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Meta-analysis

What is the effect of resveratrol on obesity? A systematic review and meta-analysis

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SUMMARY

Background & aims: Obesity is increasing worldwide. Resveratrol appears as a substance capable of helping with weight loss. This study aimed to investigate the resveratrol effect in the treatment of obesity in general population.

Methods: An online search was conducted in the following databases: Pubmed, LILACS, Scielo, Scopus and Web of Science. Experimental studies that investigated the effects between resveratrol supplementation for weight loss treatment, as well as its relationship with overweight and obesity were included. Observational and non-human studies were excluded. The Cochrane scale was used to assess the quality of the studies.

Results: Nineteen studies were included, of which only three demonstrated some type of positive effect. In the meta-analysis, there was no significant effect on weight loss [SMD: 0.03; CI95%: −0,44, 0,49; p = 0,01; I2 = 82%], and body mass index (BMI) [SMD: 0.01; CI95%: −0,39, 0,41; p = 0,01; I2 = 72%]. A small effect was found on the waist circumference [SMD: −1.04; CI95%: −1,86, −0,27; p = 0,01; I2 = 87%].

Conclusion: This systematic review with meta-analysis demonstrated that supplementation with resveratrol does not have an anti-obesity effect.

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1. Introduction

Attracted by formulas that can help with weight loss, people seek for products that are effective and safe. Today, weight loss supplements have already become the most found products in this type of market [1]. Despite this, the prevalence of overweight and obesity is increasing worldwide. In 2013, it was estimated that one in three adults in the world was overweight or obese [2]. Recent evidence suggests that by 2030 almost one in two adults will be classified as obese in the U.S., and one in four adults will have severe obesity [3]. In addition, obesity produces high costs for health systems. In the US, obesity has an annual health cost of $ 190 billion per year, which is equivalent to approximately 21% of health care expenses [2].

The increase in obesity prevalence has been related to changes in food consumption, with increased energy intake and reduced levels of physical activity [4]. In addition, obesity is a multifactorial disease, connecting several factors, such as genetic, psychosocial, nutritional, metabolic and endocrine [4]. Obesity has been consolidated as a nutritional problem and is associated with a high incidence of cardiovascular diseases, cancer and diabetes [5].

In this context, resveratrol emerges as a substance that can be promising in weight loss, in addition to some other health benefits. Resveratrol (3,5,4 'trihydroxystylbene) is a polyphenol that was first identified in 1940, from the root of a poisonous medicinal plant, and later in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine [6,7]. Resveratrol is a substance that has been widely studied recently. Studies have shown that resveratrol has health-promoting properties, such as antioxidant, anti-inflammatory, cardioprotective,

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anti-diabetes, anticancer, chemo preventive and neuroprotective characteristics [8,9]. Its highest concentrations can be found in grapes, berries, red wine and peanuts [10]. A review study showed that, in *in vitro* research, resveratrol exerts an anti-obesity action reducing adipogenesis and increasing apoptosis [11]. In rats, a study demonstrated that resveratrol combined with quercetin (natural flavonoid) can have beneficial effects for obesity, as observed by a study conducted with rats [12]. In addition, another study demonstrated that resveratrol has an anti-obesity effect in these animals [13]. In humans, a study carried out with 48 participants with type 2 diabetes showed that resveratrol supplementation was able to reduce weight and body mass index (BMI) compared to placebo [14].

Taking into consideration the high population rates of overweight and obesity and the possible obesity-related positive effects of consuming resveratrol, this study aimed to investigate the resveratrol effect in the treatment of obesity in general population.

2. Methods

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [15]. In addition, this study was prospectively registered in the International Prospective Registry for Systematic Reviews (PROSPERO) (CRD42020171537). An online search was conducted in five databases (Pubmed, LILACS, Scielo, Scopus and Web of Science). The searches were carried out between May and June 2020, and no date or language restrictions were applied. Two groups of keywords were used to locate the articles, which were selected based on the *Medical Subject Headings* (MeSH). In the first group, the term “resveratrol” was used. In the second, the terms: “obesity”, “body weight”, “anti-obesity agents”, “weight loss”, “weight losses”, “weight reduction”, “body composition”, “body compositions".

Titles, abstract and full-text screening was conducted independently by two reviewers (FMD and LMF), according to the inclusion and exclusion criteria established. Disagreement between reviewers was solved by consensus. Finally, the references of the included studies were reviewed for possible additional articles.

Experimental studies that investigated the effects between resveratrol supplementation for weight loss treatment, as well as its relationship with overweight and obesity were included. Studies that were not conducted with humans were excluded.

The Cochrane tool was used to assess risk of bias [16]. Two reviewers assessed risk of bias independently (FMD and LMF), and disagreements was solved by consensus. This tool includes items regarding to: 1- generation of random sequence (selection bias); 2- concealment of allocation (selection bias); 3- concealment of results evaluators (detection bias); 4- blinding patients and staff (performance bias); 5- incomplete results data (friction bias); 6- selective reports (reporting bias); 7- other sources of bias, (other potential bias, not included in the domains described above). For this last item, a high risk of bias was considered in studies in which resveratrol has been used in combination with other substances. Based on this tool, studies are classified as having high risk, uncertain or low risk of bias in each of the seven items.

Studies that provided data on weight, BMI and initial and final waist circumference (after the intervention) were included in quantitative analysis. Also, subgroup analysis stratified by intervention time (weeks) and dose (g), except for waist circumference due to lack of data, were conducted. Standard deviation of the mean change was assessed using the equation: SD change = square root $[(SD\ baseline^2 + SD\ final^2) - (2 \times R \times SD_{baseline} \times SD_{final})]$, for studies with no information [17]. To maintain methodological rigor, only studies that were randomized and double-blind, as well as those whose resveratrol was not combined with other substances were included. The results are presented as the Standardized mean difference (SMD) and 95% confidence intervals. The Higgins I^2 statistic was calculated to estimate the heterogeneity between studies, considering values above 75% and $p < 0.10$ as high heterogeneity [18]. Meta-analysis was performed on RStudio and the level of significance was set at $p < 0.05$.

