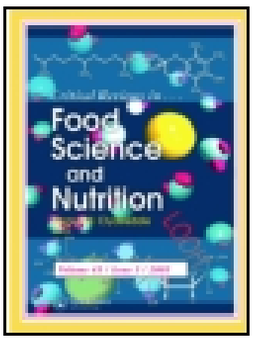

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Effect of resveratrol on blood pressure: A systematic review and meta-analysis of randomized, controlled, clinical trials

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ABSTRACT

Introduction: Results of previous clinical trials evaluating the effect of resveratrol supplementation on blood pressure (BP) are controversial.

Purpose: We aimed to assess the impact of resveratrol on BP through systematic review of literature and meta-analysis of available randomized, controlled clinical trials (RCTs).

Methods: Literature search included SCOPUS, PubMed-Medline, ISI Web of Science and Google Scholar databases up to 17th October 2017 to identify RCTs investigating the impact of resveratrol on BP. Two review authors independently extracted data on study characteristics, methods and outcomes. Overall, the impact of resveratrol on BP was reported in 17 trials.

Results: Administration of resveratrol did not significantly affect neither systolic BP [weighted mean difference (WMD): −2.5 95% CI:(-5.5, 0.6) mmHg; p=0.116; I^2=62.1%], nor diastolic BP [WMD: −0.5 95% CI:(-2.2, 1.3) mmHg; p=0.613; I^2=50.8], nor mean BP [*MAP*; WMD: −1.3 95% CI:(-2.8, 0.1) mmHg; p=0.070; I^2=39.5%] nor pulse pressure [*PP*; WMD: −0.9 95% CI:(-3.1, 1.4) mmHg; p=0.449; I^2=19.2%]. However, significant WMDs were detected in subsets of studies categorized according to high resveratrol daily dosage (≥300 mg/day) and presence of diabetes. Meta-regression analysis revealed a positive association between systolic BP-lowering resveratrol activity (slope: 1.99; 95% CI: 0.05, 3.93; two-tailed p= 0.04) and Body Mass Index (BMI) at baseline, while no association was detected neither between baseline BMI and MAP-lowering resveratrol activity (slope: 1.35; 95% CI: −0.22, 2.91; two-tailed p= 0.09) nor between baseline BMI and PP-lowering resveratrol activity (slope: 1.03; 95% CI: −1.33, 3.39; two-tailed p= 0.39). Resveratrol was fairly well-tolerated and no serious adverse events occurred among most of the eligible trials.

Conclusion: The favourable effect of resveratrol emerging from the current meta-analysis suggests the possible use of this nutraceutical as active compound in order to promote cardiovascular health, mostly when used in high daily dose (≥300 mg/day) and in diabetic patients.

KEYWORDS
Resveratrol; blood pressure; meta-analysis; metaregression; type 2 diabetes

Introduction

During the last decade a growing interested has been observed as it regards the effect of natural compounds on cardiovascular health (Sonoswka et al. 2017).

Resveratrol (3,5,4′-trihydroxystilbene) belongs to a family of polyphenolic compounds known as stilbenes, particularly concentrated in grape and red wine. Many studies have shown the antihypertensive effects of resveratrol in different preclinical models of hypertension, through a multitude of mechanisms mostly including its antioxidant properties, the stimulation of endothelial nitride oxide production, the inhibition of vascular inflammation and the prevention of platelet aggregation (Borghi and Cicero 2017; Cicero et al. 2017; Li et al. 2012). Moreover, resveratrol effects on vascular health could be increased by its parallel improving action on plasma lipids (Cicero et al. 2017b), All these effects may promote blood pressure (BP) reductions and improve BP control in hypertensive patients in a setting of clinical practice.

In this regard, several randomized clinical trials (RCTs) have demonstrated resveratrol produces systolic/diastolic BP reductions. Even if the results are relatively variable in different trials, the tolerability and safety profile of resveratrol is very high and no clinically significant pharmacological interaction of this nutraceutical with conventional drugs is known (Cicero and Colletti 2015; Sirtori et al. 2015). Moreover, the low bioavailability of resveratrol could be at least partly improved by the application of modern pharmaceutical technologies.

Today, available studies are few and explorative and yield conflicting data. Therefore, we aimed to assess the impact of resveratrol on BP through a systematic review of literature and meta-analysis of available randomized clinical trials (RCTs).

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.
*Claudio Borghi and Arrigo Cicero are co-last authors.

Methods

Search strategy

The study was designed according to guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Moher et al. 2009). PubMed-Medline, Researchgate, SCOPUS, Google Scholar and ISI Web of Science databases were searched using the following search items in titles and abstracts: ("Resveratrol" OR "*Vitis vinifera*") AND ("Clinical trial" AND "Hemodynamic parameters" OR "Blood pressure" OR "BP" OR "B P" OR "Systolic blood pressure" OR "SBP" OR "S B P" OR "Diastolic blood pressure" OR "DBP" OR "D B P"). The wild-card term "*" was used to increase the sensitivity of the search strategy. The reference lists of identified papers were checked manually for additional relevant article. No language restriction was used in literature search. The search was limited to studied in human. The literature was searched from inception to October 17, 2017.

