analyses were performed using RevMan Software V.5.3. The main findings showed that resveratrol significantly decreased systolic and diastolic blood pressure while having no significant effects on waist circumference and high-density lipoprotein levels. In addition, glucose level was significantly decreased in the subgroup of studies reporting change from baseline means, although the overall effect was not statistically significant (p = 0.81), while triglyceride levels were increased after the treatment period. In conclusion, the present meta-analysis evidenced the potential therapeutic effect of resveratrol on improving some MetS features, especially regarding systolic blood pressure, diastolic blood pressure, and glucose reduction; however, the results are still borderline and sometimes controversial, which might be justified by the methodological and statistical heterogeneity of the studies, with the latter varying from 17 to 57%.

Keywords: obesity; metabolic syndrome; resveratrol; polyphenols; glucose; meta-analysis

1. Introduction

Metabolic syndrome (MetS) is highly prevalent and considered a serious global health problem [1]. It comprises endocrine disturbances such as obesity, altered fasting glucose levels, dyslipidemia, and hypertension [2–4]. MetS is associated with an increased risk for atherosclerosis, cardiovascular diseases, and type 2 diabetes mellitus (T2D) [5]. All these disturbances have serious impacts on individuals’ quality of life.

The literature has established different MetS diagnostic criteria and treatment strategies [3,6]. According to the International Diabetes Federation (IDF), the first line of treatment for metabolic syndrome involves lifestyle changes such as weight loss, a healthy diet, and physical activity [3,7,8]. In some cases, a pharmacological intervention is indicated [9]; however, until now, there is no exclusive treatment for this syndrome. Novel treatments are under investigation, considering that preventive measures commonly fail and that current therapeutic options are insufficient [9].
Resveratrol (3,5,4-trihydroxystilbene) is a phytoalexin that is considered a natural polyphenol with antioxidant and anti-inflammatory effects. This compound is found in different amounts in more than seventy plant species, as well as in beverages and foods—such as blackberries, peanuts, and grapes (and their derivatives, e.g., red wine) [10,11]. It is present in the isomers cis and trans, with the latter being the most studied and filled with pharmacological properties [11], displaying several beneficial effects (Figure 1).

![Resveratrol benefits](image)

**Figure 1.** Resveratrol beneficial effects.

In animal models, resveratrol has been documented to exert favorable weight-reducing effects [12–14], such as total body fat and white adipose tissue reduction [12], in addition to regulating other signaling pathways [15]. Studies have proved that resveratrol’s anti-obesogenic properties are based on different mechanisms, including the inhibition of pre-adipocyte differentiation, adipocyte proliferation, lipogenesis, induction of adipocyte apoptosis, lipolysis, and fatty acid beta-oxidation (which leads to a decrease in the obesity-inflammatory profile), causing a decrease in the serum lipid levels and improvements in glucose homeostasis [13].

Furthermore, resveratrol can mimic calorie restriction effects [16]. Resveratrol supplementation effects on weight loss have been investigated in human studies, although the current results are still controversial. A study conducted by Faghizadeh et al., where 500 mg of resveratrol was administered daily for 12 weeks in individuals with non-alcoholic fatty liver disease (NAFLD) and overweight, reported improvements in body weight, body mass index (BMI), waist circumference (WC), and hepatic steatosis. Therefore, for the treatment of NAFLD, the results showed that 12 weeks of resveratrol supplementation, along with lifestyle changes, is superior to isolated lifestyle changes [17,18]. In contrast, high doses of resveratrol supplementation administered in men with obesity for 4 weeks did not affect resting energy expenditure, lipid oxidation rates, and visceral or ectopic lipid content [9,19,20].

It is well known that the abdominal circumference measurement is the main anthropometrical method that indirectly indicates visceral fat content. It is also known that central or abdominal obesity is the best predictor of adverse health effects compared to general obesity [21,22]. A randomized double-blind placebo-controlled clinical trial comprising 24 patients with MetS showed that resveratrol was capable of decreasing body weight, BMI, fat mass, waist circumference, the area under the curve of insulin, and total insulin secretion [23,24]. Batista-Jorge et al. also observed a significant decrease in visceral fat, which was assessed via WC and BMI in a similar study [25]. Experimental evidence has shown that resveratrol presents beneficial effects on cardiovascular diseases, including myocardial infarction, hypertensive cardiomyopathy, thrombosis, cardiac fibrosis, and atherosclerosis [15].
Resveratrol is metabolized by the intestinal microbiota modulating its composition. This polyphenol interaction with the host microbiome may strongly influence MetS treatment’s efficiency, increasing this compound’s availability, inducing the production of important metabolites, or even promoting the growth of beneficial bacteria [26–29]. Therefore, the resveratrol/microbiota interaction might be a key element in MetS treatment.

The scientific literature, however, presents conflicting evidence regarding the effects of oral resveratrol, which may be associated with the differences observed in this study’s design, population, resveratrol dosage, and intervention period. To the best of our knowledge, this is the first systematic review and meta-analysis aiming to summarize the available evidence from clinical studies of resveratrol’s effects on the following MetS parameters in different population profiles: waist circumference, blood pressure, glucose fasting levels, triglycerides, and high-density lipoprotein.