3. Results

Figure 1 shows the study selection flowchart. After excluding duplicates, 259 articles were retrieved, of which 211 were excluded in the first stage because they did not meet the inclusion criteria. After abstract screening, 48 articles remained, and 26 were eligible for full-text reading. Overall, 19 studies met the eligibility criteria and were included in this review. The main reasons for exclusion at this stage were: studies not conducted with humans (n = 2) and did not evaluate the outcome (obesity) (n = 6).

Of the 19 included studies, 12 were published by 2015 [8,19–28], while the other seven were published between the years 2016–2020 [14,29–34]. Five studies were carried out in North America [19,22,25,33,35], six in Asia [14,20,23,24,26,32], six in Europe [8,27–30,34] and two in Oceania [21,31]. In addition, 17 studies were double-blind randomized controlled trials [8,14,19,21,23–35], while one was just randomized [20] and one was neither randomized or double-blinded [22]. Thirteen studies had fewer than 50 participants. The smallest sample size was 10 [22,24] and the highest 179 [34]. One study was conducted only with women [35], and five only with men [8,21,24,27,29].

Table 1 shows the main characteristics and results of included studies. Three studies were carried out with elderly [19,22,31]. The first evaluated elderly people without pathologies, the second evaluated elderly people with type 2 diabetes and the third only overweight elderly. Of the other 16 studies, five were conducted with type 2 diabetes participants [14,20,24,26,34], seven assessed overweight or obese individuals [8,21,27,28,30,33,35], one assessed overweight individuals and type 2 diabetes [32], one assessed participants with non-alcoholic fatty liver disease [23], and two participants with metabolic syndrome [25,29]. Intervention time ranged from 4 [8,22,27,28] to 28 weeks [33]. Resveratrol doses varied considerably, from 75 mg per day (smallest) [35] to 3 g per day [21,24] (biggest). Two studies used resveratrol combined with other substances, such as orlistat [33] and epigallocatechin-3-gallate [30].

Two studies found significant decreases in weight and BMI in the groups that used resveratrol compared to placebo [14,25]. A third study found positive effects on weight loss only in the group that combined resveratrol with orlistat [33], without any significant effect having been observed in the group that used only resveratrol. The other 16 studies found no positive effects between resveratrol and weight loss, body composition or BMI.

Table 2 shows the risk of bias of included studies. Studies with a higher risk of bias were those not double-blinding [20] or not randomized [22]. Two studies showed high risk of bias for item 5 (incomplete results data), (20, 24) and eight had unclear risk [8,21,25,27,29,30,33,35]. On the other hand, all included studies showed low risk of bias on item 6 (reporting). In items 1, 2 (selection bias) [22], as well as in item 7 (other bias) [30] only one study presented high risk in each item.

Figure 2 shows the meta-analysis results for body weight (A), BMI (B), and waist circumference (C). For body weight, BMI and