Study selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized trial with either parallel or cross-over design, (ii) investigating the impact of chronic resveratrol supplementation on systolic BP (SBP) and diastolic BP (DBP), (iii) providing sufficient information on BP at baseline and at the end of follow-up in each group, (iv) having an appropriate controlled design, e.g., if resveratrol was administered as an adjunct to another drug/supplement, the control group had to receive the same drug/supplement. Exclusion criteria were: (i) lack of a control group for resveratrol supplementation, (ii) testing acute effect of resveratrol intake, and (iii) lack of sufficient information on baseline or follow-up SBP or DBP, (iv) use of daily resveratrol doses <50 mg. Two authors independently reviewed all articles. Then, a third author arbitrated any discrepancies in including the studies in the meta-analysis.

Data extraction

Data abstracted from the eligible studies were: (i) first author's name; (ii) year of publication; (iii) study location; (iv) study design; (v) inclusion criteria and underlying disease; vi) dose and duration of resveratrol supplementation; (vii) number of participants in the active and control group; (viii) age, gender, body mass index (BMI) and waist circumference (WC) of study participants; and (ix) baseline SBP and DBP measurements at rest.

Quality assessment

A systematic assessment of bias in the included study was performed using the Cochrane criteria. (Higgins and Green 2010). The items applied for each study assessment were the following ones: adequacy of sequence generation, allocation concealment, blinding addressing of dropouts (incomplete outcome data), selective outcome reporting, and other probable sources of bias (Sahebkar et al. 2017). Based on the recommendations of the Cochrane Handbook, risk of bias was judged to be high or low. Labelling an item as "unclear" suggested an unclear or unknown risk of bias.

Quantitative data synthesis

Mean pulse pressure (PP) was calculated as the difference between SBP and DBP (PP= SBP - DBP). PP standard deviation (SD) was estimated as follows: SD_{PP}= square root (SD_{SBP}^2 + SD_{DBP}^2). Mean arterial pressure (MAP) was obtained by adding one-third of PP to DBP (MAP= $^1/_3$PP + DBP). SD_{MAP} value resulted from the following formula: SD_{MAP}= square root ($^1/_3$ SD_{PP}^2 + SD_{DBP}^2). If the outcome measures were reported in mean and variation range or mean and inter-quartile range, SDs were calculated as described by Hozo et al. (Hozo et al. 2005). Where standard error of the mean (SEM) was only reported, SD was estimated as follows: SD= SEM × square root (n), being n the subjects' number. (Sahebkar et al. 2016).

Meta-analysis was entirely conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ) (Borenstein et al. 2005). Net changes in SBP, DBP, PP and MAP (change scores) were calculated by subtracting the value at baseline from that after intervention in the active-treated groups and in the control ones. SDs of the mean difference were obtained as follows:

$$SD = \text{square root } [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})],$$

assuming a correlation coefficient (R) = 0.5 for both pre-test / post-test (parallel groups) and crossover designed studies (Follmann et al. 1992)

When results were presented in multiple time points, only data relating to the longest duration of treatment were considered. Moreover, in order to avoid double-counting problem, in trials comparing multiple treatment arms versus a single control group, the number of subjects in the control group was divided by the number of the treatment arms. Results of the selected studies were combined using the generic inverse variance method and a fixed- or random-effects model, depending respectively on the presence of low-to-moderate (<50%) or high (≥50%) heterogeneity, which was quantitatively assessed using Higgins index (I^2). Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Finally, sensitivity analysis was executed in order to evaluate the influence of each single study on the overall effect size (Table 3). A leave-one-out method was used (i.e. one study was removed at a time and the analysis repeated). (Fogacci et al. 2017).

Additional analysis

Subgroups analyses were performed to explore the impact on resveratrol BP-lowering activity of type 2 diabetes or non-alcoholic fatty liver disease (NAFLD) (listed among the inclusion criteria), administered daily dose (> or ≤ the median dosage) and duration of treatment (> or ≤3 months).

Meta-regression analysis

A weighted fixed-effect meta-regression using unrestricted maximum likelihood model was performed to assess the

association between the significant estimated effect sizes with potential moderator variables including resveratrol daily dosage and BMI at baseline.

Publication bias

Potential publication biases were explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation test and Egger's weighted regression test. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication biases (Duval and Tweedie 2000).