2. Materials and Methods

2.1. Study Design

The present systematic review and meta-analysis was conducted and reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [30]. The protocol for this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, number CRD42022327486).

2.2. Eligibility Criteria

The inclusion criteria were as follows: this study was a clinical study performed with humans in diverse methodological designs, which was placebo-controlled, and that reported the mean and standard deviation or standard error of mean for the variables studied (waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP, respectively), glucose, triglycerides (TGs), and high-density lipoprotein (HDL)) at baseline, at the end of intervention, and/or as a change from baseline. Studies in languages other than English and without full-text access were excluded. The PICOS strategy was used to improve this study’s selection, as follows: P—population: adults, I—intervention: resveratrol, C—comparison: placebo, O—outcome: metabolic syndrome parameters, S—study design: RCTs with diverse methodological designs.

2.3. Search Strategy

A systematic search for studies that examined oral resveratrol’s effects on metabolic syndrome parameters most commonly considered for diagnosis (waist circumference, systolic blood pressure, diastolic blood pressure, glucose, triglycerides, and high-density lipoprotein) in the definitions of MetS by the World Health Organization, European Group for Study of Insulin Resistance, National Cholesterol Education Program—Adult Treatment Panel III, International Diabetes Federation, and American Association of Clinical Endocrinologists, as summarized by Grundy et al. [6], was performed on November 2021. The databases used for the papers retrieval were PubMed, Scopus, and Web of Science. The search was performed by using the following MeSH and text keywords: “Resveratrol” OR “Resveratrols” AND “waist-circumference” OR “waist circumferences” OR “WC” OR “triglyceride” OR “triaclyglycerols” OR “TG” OR “High-density lipoprotein” OR “high-density lipoproteins” OR “HDL” OR “glucose” OR “blood pressure” OR “systolic blood pressure” OR “diastolic blood pressure” OR “SBP” OR “DBP”. The search for studies reporting resveratrol’s effects on individual metabolic parameters most commonly included in the metabolic syndrome definition in different populations was performed due to the scarcity of studies that investigated oral resveratrol’s effects on individuals diagnosed with this syndrome. The full search strategy is available in the Supplementary Materials. The first search was performed in 2019, followed by updates in 2021 and 2023, where limits of the publication year of studies were applied (only publications from 2019 to 2021 and from 2021 and 2023 were used, respectively).
2.4. Study Selection

Study selection was performed manually by two authors in two phases: (1) reading the title and abstract, and (2) reading the entire text. In the first phase, the studies were selected based on the identification of the MeSH terms used in the searches, and the presence of sufficient data in the title and abstract regarding the study population, intervention details, and outcome variables studied was scanned, with duplicates being excluded (by organizing the titles in alphabetic order). Then, the remaining studies were entirely read, with the details—including methodological design, population included, the mean (±SD or SEM), and the availability of results—being identified and extracted.

2.5. Data Extraction and Quality Assessment

The following information was retrieved from each selected study: paper title, name of first author, year of publication, sample size, population characteristics (participants’ nationality and underlying diseases), intervention dose, type and duration, the mean (SD or SEM) for WC, TG, HDL, glucose, and blood pressure levels. This information was gathered on a Microsoft® Office Excel sheet and summarized in tables. The variables were reported in the following metric units (WC: cm, TG: mg/dL, HDL: mg/dL, glucose: mg/dL, and blood pressure: mmHg). To convert cholesterol, triglycerides, and glucose from mmol/L into mg/dL, the data were multiplied by 38.67, 88.57, or 18.0, respectively. The data were plotted as mean ± standard deviation, and, when necessary, the following formula was applied to convert the standard error of the mean into standard deviation: SD = SEM × sqrt(n), where n is the number of subjects.

The included studies’ quality of evidence was assessed following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for systematic reviews. The studies were classified by their quality of evidence: very low (the true effect is likely to be substantially different from the estimate of the effect), low (the true effect may be substantially different from the estimate of the effect), moderate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), and high (the true effect lies close to that of the estimate of the effect). The following criteria were evaluated for all studies included: study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.6. Publication Bias Assessment

A visual inspection of funnel plots was performed to detect publication bias according to the studies’ asymmetry.

2.7. Statistical Analysis

All statistical analyses were performed using Review Manager software version 5.4.1 (Cochrane Collaboration, Oxford, UK). A heterogeneity test (Higgins I2) was performed to assess inconsistencies among studies. The random effect model was applied when the heterogeneity was above 50%, and the fixed effect model was applied otherwise. The statistical test applied was the mean difference for all variables. The studies’ weights were evaluated according to the inverse of the variance. Data are displayed as forest plots graphs for each of the metabolic syndrome variables analyzed as main outcomes (waist circumference, systolic blood pressure, diastolic blood pressure, glucose, triglycerides, and high-density lipoprotein). To construct the forest plots, studies reporting post-intervention or change from baseline means were separated into subgroups for analyses. The significance level was set at 5% (p < 0.05).