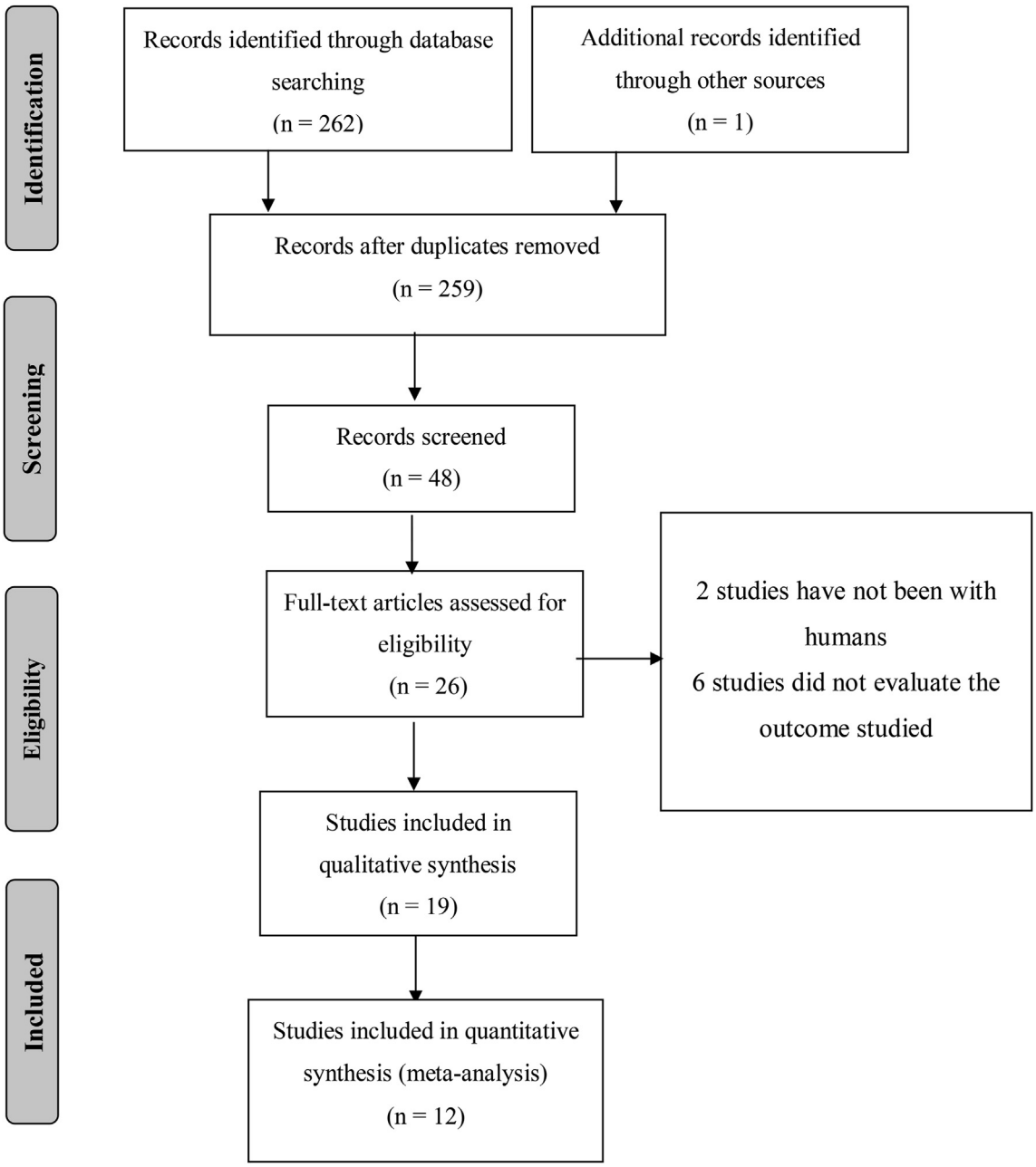

Fig. 1. Flowchart of the selection of studies presented in the review.

waist circumference, 11, nine and six studies presented data for quantitative analysis, respectively. Total participants included ranged from 131 to 235 in intervention group, and from 128 to 212 in control group. No significant effect of resveratrol was observed for body weight [SMD: 0.03; CI95%: −0,44, 0,49; p = 0,01; I2 = 82%; Fig. 2A], and BMI [SMD: 0.01; CI95%: −0,39, 0,41; p = 0,01; I2 = 72%; Fig. 2B]. For waist circumference, there was a significant effect [SMD: −1.04; CI95%: −1,86, −0,27; p = 0,01; I2 = 87%; Fig. 2C].

Subgroup analysis for intervention time and resveratrol dosage for body weight, BMI, and waist circumference are displayed in Figs. 3–5, respectively. No significant effect was observed for body weight, and BMI. For waist circumference, a significant effect was observed for studies with intervention time over 12 weeks [SMD: −1.45; CI95%: −2,55, −0,35; p = 0,01; I2 = 87%].

4. Discussion

Only three of the included studies showed a significant effect of resveratrol in weight loss, BMI or body fat. Of these, one study had significant results only when combining resveratrol with orlistat. However, when using resveratrol alone no significant effect was observed [33]. This result is possibly attributed to orlistat, which has already been proven in a review study to be effective in weight loss when compared to placebo [36]. The other two studies that found positive results were performed with diseases patients, such as metabolic syndrome and type 2 diabetes [14,25]. On the other hand, seven studies evaluated individuals with the same pathologies and found no significant results [20,24,26,29,31,32,34]. The doses do not seem to have differences in the results, since studies using 500 mg [25] or 800 mg [14] of resveratrol showed positive

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

Identification	Sample	Age	Study design	Duration in weeks	Intervention	Results
Abdollahi et al., 2019	71 overweight individuals with type 2 diabetes	Mean age of 50 years	Randomized double-blind clinical trial	8	1 g of resveratrol per day or placebo	There was no significant difference between groups
Anton et al., 2014	32 overweight elderly	Mean age 73 years	Randomized double-blind clinical trial	13	300 mg of resveratrol daily, 1 g or placebo	There was no significant difference between groups
Arzola-Paniagua et al., 2016	84 individuals with BMI between 30 and 39.9 kg/m^2	Ages between 20 and 60 years	Randomized double-blind clinical trial	28	4 groups: orlistat, 100 mg resveratrol, orlistate +120 mg resveratrol or placebo	Significant difference in weight only in the group that ingested orlistat + resveratrol
Bhatt et al., 2012	62 individuals with type 2 diabetes	Ages between 30 and 70 years	Randomized clinical trial	12	250 mg of resveratrol per day	There were no significant differences in body weight between groups
Bo et al., 2016	179 individuals with type 2 diabetes	Individuals over 40 years of age	Randomized double-blind clinical trial	26	40 mg resveratrol daily, 500 mg daily or placebo	There were no significant differences in body weight or BMI between groups
Chachay et al., 2014	20 overweight or obese men	Mean age of 48 years in the intervention group and 47 in the control group	Randomized double-blind clinical trial	8	3 g of resveratrol per day or placebo	There were no differences in the decrease in body fat between groups
Crandall et al., 2012	10 subjects with impaired glucose tolerance	Average age 72 years	Clinical trial	4	Doses of 1 g of resveratrol, 1.5 g or 2 g per day	No changes in body weight, regardless of dose ingested
Faghihzadeh et al., 2014	50 individuals with non-alcoholic fatty liver disease	Mean age of 44 years in the resveratrol group and 46 in the placebo	Randomized double-blind clinical trial	12	500 mg resveratrol daily or placebo	No significant differences in weight loss between groups
Goh et al., 2014	10 men with type 2 diabetes	Ages between 40 and 69 years	Randomized double-blind clinical trial	12	3 g of resveratrol per day or placebo	No significant differences in weight loss between groups
Kjaer et al., 2017	74 men with metabolic syndrome	Mean age of 49 in the low dose group, 51 in the high dose and 47 in the placebo	Randomized double-blind clinical trial	16	150 mg of resveratrol per day in the low dose group, 1 g in the high dose group or placebo	There was no difference in body composition between groups
Méndez-del Villar et al., 2014	24 individuals with metabolic syndrome	Age between 30 and 50 years	Randomized double-blind clinical trial	12	500 mg resveratrol daily or placebo	The group that ingested resveratrol had greater weight loss, BMI and body fat
Most et al., 2016	38 overweight or obese individuals	Mean age of 36 in the resveratrol group and 38 in the placebo	Randomized double-blind clinical trial	12	80 mg resveratrol +282 epigallocatechin-3-gallate per day or placebo	There was no difference in weight and body composition between groups
Movahed et al., 2013	66 individuals with type 2 diabetes	Age between 20 and 65 years	Randomized double-blind clinical trial	6	1 g of resveratrol per day or placebo	There was no difference in weight and composition and BMI between groups
Poulsen et al., 2013	24 obese men	Mean age of 44 in the resveratrol group and 31 in the placebo	Randomized double-blind clinical trial	4	500 mg resveratrol daily or placebo	There was no difference in body composition between groups
Seyyedebrahimi et al., 2018	46 individuals with type 2 diabetes	Age between 30 and 70 years	Randomized double-blind clinical trial	8	800 mg resveratrol daily or placebo	Significant reduction in weight and BMI in the group that took resveratrol compared to placebo
Thazhath et al., 2016	28 individuals with controlled type 2 diabetes	Mean age of 67 years	Randomized double-blind clinical trial	5	500 mg resveratrol twice daily or placebo	There was no difference in body weight between groups
Timmers et al., 2011	11 obese men	Mean age 52 years	Randomized double-blind clinical trial	4	150 mg resveratrol daily or placebo	There was no difference in body mass between groups
Van der Made et al., 2015	45 individuals with overweight or mild obesity	Mean age 61 years	Randomized double-blind clinical trial	4	150 mg resveratrol daily or placebo	There was no difference in weight and composition and BMI between groups
Yoshino et al., 2012	45 eutrophic or overweight women	Mean age of 58 years in the intervention group and 59 in the control group	Randomized double-blind clinical trial	12	75 mg resveratrol daily or placebo	There was no difference in body composition between groups