Results

Flow and characteristics of the included study

After database searches according to inclusion and exclusion criteria, 297 published studies were identified and the abstracts reviewed. Of these, 93 were non-original article and were excluded. Then, other 175 studies were eliminated because they did not meet the inclusion criteria. Thus, 29 full text articles were careful assessed and reviewed. After assessment, 12 studies were excluded because: testing different phytochemicals in combination (n=2), testing acute effect of resveratrol intake (n=1), and reporting incomplete data (n=9). Finally, 17 studies were eligible and included in the present systematic review and meta-analysis. (Kjær et al. 2017; Imamura et al. 2017; Heebøll et al. 2016; Timmers et al. 2016; Chen et al. 2015; Faghihzadeh et al. 2015; van der Made et al. 2015; Anton et al. 2014; Chachay et al. 2014; Méndez-del Villar et al. 2014; Kumar and Joghee 2013; Tomé-Carneiro et al. 2013; Movahde et al. 2013; Wong et al. 2013; Bhatt et al. 2012; Yoshino et al. 2012; Timmers et al. 2011). The study selection process is shown in Figure 1.

Data were pooled from 17 RCTs comprising 36 treatment arms, which included 681 subjects, with 407 in the resveratrol arm and 375 in the control one (the sum is higher than the total because patients enrolled in cross-over trials were treated both with resveratrol and placebo). Included studies were published between 2011 and 2017, and were conducted in the Netherlands (3), Denmark (2), Spain, US of America (2), Mexico, Australia (2), India (2), Iran (2), China (1) and Japan (1). Intervention periods ranged between 30 days and 6 months and several dosage resveratrol forms were tested. Selected trials were designed cross-over, (Timmers et al. 2016; van der Made et al. 2015; Wong et al. 2013; Timmers et al. 2011). or per parallel groups. (Kjær et al. 2017; Imamura et al. 2017; Heebøll et al. 2016; Chen et al. 2015; Faghihzadeh et al. 2015; Anton et al. 2014; Chachay et al. 2014; Méndez-del Villar et al. 2014; Kumar and Joghee 2013; Tomé-Carneiro et al. 2013; Movahde et al. 2013; Bhatt et al. 2012; Yoshino et al. 2012) .Enrolled subjects were overweight or slightly obese individuals without any major disease (van der Made et al. 2015; Anton et al. 2014; Wong et al. 2013; Yoshino et al. 2012; Timmers et al. 2011). or individuals affected by MetS, (Kjær et al. 2017; Méndez-del Villar et al. 2014). well controlled T2DM, [Imamura et al. 2017; Timmers et al. 2016; Kumar and Joghee 2013; Movahde et al. 2013; Bhatt et al. 2012], NAFLD, (Heebøll et al. 2016; Chen et al. 2015; Faghihzadeh et al. 2015; Chachay et al. 2014) stable angina or acute coronary syndrome. (Tomé-Carneiro et al. 2013). Anthropometric and hemodynamic characteristics of the evaluated studies are presented in Table 1.

BP measurements methods

Not all the included studies reported BP assessment methods. When specified, BP was always assessed from the brachial artery, according to standardized protocols by the use of mercury sphygmomanometers. Subjects were seated at rest for at

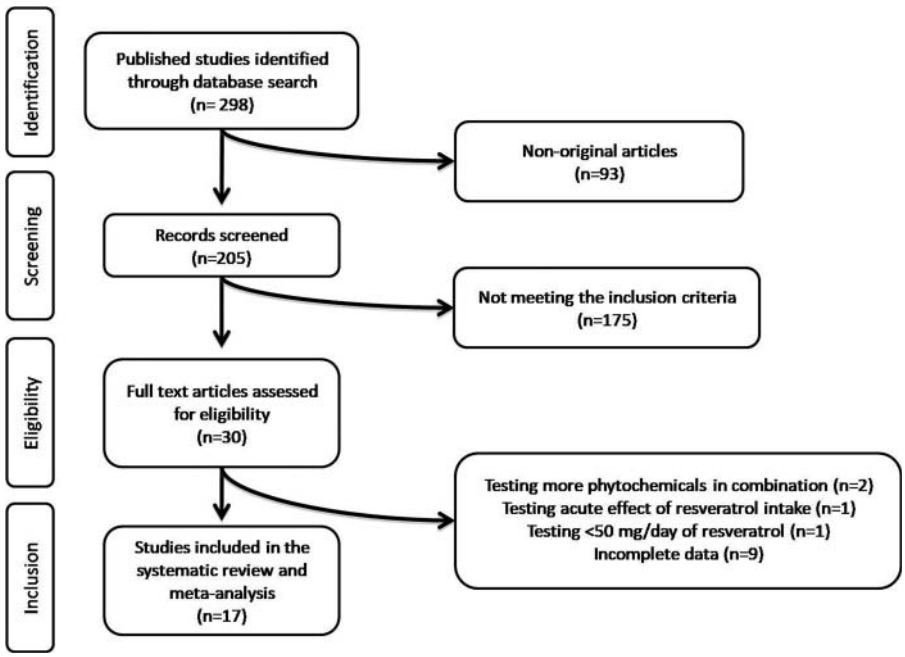

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Table 1. Baseline characteristics of the studies included in the meta-analysis. Data are reported as mean ± standard deviation, unless otherwise specified.