3. Results

3.1. Eligibility Criteria and Search Strategy

The bibliographic search in the chosen databases (PubMed, Web of Science, and Scopus) retrieved 8105 papers. In the next phase, 7494 were excluded after screening for titles and abstracts, 668 were excluded for duplicates. After this phase, 139 papers
remained, from which 9 papers could not be retrieved due to restricted access, 130 were fully read, and 93 were excluded for several reasons. In total, 37 papers were included in this systematic review and meta-analysis. Figure 2 details the study selection update flow diagram, according to the PRISMA template [31].

**3.2. Characteristics of the Selected Studies**

Table 1 depicts the main characteristics of the studies included, comprising 1649 participants included in the present systematic review and meta-analysis. Among them, the earliest study was published in 2012, and the latest was published in 2023. The sample size of the included studies was considerably heterogeneous, with the number of participants varying from 5 to 65 (per group—placebo/intervention). Furthermore, the studies were performed with several different populations—which presented comorbidities such as diabetes, hypertension, metabolic syndrome, overweight, obesity, schizophrenia, coronary heart disease, polycystic ovary syndrome, non-alcoholic fatty liver disease, and dyslipidemia—from different nationalities, including American countries (Brazil, The United States of America, and Mexico), European countries (Germany, Hungary, The Netherlands, Amsterdam, and Denmark), Asian (Iran and China), Singapore, and Australia.
Table 1. Characteristics of the studies included in the present systematic review and meta-analysis (n = 37).