Table 2
Cochrane risk of bias toll results for included studies.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of patients and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdollahi et al., 2019	Low	Low	Low	Low	Low	Low	Low
Anton et al., 2014	Low	Low	Low	Low	High	Low	Low
Arzola-Paniagua et al., 2016	Low	Low	Low	Low	Unclear	Low	Low
Bhatt et al., 2012	Low	Low	High	High	Low	Low	Low
Bo et al., 2016	Low	Low	Low	Low	Low	Low	Low
Chachay et al., 2014	Low	Low	Low	Low	Unclear	Low	Low
Crandall et al., 2012	High	High	High	High	Low	Low	Low
Faghihzadeh et al., 2014	Low	Low	Low	Low	Low	Low	Low
Goh et al., 2014	Low	Low	Low	Low	High	Low	Low
Kjaer et al., 2017	Low	Low	Low	Low	Unclear	Low	Low
Méndez-del Villar et al., 2014	Low	Low	Low	Low	Unclear	Low	Low
Most et al., 2016	Low	Low	Low	Low	Unclear	Low	High
Movahed et al., 2013	Low	Low	Low	Low	Low	Low	Low
Poulsen et al., 2013	Low	Low	Low	Low	Unclear	Low	Low
Seyyedebrahimi et al., 2018	Low	Low	Low	Low	Low	Low	Low
Thazhath et al., 2015	Low	Low	Low	Low	Low	Low	Low
Timmers et al., 2011	Low	Low	Low	Low	Unclear	Low	Low
Van der Made et al., 2015	Low	Low	Low	Low	Low	Low	Low
Yoshino et al., 2012	Low	Low	Low	Low	Unclear	Low	Low

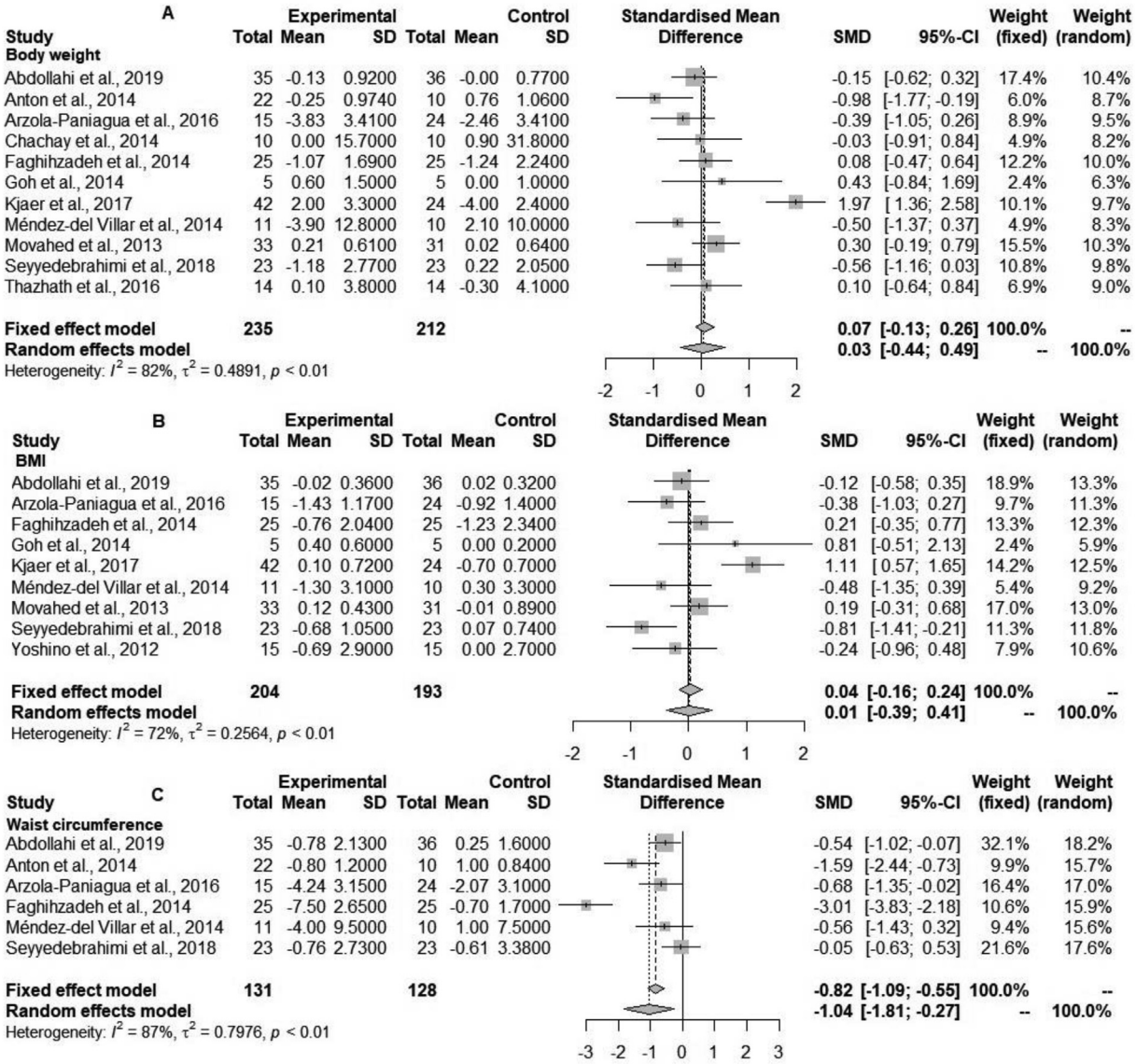

Fig. 2. Resveratrol effects on body weight (A), BMI (B) and waist circumference (C).