First author (year)	Study location	Design	Main inclusion criteria for the studies	Resveratrol treatment duration	Participants (n)	Study group	Age (years)	BMI (Kg/m^2)	WC (cm)	Male (n,%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PP (mmHg)
Kjær, TN (2017)	Denmark	Randomized, double-blind, placebo-controlled, parallel group clinical study	-Male sex -30–60 years -MetS diagnosis (according to the International Diabetes Federation criteria for MetS) but otherwise healthy	16 weeks	21	Resveratrol 1000 mg/day (standardization to trans-resveratrol not reported)	51.9 ± 6	33.8 ± 3.2	114 ± 9.6	21 (100)	146 ± 10.5	89.3 ± 7.8	108.2 ± 8.8	56.7 ± 13.1
					21	Resveratrol 150 mg/day (standardization to trans-resveratrol not reported)	49.1 ± 6.9	33.4 ± 4.1	116 ± 8.7	21 (100)	140 ± 10.5	86.9 ± 6.9	104.6 ± 8.3	53.1 ± 12.6
					24	Placebo	47.8 ± 6.4	34.1 ± 3.9	116 ± 10.3	24 (100)	150 ± 16.7	91.3 ± 10.3	110.9 ± 12.8	58.7 ± 19.6
Imamura, H (2017)	Japan	Randomized, double-blind, placebo-controlled, parallel group clinical study	-T2DM (HbA1c >7.0%)	12 weeks	25	Resveratrol 100 mg/day (standardized in resveratrol-ε)	57.4 ± 10.6	26.1 ± 4.2	NA	15 (60)	137.1 ± 18.7	82 ± 9.5	100.4 ± 13.3	55.1 ± 21
					25	Placebo	58.2 ± 10.1	24.1 ± 4	NA	11(44)	137.1 ± 25	80.8 ± 11.5	99.6 ± 17.2	56.3 ± 27.5
Heebøll, S (2016)	Denmark	Randomized, double-blind, placebo-controlled, parallel group clinical study	-Elevated serum ALT (>70 U/L for men and >45 for women) -NAFLD (diagnosed by the presence of steatosis at US examination) -18–70 years -BMI ≥25 Kg/m^2 -at least one additional element of MetS (excluding diabetes)	6 months	13	Resveratrol 1500 mg/day (standardization to trans-resveratrol not reported)	43.2 (22–67)§	32.1 ± 3.1	NA	9 (69)	142 ± 15	89 ± 8	106.7 ± 10.8	53 ± 17
					13	Placebo	43.5 (21–69)§	32 ± 5.4		8 (62)	136 ± 15	79 ± 8	98 ± 10.8	57 ± 17
Timmers, S (2016)	The Netherlands	Randomized, double-blind, placebo-controlled, crossover clinical study	-Well-controlled T2DM (HbA1c <8.0%) -male sex -40–70 years -BMI ≥27 Kg/m^2 and ≤35 Kg/m^2	30 days	17	Resveratrol 150 mg/day (99.9% trans-resveratrol)	64 (59.2–67.3)*	30.5 ± 2.3	NA	17 (100)	139 ± 17.3	85 ± 11.1	103 ± 13.5	54 ± 20.6
					17	Placebo		30.5 ± 2.5	NA	17 (100)	142 ± 16.1	87 ± 11.1	105.3 ± 13	55 ± 19.6
Chen, S (2015)	China	Randomized, double-blind, placebo-controlled, parallel group clinical study	-NAFLD (diagnosed by the presence of "bright liver" at US examination in absence of known aetiologies of chronic liver disease) -20–60 years -BMI >20 -Kg/m^2 and <30 Kg/m^2 -FPG <140 mg/dL	3 months	30	Resveratrol 600 mg/day (≥98% trans-resveratrol)	45.2 ± 10	25.3 ± 2.1	88.4 ± 7	22 (73)	124.1 ± 13.1	80.6 ± 8.8	95.1 ± 10.4	43.5 ± 15.8
					30	Placebo	43.5 ± 11	26.2 ± 3.1	88.2 ± 7.1	20 (67)	131.7 ± 21.7	84.5 ± 14.4	100.2 ± 17	47.2 ± 25.9
Faghihzadeh, F (2015)	Iran	Randomized, double-blind, placebo-controlled, parallel group clinical study	-Persistent elevated serum ALT (>30 U/L for men and >19 for women) for 6 months -NAFLD (diagnosed by the presence of steatosis on both US examinations and fibrosis on FibroScan)	12 weeks	24	Resveratrol 500 mg/day (pure trans-resveratrol)	44 ± 10.1°	28.4 ± 3.5	95.5 ± 7.8	18 (72)°	119 ± 13.8	79.7 ± 8.4	92.8 ± 10.5	39.3 ± 16.2
					24	Placebo	46.3 ± 9.5°	28.8 ± 3.5	96.2 ± 7.8	17 (68)°	116.4 ± 14	78 ± 8.4	90.8 ± 10.6	38.4 ± 16.3
Van der Made, SM (2015)	The Netherlands	Randomized, double-blind, placebo-controlled, crossover clinical study	-Non-smoking -45–70 years -TC <309.4 mg/dL -HDL-C <46.8 mg/dL for men and <59.2 for women -FPG <126 mg/dL -BMI ≥25 Kg/m^2 and ≤35 Kg/m^2 -mean alcohol consumption <20 units/week for men and <14 units/week for women	4 weeks	45	Resveratrol 150 mg/day (99% trans-resveratrol)	60 ± 7	28.8 ± 3.2	NA	25 (56)	136 ± 17	88 ± 9	104 ± 12.3	48 ± 19.2
					45	Placebo								