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sample Size (Placebo/Intervention)</th>
<th>Population/Country</th>
<th>Resveratrol (Daily Dosage)</th>
<th>Intervention Duration</th>
<th>Data Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Javid et al., 2016 [32]</td>
<td>22/21</td>
<td>Adult men and women with diabetes/Iran</td>
<td>480 mg</td>
<td>28 days</td>
<td>Glucose/TG</td>
</tr>
<tr>
<td>Movahed et al., 2013 [33]</td>
<td>31/33</td>
<td>Adult men and women with diabetes/Iran</td>
<td>1000 mg</td>
<td>45 days</td>
<td>Glucose/TGHDLP/SBP/DBP</td>
</tr>
<tr>
<td>Korsholm et al., 2017 [34]</td>
<td>24/21</td>
<td>Adult men with metabolic syndrome (MetS)/Denmark</td>
<td>1000 mg</td>
<td>120 days</td>
<td>SBP/DBP</td>
</tr>
<tr>
<td>Hoseini et al., 2019 [35]</td>
<td>28/28</td>
<td>Adults with type 2 diabetes mellitus and coronary heart disease/Iran</td>
<td>500 mg</td>
<td>28 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Marques et al., 2018 [36]</td>
<td>12/12</td>
<td>Adult men with hypertension/Brazil</td>
<td>300 mg</td>
<td>1 day</td>
<td>SBP/DBP</td>
</tr>
<tr>
<td>Banaszeewska et al., 2016 [37]</td>
<td>15/15</td>
<td>Women with polycystic ovary syndrome/United States</td>
<td>1500 mg</td>
<td>90 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Faghihzadeh et al., 2015 [19]</td>
<td>25/25</td>
<td>Adults with non-alcoholic fatty liver disease/Iran</td>
<td>500 mg</td>
<td>84 days</td>
<td>Glucose/TGHDLP/SBP/DBP</td>
</tr>
<tr>
<td>Faghihzadeh et al., 2014 [17]</td>
<td>25/25</td>
<td>Adults with non-alcoholic fatty liver disease/Iran</td>
<td>500 mg</td>
<td>84 days</td>
<td>WC</td>
</tr>
<tr>
<td>Batista-Jorge et al., 2020 [25]</td>
<td>9/13</td>
<td>Adults with obesity/Brazil</td>
<td>250 mg</td>
<td>90 days</td>
<td>WC/Glucose/TG/HDL</td>
</tr>
<tr>
<td>Goncalinho et al., 2021 [38]</td>
<td>24/24</td>
<td>Healthy men and women/Brazil</td>
<td>500 mg</td>
<td>30 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Khodabandehloo et al., 2018 [39]</td>
<td>20/25</td>
<td>Adults with diabetes/Iran</td>
<td>800 mg</td>
<td>56 days</td>
<td>Glucose/WC/TG/HDL/SBP/DBP</td>
</tr>
<tr>
<td>Zaw et al., 2020 [40]</td>
<td>65/59</td>
<td>Post-menopausal women in Australian/New Zealand</td>
<td>150 mg</td>
<td>360 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Andrade et al., 2019 [41]</td>
<td>10/10</td>
<td>Adults with obesity/Brazil</td>
<td>500 mg</td>
<td>56 days</td>
<td>Glucose/TG</td>
</tr>
<tr>
<td>Yoshino et al., 2012 [42]</td>
<td>14/15</td>
<td>Adult lean and overweight women/United States</td>
<td>75 mg</td>
<td>84 days</td>
<td>Glucose/TGHDLP/SBP/DBP</td>
</tr>
<tr>
<td>Magyar et al., 2012 [43]</td>
<td>20/20</td>
<td>Adults after myocardial infarction/Hungary</td>
<td>10 mg</td>
<td>90 days</td>
<td>TG/HDL</td>
</tr>
<tr>
<td>Zortea et al., 2016 [44]</td>
<td>9/10</td>
<td>Adults with schizophrenia/Brazil</td>
<td>200 mg</td>
<td>30 days</td>
<td>Glucose/WC/HDL</td>
</tr>
<tr>
<td>Goh et al., 2014 [45]</td>
<td>5/5</td>
<td>Adults with diabetes/Singapore</td>
<td>500 mg</td>
<td>84 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Kantartzis et al., 2018 [46]</td>
<td>52/53</td>
<td>Adults with overweight and insulin resistance/Germany</td>
<td>150 mg</td>
<td>84 days</td>
<td>Glucose/TGHDLP/SBP/DBP</td>
</tr>
<tr>
<td>Gliemann et al., 2013 [47]</td>
<td>13/14</td>
<td>Healthy older men/Denmark</td>
<td>250 mg</td>
<td>56 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Simental-Mendia et al., 2018 [48]</td>
<td>31/31</td>
<td>Adults with dyslipidemia/Mexico</td>
<td>100 mg</td>
<td>60 days</td>
<td>Glucose/WC/TG/HDL/SBP/DBP</td>
</tr>
<tr>
<td>Ligt et al., 2020 [49]</td>
<td>21/20</td>
<td>Overweight men and women/The Netherlands</td>
<td>150 mg</td>
<td>180 days</td>
<td>Glucose/TG/HDL</td>
</tr>
</tbody>
</table>
### Table 1. Cont.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sample Size (Placebo/Intervention)</th>
<th>Population/Country</th>
<th>Resveratrol (Daily Dosage)</th>
<th>Intervention Duration</th>
<th>Data Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villar et al., 2014 [23]</td>
<td>10/11</td>
<td>Adults with metabolic syndrome/Mexico</td>
<td>1500 mg</td>
<td>90 days</td>
<td>WC/TG/HDL SBP/DBP</td>
</tr>
<tr>
<td>Poulsen et al., 2013 [9]</td>
<td>12/12</td>
<td>Adult obese men/Denmark</td>
<td>1500 mg</td>
<td>28 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Wong et al., 2013 [50]</td>
<td>15/13</td>
<td>Healthy obese adults/Australia</td>
<td>75 mg</td>
<td>42 days</td>
<td>SBP/DBP</td>
</tr>
<tr>
<td>Heeboll et al., 2016 [51]</td>
<td>13/13</td>
<td>Patients with non-alcoholic fatty liver disease/Denmark</td>
<td>1500 mg</td>
<td>42 days</td>
<td>Glucose/SBP/DBP</td>
</tr>
<tr>
<td>Huhn et al., 2018 [52]</td>
<td>26/27</td>
<td>Older adults/Amsterdam</td>
<td>200 mg</td>
<td>182 days</td>
<td>Glucose/SBP/DBP</td>
</tr>
<tr>
<td>Seyyedebrahimi et al., 2018 [53]</td>
<td>23/23</td>
<td>Adults with diabetes/Iran</td>
<td>800 mg</td>
<td>60 days</td>
<td>Glucose WC/TG/HDL/SBP/DBP</td>
</tr>
<tr>
<td>Chen et al., 2015 [54]</td>
<td>30/30</td>
<td>Adults with non-alcoholic fatty liver disease/China</td>
<td>600 mg</td>
<td>90 days</td>
<td>Glucose WC/TG/HDL/SBP/DBP</td>
</tr>
<tr>
<td>Abdollahi et al., 2019 [55]</td>
<td>35/36</td>
<td>Patients with type 2 diabetes/Iran</td>
<td>1000 mg</td>
<td>56 days</td>
<td>Glucose WC/TG/HDL</td>
</tr>
<tr>
<td>Timmers et al., 2016 [56]</td>
<td>17/17</td>
<td>Adults with diabetes/Netherlands</td>
<td>150 mg</td>
<td>30 days</td>
<td>Glucose TG/HDL/SBP/DBP</td>
</tr>
<tr>
<td>Asghari et al., 2018 [57]</td>
<td>30/30</td>
<td>Adults with non-alcoholic fatty liver disease/United States</td>
<td>600 mg</td>
<td>84 days</td>
<td>Glucose WC/TG/HDL</td>
</tr>
<tr>
<td>Thazhath et al., 2016 [58]</td>
<td>14/14</td>
<td>Adults with diabetes/Australia</td>
<td>1000 mg</td>
<td>35 days</td>
<td>Glucose</td>
</tr>
<tr>
<td>Anton et al., 2014 [59]</td>
<td>10/12</td>
<td>Healthy overweight older adults/United States</td>
<td>300 mg</td>
<td>90 days</td>
<td>Glucose WC/SBP/DBP</td>
</tr>
<tr>
<td>Kjær et al., 2017 [60]</td>
<td>24/20</td>
<td>Adults with metabolic syndrome/Denmark</td>
<td>150 mg</td>
<td>42 days</td>
<td>Glucose SBP/DBP</td>
</tr>
<tr>
<td>Chachay et al., 2014 [61]</td>
<td>10/10</td>
<td>Adults with non-alcoholic fatty liver disease/Denmark</td>
<td>3000 mg</td>
<td>56 days</td>
<td>Glucose SBP/DBP</td>
</tr>
<tr>
<td>Zhou et al., 2023 [62]</td>
<td>43/41</td>
<td>Adults with dyslipidemia</td>
<td>600 mg</td>
<td>56 days</td>
<td>Glucose/TG/HDL</td>
</tr>
<tr>
<td>Sariaslane et al., 2022 [63]</td>
<td>34/40</td>
<td>Patients with ischemic stroke</td>
<td>510 mg</td>
<td>30 days</td>
<td>SBP/DBP</td>
</tr>
</tbody>
</table>