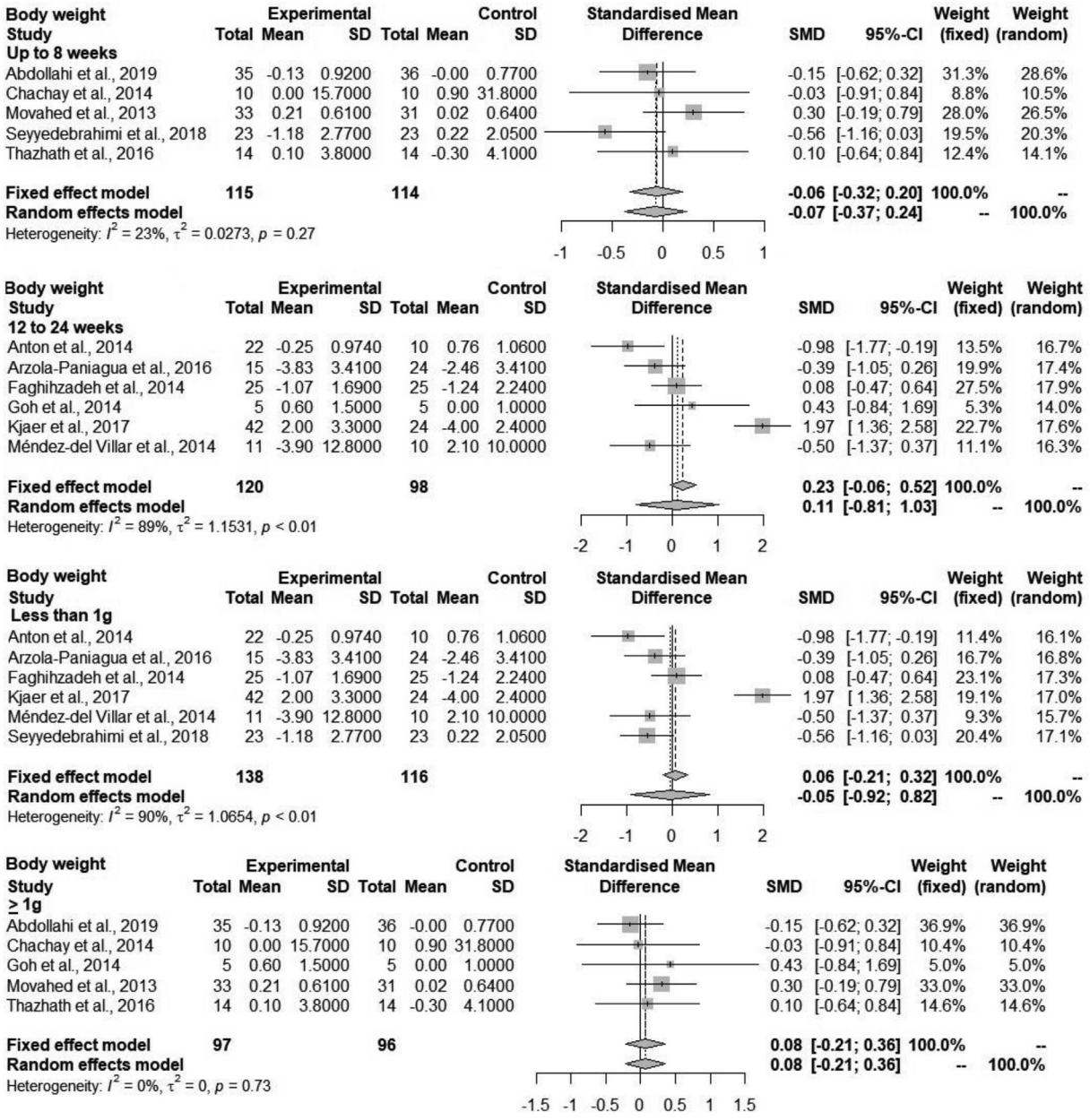

Fig. 3. Subgroup analysis of resveratrol effects for body weight intervention time and dose.

results in weight loss, BMI or body fat, while two studies that used larger doses, reaching three grams per day, did not observed significant effects [21,24]. Thus, it was not possible to identify a dose–response effect of resveratrol. The studies intervention time reflecting the longer duration of the intervention also did not show significant results [33,34].

Resveratrol had no positive effects on weight loss or BMI according to the meta-analysis results. For waist circumference, a significant effect was found. However, only six studies were included due to the lack of data available from the studies. When stratified by intervention time, only studies longer than 12 weeks positively affected waist circumference. These results must be interpreted with caution. Only four studies were positive, and the results were small. Our data corroborate with another systematic review, which not found positive results of resveratrol in weight loss [37]. Authors concluded that evidence up to the time of publication (2015) was not sufficient to demonstrate that resveratrol had a positive effect on obesity [37]. In contrast, a recent meta-analysis identified positive results, demonstrating that resveratrol was able to decrease body weight, BMI, waist circumference and body fat [38]. Although with a small effect of resveratrol on body weight (SMD: −0.17; 95% CI: −0.33–0.01; p = 0.03), studies combining resveratrol with other substances were included in this meta-analysis (37), which may explain the differences with our study.