Anton, SD (2014)	US of America	Randomized, placebo-controlled, parallel group clinical pilot study	-Non-smoking -BMI ≥25 Kg/m^2 and ≤34.9 Kg/m^2 -sedentary lifestyle (physical exercising <120 min per week) -self-reported ability to walk 1 mile	90 days	10	Resveratrol 1000 mg/day (standardization to trans-resveratrol not reported)	73.6 ± 2.5	29 ± 1	47.6 ± 5.8	5 (50)	132.1 ± 5.5	73.5 ± 3.7	93 ± 4.4	58.6 ± 6.6
					12	Resveratrol 300 mg/day (standardization to trans-resveratrol not reported)	73.2 ± 2.1	29.8 ± 0.6	42.6 ± 1.5	6 (50)	125.5 ± 3.2	71.5 ± 2.8	89.5 ± 2.9	54 ± 4.3
					10	Placebo	73.3 ± 2.1	29.7 ± 0.6	46.8 ± 4.8	5 (50)	136.1 ± 3.4	77.2 ± 2.9	96.8 ± 3.1	58.9 ± 4.5
Chachay, VS (2014)	Australia	Randomized, double-blind, placebo-controlled, parallel group clinical study	-NAFLD (diagnosed by the presence of steatosis at US examinations in absence of known aetiologies of chronic liver disease) -male sex -BMI >25 Kg/m^2 -WC >90 cm -mean alcohol consumption <40 g/day	8 weeks	10	Resveratrol 3000 mg/day (s standardization to trans-resveratrol not reported)	48.8 ± 12.2	31.8 (30.2–37.0)*	NA	10 (100)	130 ± 12	83 ± 7	98.7 ± 9	47 ± 13.9
					10	Placebo	47.5 ± 11.2	31.2 (27.4–39.3)*		10 (100)	130 ± 10	82 ± 6	98 ± 75.6	48 ± 11.7
Méndez-del Villar, M (2014)	Mexico	Randomized, double-blind, placebo-controlled, parallel group clinical study	-MetS diagnosis (according to the International Diabetes Federation criteria for MetS) -non-smoking -30–50 years	90 days	11	Resveratrol 1500 mg/day (pure trans-resveratrol)	39.8 ± 5.4	35.6 ± 3.2	109 ± 9	1 (9)	120 ± 13	78 ± 8	92 ± 9.9	42 ± 15.3
					10	Placebo	40.3 ± 5.4	33.7 ± 3.7	104 ± 8	5 (50)	116 ± 13	77 ± 8	90 ± 9.9	39 ± 15.3
Kumar, BJ (2013)	India	Prospective, open-label, randomized, controlled, parallel group clinical study	-T2DM (minimum 3 years duration of the disease) -30–70 years –minimum of 6 months of ongoing oral hypoglycaemic treatment or combination therapy (metformin and/or glibenclamide)	6 months	28	Resveratrol 250 mg/day (standardization to trans-resveratrol not reported)	NA	24.7 ± 3.6	NA	12 (43)	139.7 ± 16.1	81.4 ± 9.6	100.8 ± 12.2	58.3 ± 18.7
					29	Placebo		24.9 ± 3.1		9 (31)	134.5 ± 14.6	78.6 ± 10.9	97.2 ± 12.3	55.9 ± 18.2
Tomé-Carneiro, J (2013)	Spain	Randomized, double-blind, placebo-controlled, parallel group clinical study	-Stable angina or acute coronary syndrome for at least 6 months before the inclusion in the study -left ventricular ejection fraction ≥45% -NYHA functional class I-II -18–80 years -more than 3 months of ongoing pharmacological therapy according to ESC guidelines	6 months	25	Resveratrol 350 mg/day (standardization to trans-resveratrol not reported)and grape extract (∼25 mg anthocyanins, ∼1 mg flavonols, ∼40 mg procyanidins, and ∼0.8 mg hydroxycinnamic acids)	60 ± 12	29.7 ± 5.1	NA	24 (96)	126 ± 16	71 ± 9	89.3 ± 11.8	55 ± 18.4
					25	Grape extract (∼25 mg anthocyanins, ∼1 mg flavonols, ∼40 mg procyanidins, and ∼0.8 mg hydroxycinnamic acids)	59 ± 10	30.8 ± 4.6	NA	19 (76)	124 ± 18	73 ± 10	90 ± 13.2	51 ± 20.6
Movahed, A (2013)	Iran	Randomized, double-blind, placebo-controlled, parallel group clinical study	-T2DM -20–65 years –minimum of 6 months of ongoing oral hypoglycaemic treatment or combination therapy	45 days	33	Resveratrol 1000 mg/day (99% trans-resveratrol)	52.5 ± 6.2	27.1 ± 3.1	NA	16 (47)	129 ± 15.0	76.9 ± 19.5	94.3 ± 18.1	52.1 ± 24.6
					31	Placebo	51.8 ± 7.0	27.8 ± 4.2	NA	17 (55)	129.3 ± 15.2	78.6 ± 15.4	95.5 ± 15.3	50.7 ± 21.6
Wong, RHX (2013)	Australia	Randomized, double-blind, placebo-controlled, crossover clinical study	-Male sex or women in postmenopausal status (defined on the basis of self-reported cassation of menses for at least 12 months) -40–75 years –BMI ≥30 Kg/m^2 and ≤45 Kg/m^2	6 weeks	28	Resveratrol 75 mg/day (99% trans-resveratrol)	61 ± 6.9	33.3 ± 3.2	NA	12 (43)	127.4 ± 12.7	73.3 ± 6.9	91.3 ± 9.2	54.1 ± 14.5
					28	Placebo								