Abbreviations: WC: waist circumference; TGs: triglycerides; SBP: systolic blood pressure; DBP: Diastolic blood pressure; HDL: high-density lipoprotein.

Regarding the oral resveratrol treatment characteristics of the studies included, resveratrol was applied in dosages ranging from 10 mg to 3000 mg/day, with 100 mg/day being the lowest effective dose of resveratrol capable of reducing at least one of the studied parameters when administered for 2 months. Another factor with great variability was the time of intervention, which varied from a single-dose treatment to 12 months of treatment. Most studies were conducted with adults, and one of the five metabolic syndrome variables was evaluated in each of the included studies. This study’s methodological heterogeneity, however, hindered the data analysis and the conclusions regarding resveratrol’s beneficial effects.
3.3. Quality of Evidence of the Included Studies

The quality of evidence of all included studies was evaluated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Most of the studies displayed very low to moderate quality of evidence, with only three studies being classified as high and one as very high quality (Table 2), which emphasizes the need in the literature for more high-quality studies that evaluate resveratrol’s effects on metabolic parameters. The main limitations that contributed to the poor quality of evidence found in the evaluated studies are the inclusion of small convenient samples composed of specific groups of participants (e.g., individuals with specific comorbidities, gender-specific samples), the concomitant use of other medications/interventions (e.g., balanced energy diets, physical activity programs, use of anti-hypertensive and hypoglycemic agents, etc.), and no specification of resveratrol purity.

Table 2. Summary of findings and quality of evidence assessment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>No Patients</th>
<th>Limitation</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMS-IE</td>
<td>Short term</td>
<td>363 [32,33,35,36,41,47,50,53,56,58,61]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>IMMS-IE</td>
<td>Short term</td>
<td>19 [44]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Very low</td>
</tr>
<tr>
<td>IMMS-IE</td>
<td>Long term</td>
<td>105 [34,54]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>IMMS-IE</td>
<td>Long term</td>
<td>506 [19,37,40,43,45,46,51,52,59]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>IMMS-IE</td>
<td>Long term</td>
<td>74 [60]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Short term</td>
<td>93 [38,39,63]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Short term</td>
<td>71 [48]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Very low</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Short term</td>
<td>24 [9]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Long term</td>
<td>25 [25]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Long term</td>
<td>114 [23,57]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Long term</td>
<td>45 [42]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Long term</td>
<td>50 [17]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Long term</td>
<td>71 [55,62]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>IMMS-DE</td>
<td>Long term</td>
<td>41 [49]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Abbreviations: Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Improvement in markers of metabolic syndrome—indirect evidence (IMMS-IE); improvement in markers of metabolic syndrome—direct evidence (IMMS-DE). The table shows short-term follow-up evaluations of 8 weeks or less and long-term follow-up evaluations longer than 8 weeks. Each line includes the studies that received the same quality of evidence classification, according to the GRADE categories.

3.4. Meta-Analysis

The effects of resveratrol on metabolic syndrome (waist circumference (WC), systolic blood pressure, diastolic blood pressure, glucose, TG, and HDL) were evaluated, and each parameter was individually analyzed in the present study. The pooled results showed that resveratrol had no significative effect on waist circumference (mean difference: $-0.43$; 95% confidence interval, $-1.51, 0.66$; $p = 0.44$; I²: 24%) (Figure 3) and that a significant decreased systolic blood pressure (mean difference: $-2.97$; 95% confidence interval, $-4.58, -1.36$; $p = 0.0003$; I²: 39%) (Figure 4) and diastolic blood pressure (mean difference: $-1.22$; 95% confidence interval, $-2.28, -0.16$; $p = 0.02$; I²: 43%) were observed (Figure 5). The overall effect of resveratrol on glucose levels was not statistically significant (mean difference: $-0.25$; 95% confidence interval, $-2.26, 1.77$; $p = 0.81$; I²: 57%); however, the analyses differed between subgroups (post-intervention mean subgroup: mean difference: $0.83$; 95% confidence interval, $-0.96, 2.62$; $p = 0.36$; I²: 45%); change from baseline subgroup: mean difference: $-9.47$; 95% confidence interval, $-13.53, -5.40$; $p < 0.00001$; I²: 0%) (Figure 6). Surprisingly, resveratrol was associated with increased triglyceride levels (mean difference: $8.81$; 95% confidence interval 1.98, 15.64; $p = 0.01$; I²: 29%), although the subgroup analyses were in disagreement (Figure 7). Finally, HDL levels seemed not to be affected by resveratrol (mean difference: $-0.51$; 95% confidence interval: $-1.64, 0.62$; $p = 0.37$; I²: 17%) (Figure 8).
Subgroup 1.1.1 summarizes the studies that provided post-intervention means [17,23,25,38,39,44,48,53,55,57]. Subgroup 1.1.2 summarizes the studies that provided a mean change from baseline [54,59].