An *in vitro* studies review showed that resveratrol has a slimming effect [11]. It has also been found that, in rodents, resveratrol induces a reduction in body fat [11]. Another review study showed that, in non-human primates, resveratrol reduced body mass gain by increasing satiety and resting metabolic rate [39]. Studies included in the first review suggest that resveratrol induces a reduction in body fat, inhibiting fat accumulation processes and

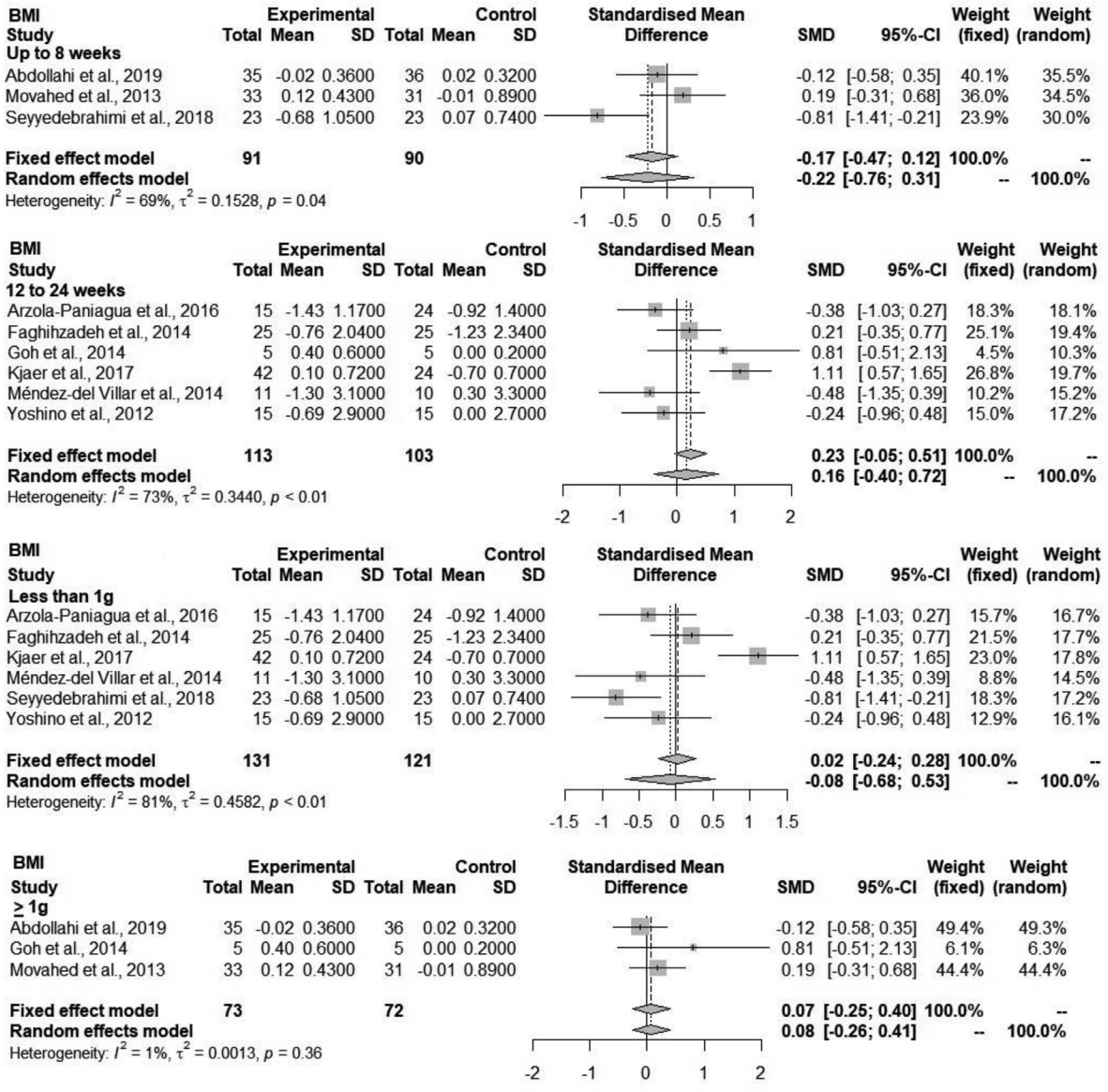

Fig. 4. Subgroup analysis of resveratrol effects for BMI intervention time and dose.

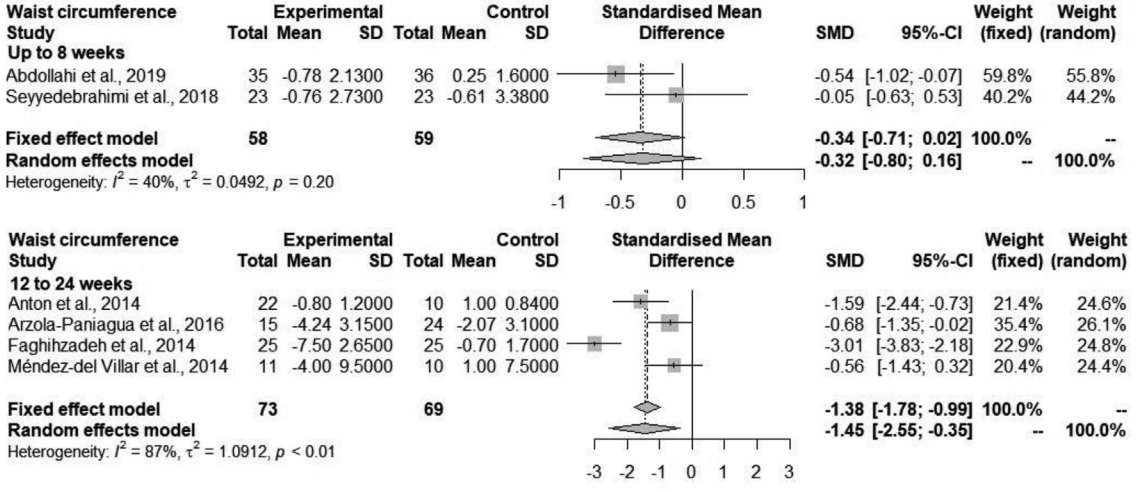

Fig. 5. Subgroup analysis of resveratrol effects for waist circumference intervention time.

stimulating the lipolytic and oxidative pathways, but these effects may not be as clear in humans [11].