(*Continued on next page*)

Table 1. (*Continued*).

First author (year)	Study location	Design	Main inclusion criteria for the studies	Resveratrol treatment duration	Participants (n)	Study group	Age (years)	BMI (Kg/m^2)	WC (cm)	Male (n,%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PP (mmHg)
Bhatt, JK (2012)	India	Prospective, open-label, randomized, controlled, parallel group clinical study	-T2DM (minimum 3 years duration of the disease) -30–70 years -minimum of 6 months of ongoing oral hypoglycaemic treatment (metformin and/or glibenclamide)	3 months	28	Resveratrol 250 mg/day (pure trans-resveratrol)	56.7 ± 8.9	24.7 ± 3.6	212.8 ± 64.5	12 (43)	139.7 ± 16.1	81.4 ± 9.6	100.8 ± 12.2	58.3 ± 18.7
					29	No treatment	57.8 ± 8.7	24.9 ± 3.1	182 ± 46.22	9 (31)	134.5 ± 14.6	78.6 ± 10.9	97.2 ± 12.3	55.9 ± 18.2
Yoshino, J (2012) [16]	US of America	Randomized, double-blind, placebo-controlled, parallel group clinical study	-Female sex -post-menopausal status (at least 1 year since last spontaneous menstrual bleeding) -35–70 years -BMI ≥20 Kg/m^2 and ≤30 Kg/m^2 -mean alcohol consumption >20 g/day	12 weeks	15	Resveratrol 75 mg/day (99.7% trans-resveratrol)	58.2 ± 4	24.2 ± 2.8	NA	0 (0)	118 ± 16	67 ± 11	84 ± 12.9	51 ± 19.4
					14	Placebo	59.8 ± 4.3	24.3 ± 2.7	NA	0 (0)	123 ± 15	65 ± 10	84.3 ± 11.9	58 ± 18
Timmers, S (2011)	The Netherlands	Randomized, double-blind, placebo-controlled, crossover clinical study	-Male sex -obesity -good health	30 days	11	Resveratrol 150 mg/day (99% trans-resveratrol)	52.5 ± 7	31.45 ± 2.7	NA	11 (100)	132 ± 9.9	83 ± 8.6	99.3 ± 9.1	49 ± 13.1
					11	Placebo	52.5 ± 7	31.59 ± 2.5	NA	11 (100)	131 ± 10.3	82 ± 8.3	98.3 ± 9	49 ± 11.1