Figure 3. Forest plot depicting resveratrol versus placebo effects on waist circumference. Subgroup 1.1.1 summarizes the studies that provided post-intervention means. Subgroup 1.1.2 summarizes the studies that provided a mean change from baseline.

Figure 4. Forest plot depicting resveratrol versus placebo effects on systolic blood pressure. Subgroup 1.2.1 summarizes the studies that provided post-intervention means [19,23,33,34,36,38,42,46,48,50–52,56,60,61,63]. Subgroup 1.2.2 summarizes the studies that provided a mean change from baseline [39,53,54,59].
Figure 4. Forest plot depicting resveratrol versus placebo effects on systolic blood pressure. Subgroup 1.2.1 summarizes the studies that provided post-intervention means. Subgroup 1.2.2 summarizes the studies that provided a mean change from baseline.

Figure 5. Forest plot depicting resveratrol versus placebo effects on diastolic blood pressure. Subgroup 1.3.1 summarizes the studies that provided post-intervention means [19,23,33,34,36,38,42,46,48,50–52,56,60,61,63]. Subgroup 1.3.2 summarizes the studies that provided a mean change from baseline [39,53,54,59].

Figure 6. Forest plot depicting resveratrol versus placebo effects on glucose levels. Subgroup 1.4.1 summarizes the studies that provided post-intervention means [9,19,25,32,33,35,37,38,40–42,44,46–49,51–53,55–58,60–62]. Subgroup 1.4.2 summarizes the studies that provided a mean change from baseline [39,45,54,59].
Figure 7. Forest plot depicting resveratrol versus placebo effects on triglycerides levels. Subgroup 1.5.1 summarizes the studies that provided post-intervention means [9, 19, 23, 25, 32, 33, 35, 37–43, 46–49, 52, 53, 55–57, 62]. Subgroup 1.5.2 summarizes the studies that provided a mean change from baseline [45, 54].

Figure 8. Forest plot depicting resveratrol versus placebo effects on high-density lipoprotein levels. Subgroup 1.6.1 summarizes the studies that provided post-intervention means [9, 19, 23, 25, 33, 35–37, 40, 42–44, 46–49, 53, 55–57, 62]. Subgroup 1.6.2 summarizes the studies that provided a mean change from baseline [45, 54].
3.5. Publication Bias Assessment

The assessment of publication bias was performed via the visual evaluation of the funnel plots generated in the meta-analysis. It was possible to observe a significant asymmetry for the studies included in all variables analyses (Supplementary Materials), indicating the potential influence of publication bias.

4. Discussion

The present systematic review and meta-analysis summarizes the evidence obtained from 37 scientific studies investigating the effects of resveratrol on MetS parameters (waist circumference, blood pressure, glucose, triglycerides, and high-density lipoprotein). The main findings showed that resveratrol supplementation significantly decreased systolic blood pressure and diastolic blood pressure. Moreover, resveratrol significantly decreased glucose levels from baseline. Finally, triglyceride levels seemed to be increased via resveratrol supplementation. The other studied parameters were not significantly changed.

The overall results of the present meta-analysis indicate that resveratrol supplementation may significantly decrease systolic blood pressure and diastolic blood pressure. By analyzing the studies included in the meta-analysis, it was possible to observe that resveratrol’s blood pressure-lowering effects were observed in studies mainly reporting dosages starting at 300 mg/day for at least 3 months and higher dosages (600–1000 mg/day) for 2 to 3 months. In contrast, dosages as low as 75 mg/day for 45 days or 3 months had no significant effects on systolic blood pressure and diastolic blood pressure. Sariaslani et al. carried out a double-blind clinical trial, which evaluated resveratrol’s effect following an acute ischemic stroke. The patients were randomly allocated to receive resveratrol (500 mg/day) for 30 consecutive days or a placebo, but no significant effects were observed on their results with regard to systolic or diastolic blood pressure [63].

Corroborating our findings, animal studies suggested that a higher resveratrol dosage may significantly reduce arterial pressure in different hypertension models [64]. Interestingly, Zivarpour P et al. [15] showed that low doses of resveratrol (20–25 mg/day) may reduce or regulate diastolic arterial pressure in patients with cardiovascular diseases. The administration of a minimum dosage of 10 mg/kg of resveratrol may be necessary for a significant reduction in arterial pressure in the majority of animal models. In contrast, other studies with dosages lower than 2.5 mg/kg reported no significant effects of resveratrol on this parameter [65,66].