A high heterogeneity was observed in our study, mainly regarding to the doses used, which ranged from 75 mg [35] to 3 g per day [21,24]. The intervention time also varied considerably. The longest study had an intervention time 7*x* higher [33] than the other four studies with short intervention time [8,22,27,28]. Sample size ranged from 10 [22] to 74 participants [29], which might also explain the high heterogeneity observed.

This study is extremely important, as it answers two other reviews that had different results, one negative and the other positive, in addition to being the only review registered in PROSPERO. In addition, this review was carried out following the rules of PRISMA to add quality to the study. As a strong point, the language and year of publication of the studies are characteristics that deserve to be highlighted, as there were no restrictions on these criteria. Finally, it should be noted that the search was carried out in the main databases, in order to identify all articles published on the topic.

Although efforts were made to find all studies, those published in gray literature were not included, such as thesis which can provide null or negative results that end up not being published [40]. Another limitation, is that not all 17 randomized, double-blind studies could be included in the meta-analysis. This was because not all studies had the information needed to assess the effect of resveratrol on changes in weight, BMI and abdominal fat. Thus, only 12 studies were included in the meta-analysis.

5. Conclusion

The present systematic review with meta-analysis demonstrated that supplementation with resveratrol does not have benefits in weight loss or body composition. A small positive result was observed in the waist circumference. However, due to the low number of studies included, it is not possible to state that resveratrol has an anti-obesity effect.

6. Authors' contributions

FMD contributed to Design, Conduct/data collection, analysis, and Writing manuscript. LMF contributed to data collection and Writing manuscript. ELC contributed to the analysis and Writing manuscript. GCM contributed to Writing manuscript. DPG contributed to Writing manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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PROSPERO registration

CRD42020171537.

Declaration of competing interest

There are no potential conflicts of interest, real or perceived.

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All authors contributed to data interpretation and reviewed, edited and approved the final manuscript.

References

[1] Ansari RM, Omar NS. Weight loss supplements: boon or bane? Malays J Med Sci 2017;24:1–4. https://doi.org/10.21315/mjms2017.24.3.1.
[2] Hruby A, Hu FB. The epidemiology of obesity: a big picture. Pharmacoeconomics 2015;33:673–89. https://doi.org/10.1007/s40273-014-0243-x.
[3] Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. N Engl J Med 2019;381:2440–50. https://doi.org/10.1056/NEJMsa1909301.
[4] Coutinho W. Consenso latino-americano de obesidade. Arq Bras Endocrinol Metabol 1999;43:21–67. https://doi.org/10.1590/s0004-27301999000100003.
[5] Kac G, Velásquez-Meléndez G. A transição nutricional e a epidemiologia da obesidade na América Latina. Cad Saúde Pública 2003;19:S4–5. https://doi.org/10.1590/s0102-311x2003000700001.
[6] Takaoka M. Of the phenolic substrate of hellebore (Veratrum grandiflorum Loes. fil.). J Fac Sci Hokkaido Imper Univ 1940;3:1–16.
[7] Nonomura S, Kanagawa H, Makimoto A. [CHEMICAL constituents OF POLYGONACEOUS plants. I. Studies ON the components OF KO-J O-KON. (POLYGONUM cuspidatum sieb. ET zucc.)]. Yakugaku Zasshi 1963;83:988–90.
[8] Timmers S, Konings E, Bilet L, Houtkooper RH, Van De Weijer T, Goossens GH, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metabol 2011;14:612–22. https://doi.org/10.1016/j.cmet.2011.10.002.
[9] Catalgol B, Batirel S, Taga Y, Ozer NK. Resveratrol: French paradox revisited. Front Pharmacol 2012;3(JUL):141. https://doi.org/10.3389/fphar.2012.00141.
[10] Bertelli AAA, Das DK. Grapes, wines, resveratrol, and heart health. J Cardiovasc Pharmacol 2009;54:468–76. https://doi.org/10.1097/FJC.0b013e3181bfaff3.
[11] Aguirre L, Fernández-Quintela A, Arias N, Portillo MP. Resveratrol: anti-obesity mechanisms of action. Molecules 2014;19:18632–55. https://doi.org/10.3390/molecules191118632.
[12] Zhao L, Zhang Q, Ma W, Tian F, Shen H, Zhou M. A combination of quercetin and resveratrol reduces obesity in high-fat diet-fed rats by modulation of gut microbiota. Food Funct 2017;8:4644–56. https://doi.org/10.1039/c7fo01383c.
[13] Macarulla MT, Alberdi G, Gómez S, Tueros I, Bald C, Rodríguez VM, et al. Effects of different doses of resveratrol on body fat and serum parameters in rats fed a hypercaloric diet. J Physiol Biochem 2009;65:369–76. https://doi.org/10.1007/BF03185932.
[14] Seyyedebrahimi SS, Khodabandehloo H, Nasli Esfahani E, Meshkani R. The effects of resveratrol on markers of oxidative stress in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. Acta Diabetol 2018;55:341–53. https://doi.org/10.1007/s00592-017-1098-3.
[15] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6. https://doi.org/10.1371/journal.pmed.1000097.
[16] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343. https://doi.org/10.1136/bmj.d5928.
[17] Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. 2009. https://doi.org/10.1002/9780470743386.
[18] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.
[19] Anton SD, Embry C, Marsiske M, Lu X, Doss H, Leeuwenburgh C, et al. Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. Exp Gerontol 2014;57:181–7. https://doi.org/10.1016/j.exger.2014.05.015.
[20] Bhatt JK, Thomas S, Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. Nutr Res 2012;32:537–41. https://doi.org/10.1016/j.nutres.2012.06.003.
[21] Chachay VS, Macdonald GA, Martin JH, Whitehead JP, O'Moore-Sullivan TM, Lee P, et al. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2014;12:2092–103. https://doi.org/10.1016/j.cgh.2014.02.024. e6.
[22] Crandall JP, Oram V, Trandafirescu G, Reid M, Kishore P, Hawkins M, et al. Pilot study of resveratrol in older adults with impaired glucose tolerance. Journals Gerontol - Ser A Biol Sci Med Sci 2012;67:1307–12. https://doi.org/10.1093/gerona/glr235.
[23] Faghihzadeh F, Adibi P, Rafiei R, Hekmatdoost A. Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease. Nutr Res 2014;34:837–43. https://doi.org/10.1016/j.nutres.2014.09.005.
[24] Goh KP, Lee HY, Lau DP, Supaat W, Chan YH, Koh AFY. Effects of resveratrol in patients with type 2 diabetes mellitus on skeletal muscle SIRT1 expression and energy expenditure. Int J Sport Nutr Exerc Metabol 2014;24:2–13. https://doi.org/10.1123/ijsnem.2013-0045.
[25] Méndez-del Villar M, González-Ortiz M, Martínez-Abundis E, Pérez-Rubio KG, Lizárraga-Valdez R. Effect of resveratrol administration on metabolic syndrome, insulin sensitivity, and insulin secretion. Metab Syndr Relat Disord 2014;12:497–501. https://doi.org/10.1089/met.2014.0082.
[26] Movahed A, Nabipour I, Louis XL, Thandapilly SJ, Yu L, Kalantarhormozi M, et al. Antihyperglycemic effects of short term resveratrol supplementation in type 2 diabetic patients. Evidence-Based Complement Altern Med 2013;2013:11. https://doi.org/10.1155/2013/851267.
[27] Poulsen MM, Vestergaard PF, Clasen BF, Radko Y, Christensen LP, Stødkilde-Jørgensen H, et al. High-dose resveratrol supplementation in obese men an