°values calculated by the inclusion in the analysis of the patients who dropped out (n=1 in the active treated group and in the placebo treated one)
*expressed as median and 95% CI
§expressed as mean and variation range
ALT= ALanine aminoTransferase; BMI= Body Mass Index; DBP= Diastolic Blood Pressure; ESC= European Society of Cardiology; FPG= Fasting Plasma Glucose; HbA1c= Haemoglobin A1c; HDL-C= High Density Lipoprotein Cholesterol; MAP= Mean Arterial Pressure; MetS= Metabolic Syndrome; MMSE= Mini Mental State Examination; n= subjects; NA= Not Available; NAFLD= Non-Alcoholic Fatty Liver Disease; NYHA= New York Heart Association; PP= Pulse Pressure; SBP= Systolic Blood Pressure; T2D= Type 2 Diabetes; TC= Total Cholesterol; US= United States; WC= Waist Circumference.

least 10 minutes in a quiet room, and three readings were taken at intervals of at least 1-minute. The first reading was discarded, and the last two readings were averaged.

Risk of bias assessment

Almost all the included studies were characterized by sufficient information regarding sequence generation, allocation concealment and personnel and outcome assessments, and showed low risk of bias because of incomplete outcome data and selective outcome reporting. Details of the quality of bias assessment are reported in Table 2.

Effect of resveratrol on BP

The effect of resveratrol on BP was reported in 19 treatment arms. Resveratrol intervention did not significantly affect neither SBP [*SBP*: WMD: -2.5 95% CI:(-5.5, 0.6) mmHg; p=0.116; I^2=62.1%] nor DBP [*DBP*= WMD: -0.5 95% CI:(-2.2, 1.3) mmHg; p=0.613; I^2=50.8] nor MAP [*MAP*= WMD: -1.3 95% CI:(-2.8, 0.1) mmHg; p=0.070; I^2=39.5%] nor PP [*PP*= WMD: -0.9 95% CI:(-3.1, 1.4) mmHg; p=0.449; I^2=19.2%] (Figure 2). These results were robust in the leave-one-out sensitivity analysis (Figure 3).

When the studies were categorized according to resveratrol administered dose, there was a comparable DBP-lowering resveratrol effect between the subsets of studies with <300 mg/day and ≥300 mg/day (Table 3). Moreover, changes in mean SBP, MAP and PP were comparable in subsets of trials with and without diabetes as inclusion criterion (Table 3).

Additional analysis

Significant WMDs were detected in subsets of studies categorized according to resveratrol daily dosage (< or ≥300 mg/day) and presence of diabetes or NAFLD as inclusion criteria (Table 4). With respect to treatment duration (< or ≥3 months), no significant change in BP was observed between subsets of trials lasting less than 3 months or more (Table 4).

Meta-regression analysis

Meta-regression analysis was conducted to evaluate the association between changes in BP with either resveratrol daily dosage and BMI at baseline. Considering diabetes, results revealed a positive association between SBP-lowering resveratrol activity (slope: 1.99; 95% CI: 0.05, 3.93; two-tailed p= 0.04) and BMI at baseline, while no association was detected neither between baseline BMI and MAP-lowering resveratrol activity (slope: 1.35; 95% CI: −0.22, 2.91; two-tailed p= 0.09) nor between baseline BMI and PP-lowering resveratrol activity (slope: 1.03; 95% CI: −1.33, 3.39; two-tailed p= 0.39) (Figure 4). Resveratrol daily dosage was not associated neither with SBP- (slope: −0.002; 95% CI: −0.01, 0.01; two-tailed p= 0.73) nor MAP- (slope: −0.001; 95% CI: −0.01, 0.01; two-tailed p= 0.84) nor PP- (slope: −0.003; 95% CI: −0.02, 0.01; two-tailed p= 0.68) lowering effects (Figure 5).

In the subset of studies characterized by the presence of NAFLD as inclusion criterion, meta-regression analysis did not reveal any association between DBP-lowering resveratrol activity and BMI at baseline (slope: −0.31; 95% CI: −1.54, 0.91; two-tailed p= 0.62) or resveratrol daily dosage (slope: 0.001; 95% CI: −0.002, 0.004; two-tailed p= 0.49) (Figure 6).

Publication biases

The funnel plots of standard error by effect size (WMD) were asymmetric (Figure 7), suggesting potential publication biases in the meta-analysis of resveratrol effect on all the considered hemodynamic parameters. The presence of publication biases was confirmed by Egger's linear regression only for PP (*SBP*:

Table 2. Quality of bias assessment of the included studies according to Cochrane guidelines.