It is possible to suggest a few effects and mechanisms by which resveratrol may act on blood pressure control. The scientific literature already showed that resveratrol has a calorie restriction-like effect on the metabolic profile, being beneficial regarding the blood pressure levels of individuals with obesity [67]. Animal studies establish that resveratrol may restore the mesenteric and cardiac eNOS activity and reduce thiobarbituric acid-reactive substance (TBARS) levels, which are oxidative species [68]; however, it may still modulate the production of ET-1, Ang II, and NO, preventing an increase in systolic blood pressure levels in nephrectomized rat models [69].

Regarding the evaluation of resveratrol on glucose levels, conflicting findings were observed. In the subgroup of studies that reported a change from baseline, resveratrol supplementation significantly decreased glucose levels. In the other group of studies (those reporting post-intervention means), no differences were found. One of the studies included, which was performed by Movahed et al., carried out testing on individuals with T2D, reporting that a dosage of 1000 mg/day of resveratrol supplementation for 45 days was capable of significantly reducing fasting glucose levels and systolic blood pressure [33]. In fact, in a meta-analysis performed by Gu et al., resveratrol reduced fasting glucose levels in individuals with T2D [70].

Interestingly, in the present study with six studied variables, glucose was reduced in a greater number of the reported researches, including Movahed et al.’s study with 1000 mg/day/45 days) \((p = 0.0001)\) [33]; Abdollahi et al.’s study with 1000 mg/day/8 weeks [55]; Anton et al.’s study with 300 mg/day and 1000 mg/day/3 months) \((p = 0.023 \text{ and } p = 0.008,\)
respectively) [59]; Khodabandehloo et al.’s study with 800 mg/day/2 months ($p = 0.048$) [39]; and Chen et al.’s study with 600 mg/day/3 months ($p = 0.001$) [54]. It is noteworthy that the lowest effective dose of resveratrol for glucose reduction was verified by Stephen D. Anton et al., with 300 mg/day for 3 months [59]. It is known that the reduction in blood glucose levels is important for diabetes treatment. Diabetes is one of the most important causes of cardiovascular diseases, mainly due its effect on cardiac remodeling that induces cardiac fibrosis, which is characterized by the accumulation of proteins in the extracellular matrix of the myocardium [15].

In this perspective, several studies, clinical and experimental, were performed to evaluate resveratrol’s effects in hyperglycemic conditions observed in patients with T2D. Evidence supports a consistent reduction in glucose following treatment with this compound [71]. Interestingly, a meta-analysis performed by Hausenblas et al. reported that supplementation with resveratrol significantly reduced the HbA1c values in individuals with T2D, but not in fasting glucose levels [72]. In contrast, Faghizadeh et al. reported that supplementation with 500 mg of resveratrol for 3 months had no beneficial effect on fasting glycemia and insulin resistance markers in individuals with NAFLD [19,73].

It is hypothesized, based on the inconsistent and controversial findings regarding resveratrol’s effects on glucose metabolism, that individuals without diabetes have normal basal levels of glucose and insulin, and that resveratrol consumption may not affect the physiological glucose and insulin regulation in these individuals. In individuals with diabetes, on the other hand, animal and human studies have evidenced that resveratrol is a potential agent in the reduction in glucose levels [74,75]. It is worth mentioning that although insulin resistance is considered a key aspect of MetS, its difficult assessment hinders its measurement in clinical and scientific settings. Thus, it not considered as a criterion for some definitions of this syndrome [6], nor is it included as an outcome in all studies performed in the metabolic field.

It is known that obesity is associated with several metabolic consequences that increase morbidity and mortality risks [76,77], especially abdominal obesity (android or central obesity), which is assessed by waist circumference and associated with increased cardiovascular disease and type 2 diabetes risks [78]. WC is recognized as a predictor of CVD risk as it reflects visceral adiposity deposition [79,80]. Increased food intake and decreased physical activity explain most of cases of obesity. Furthermore, other factors including genetics, medical conditions, sleep disturbances, and the use of a few medications may predispose individuals to weight gain [81,82]. Diet changes (low-calorie foods rich in fiber, such as fruits and vegetables) and physical activity (150 to 250 min of moderate to intense physical activity per week) represent the first step in obesity control and are good options to be included in a health-oriented routine [25].

However, obesity treatment and prevention are difficult tasks to achieve as preventive measures usually fail and therapeutic options are insufficient. Therefore, new treatment approaches are being investigated, raising the need for the study of nutraceutical therapeutic alternatives. In the present study, resveratrol supplementation did not decrease WC. However, several pre-clinical trials offer substantial evidence to support the concept that resveratrol may neutralize the negative effects of obesity [83], which was not corroborated by the clinical trials performed in the context of obesity and its inflammatory-associated state included in the present meta-analysis, reporting inconsistent results [17]. Mendez et al., in a study included in the present meta-analysis, months reported statistically significant reductions in WC when administering a resveratrol dose of 1500 mg/day for 3 ($p = 0.004$) [23].