investigator- initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes 2013;62:1186–95. https://doi.org/10.2337/db12-0975.
[28] Van Der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. PloS One 2015;10. https://doi.org/10.1371/journal.pone.0118393.
[29] Kjær TN, Ornstrup MJ, Poulsen MM, Stødkilde-Jørgensen H, Jessen N, Jørgensen JOL, et al. No beneficial effects of resveratrol on the metabolic syndrome: a randomized placebo-controlled clinical trial. J Clin Endocrinol Metab 2017;102:1642–51. https://doi.org/10.1210/jc.2016-2160.
[30] Most J, Timmers S, Warnke I, Jocken JWE, Van Boekschoten M, De Groot P, et al. Combined epigallocatechin-3-gallate and resveratrol supplementation for 12 wk increases mitochondrial capacity and fat oxidation, but not insulin sensitivity, in obese humans: a randomized controlled trial. Am J Clin Nutr 2016;104:215–27. https://doi.org/10.3945/ajcn.115.122937.
[31] Thazhath SS, Wu T, Bound MJ, Checklin HL, Standfield S, Jones KL, et al. Administration of resveratrol for 5 wk has no effect on glucagon-like peptide 1 secretion, gastric emptying, or glycemic control in type 2 diabetes: a randomized controlled trial. Am J Clin Nutr 2016;103:66–70. https://doi.org/10.3945/ajcn.115.117440.
[32] Abdollahi S, Salehi-Abargouei A, Toupchian O, Sheikhha MH, Fallahzadeh H, Rahmanian M, et al. The effect of resveratrol supplementation on cardiometabolic risk factors in patients with type 2 diabetes: a randomized, double-blind controlled trial. Phyther Res 2019;33:3153–62. https://doi.org/10.1002/ptr.6487.
[33] Arzola-Paniagua MA, García-Salgado López ER, Calvo-Vargas CG, Guevara-Cruz M. Efficacy of an orlistat-resveratrol combination for weight loss in subjects with obesity: a randomized controlled trial. Obesity 2016;24:1454–63. https://doi.org/10.1002/oby.21523.
[34] Bo S, Ponzo V, Ciccone G, Evangelista A, Saba F, Goitre I, et al. Six months of resveratrol supplementation has no measurable effect in type 2 diabetic patients. A randomized, double blind, placebo-controlled trial. Pharmacol Res 2016;111:896–905. https://doi.org/10.1016/j.phrs.2016.08.010.
[35] Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai SI, Schechtman KB, et al. Resveratrol supplementation does not improve metabolic function in non-obese women with normal glucose tolerance. Cell Metabol 2012;16:658–64. https://doi.org/10.1016/j.cmet.2012.09.015.
[36] Jain S, Ramanand S, Ramanand J, Akat P, Patwardhan M, Joshi S. Evaluation of efficacy and safety of orlistat in obese patients. Indian J Endocrinol Metab 2011;15:99. https://doi.org/10.4103/2230-8210.81938.
[37] Christenson J, Whitby SJ, Mellor D, Thomas J, McKune A, Roach PD, et al. The effects of resveratrol supplementation in overweight and obese humans: a systematic review of randomized trials. Metab Syndr Relat Disord 2016;14:323–33. https://doi.org/10.1089/met.2016.0035.
[38] Tabrizi R, Tamtaji OR, Lankarani KB, Akbari M, Dadgostar E, Dabbaghmanesh MH, et al. The effects of resveratrol intake on weight loss: a systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr 2020;60:375–90. https://doi.org/10.1080/10408398.2018.1529654.
[39] Dal-Pan A, Blanc S, Aujard F. Resveratrol suppresses body mass gain in a seasonal non-human primate model of obesity. BMC Physiol 2010;10:11. https://doi.org/10.1186/1472-6793-10-11.
[40] Paez A. Gray literature: an important resource in systematic reviews. J Evid Base Med 2017;10:233–40. https://doi.org/10.1111/jebm.12266.

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