The results found in the present meta-analysis are different from those reported by Sahebkar et al. [84] regarding resveratrol’s effects on lipid fractions. We showed that resveratrol did not affect the circulating levels of HDL-c, while TG seemed to have increased, although it was a small increase that might not have clinical importance. However, this finding is conflicting as in the one in the subgroup of studies reporting a change from baseline, in which no differences were found. TG may have increased in the former
subgroup because of the individuals’ life habits and not the use of resveratrol per se. It is known that the current therapeutic approaches to modify triglycerides are limited, making the management of lifestyle habits the most important principle adopted [85].

The study performed by Kjæ et al. (included in our analysis), which investigated resveratrol’s effects on all parameters of MetS in middle-aged men, reported no beneficial clinical effects, as determined by a series of defined outcomes. High doses of resveratrol (1000 mg/day) were associated with increased levels of fructosamine, total cholesterol, and LDL cholesterol [60]. However, the literature reports several studies performed in animals and humans signaling that the long-term oral use of resveratrol supplementation has a protective effect for individuals at a high risk of developing cardiovascular diseases [86–88]. Studies performed by our group highlighted resveratrol’s beneficial effects on several metabolic parameters [25, 41, 89, 90]. In this context, the absence of statistically significant differences regarding resveratrol’s effects on a few parameters might be related to the fact that the studies included here were performed with normocholesterolemic individuals or due to the short durations of the treatments.

Zhou et al. investigated if resveratrol was able to improve the profile of serum lipids and other metabolic markers in a dose–response manner in individuals with dyslipidemia. In their study, individuals received resveratrol (600 mg/day) or a placebo for approximately 2 months. Clinical trials, however, show inconclusive findings regarding this compound’s effect on dyslipidemia, which might be attributed to the heterogeneity of dosages among studies. Zhou et al. failed to show the beneficial effects of resveratrol on the lipid profile. However, this polyphenol antilipidemic effect must be questioned with caution as more studies are needed [62].

In summary, given the still-controversial and borderline findings regarding resveratrol’s effects, determining an ideal dosage of this compound for human usage is still a challenge. However, based on the studies included in the present review, the consumption of 300 mg/day of resveratrol seems to be an appropriate dose. Despite this, further studies are necessary. The study performed by Simental-Mendía et al., for example, used a lower effective dose (100 mg/day) of resveratrol in a short-term treatment (2 months) and evaluated WC, HDL-c, and TG, with the latter being the only one that was significantly reduced ($p = 0.04$) [48]. Mohaved et al., on the other hand, administered a higher dose (1000 mg/day) during a shorter intervention period (45 days) and reported significant reductions in glucose ($p = 0.001$) and blood pressure ($p = 0.000$) levels and increased HDL-c levels ($p = 0.001$), in addition to a borderline reduction in TG levels ($p = 0.051$) [33].

A few limitations of the present meta-analysis must be disclosed. First, potential basal differences in the diets of the intervention and placebo groups might have existed and interfered with the results. The short period of the interventions reported in most of the studies, participants coming from different health backgrounds, and the different dosages of resveratrol are among the discrepancies observed among the analyzed studies, which might explain the controversies that we observed. The period of the interventions must be highlighted, with the length of studies differing from a single-dose administration to a long-term 12-month treatment. From all the papers included, most reported treatment periods administered were up to 4 months, which is a limiting factor as metabolic responses usually require a minimum of a 12-week treatment period to be initiated. Another potential limitation of the results is resveratrol bioavailability [91], which varied with respect to the formulation chosen between the studies. A few trials used formulations with pure trans-resveratrol, while others used extracts in combination with trans-resveratrol.

Additionally, several studies did not provide the necessary data for the performance of the meta-analysis (mean and standard deviation/error), hindering their inclusion criteria. Sample size was also considered a limitation, as the number of participants varied from 5 to 65 per group (placebo vs. intervention). The studies included different populations (from several nationalities) with specific comorbidities such as diabetes, hypertension, metabolic syndrome, overweight, obesity, and even schizophrenia. In this context, the methodological, clinical, and statistical heterogeneity (with the latter varying from 17 to
57%) observed among the studies, in addition to their general low quality of evidence, may have had an important effect on the results observed in the present meta-analysis.

5. Conclusions

In conclusion, the present systematic review and meta-analysis evidenced the potential therapeutic effect of resveratrol under some aspects of metabolic syndrome, especially regarding reductions in systolic blood pressure, diastolic blood pressure, and glucose levels. However, the results are still borderline and somewhat controversial, which might be justified by the large heterogeneity and low quality of the studies retrieved from the literature. In this sense, the need for additional studies that would further investigate resveratrol’s effects on metabolic parameters is urgent, especially due to the vast literature that is already published regarding this compound’s effects on experimental studies with animal models, showing that resveratrol may have the potential of being more widely used in clinical practice if more robust evidence would be available.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines5020016/s1, Figure S1: Funnel plots for assessment of publication bias.


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