AUTHOR	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE OUTCOME REPORTING	OTHER POTENTIAL THREATS TO VALIDITY
Kjær, TN (2017)	L	L	L	L	L	U
Imamura, H (2017)	L	U	L	L	L	L
Heebøll, S (2016)	L	L	L	L	L	L
Timmers, S (2016)	L	U	L	L	U	U
Chen, S (2015)	L	L	U	L	L	L
Faghihzadeh, F (2015)	L	U	L	L	L	H
Van der Made, SM (2015)	L	L	L	L	L	L
Anton, SD (2014)	L	L	L	L	L	L
Chachay, VS (2014)	L	U	U	L	L	L
Méndez-del Villar, M (2014)	L	L	L	L	L	L
Kumar, BJ (2013)	L	L	H	L	L	L
Tomé-Carneiro, J (2013)	L	U	U	L	L	U
Movahed, A (2013)	L	L	L	L	L	L
Wong, RHX (2013)	L	L	L	L	L	L
Bhatt, JK (2012)	L	L	H	L	L	L
Yoshino, J (2012)	L	U	U	L	U	U
Timmers, S (2011)	L	U	L	L	U	L

L= low risk of bias; H= high risk of bias; U= unclear risk of bias.

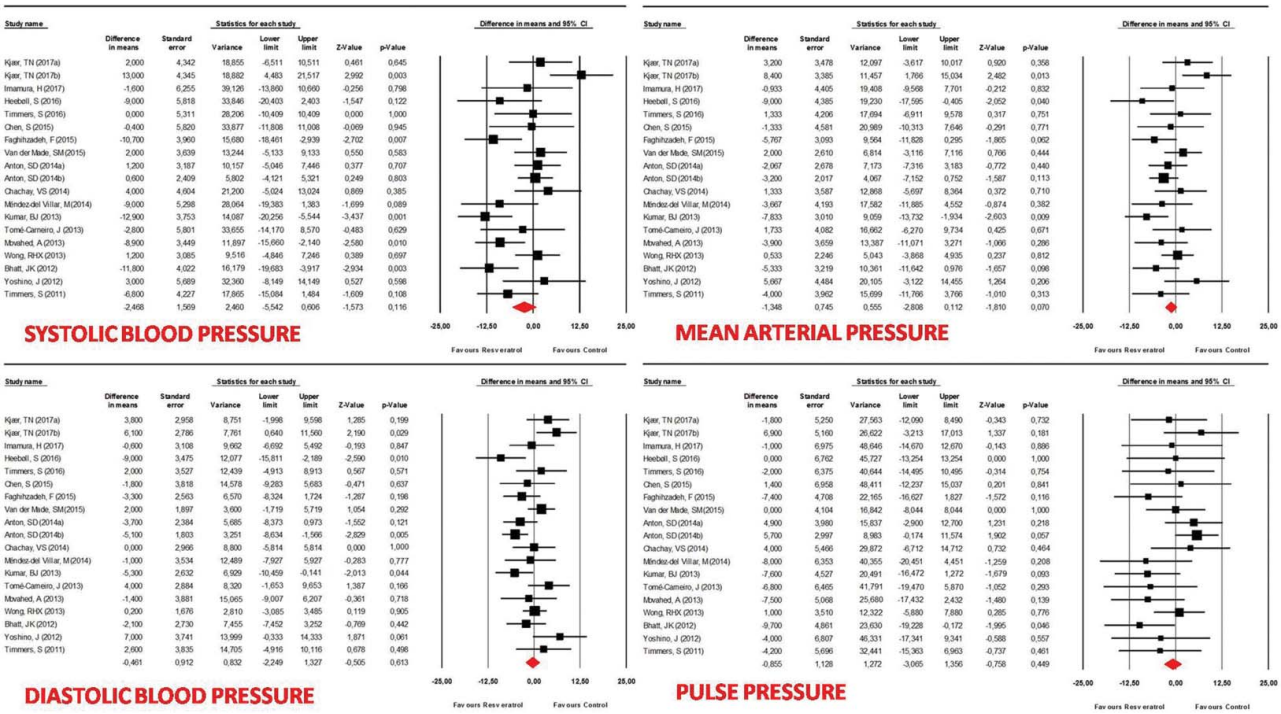

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the studies included in the meta-analysis.

intercept= −0.56; standard error= 1.47; 95% CI: −3.66, 2.54; t= 0.38, df= 17; two-tailed p= 0.71; *DBP*: intercept= 0.91; standard error= 1.25; 95% CI: −1.73, 3.56; t= 0.73, df= 17; two-tailed p= 0.48; *MAP*: intercept= 0.37; standard error= 1.22; 95% CI: −2.20, 2.95; t= 0.31, df= 17; two-tailed p= 0.76; *PP*: intercept= −1.93; standard error= 0.95; 95% CI: −3.93, 0.06; t= 2.04, df= 17; two-tailed p= 0.06). In contrast, Begg's rank correlation did not highlight any publication bias (*SBP*: Kendall's Tau with continuity correction= −0.08; z= 0.49; two-tailed p= 0.62; *DBP*: Kendall's Tau with continuity correction= 0.12; z= 0.70; two-tailed p= 0.48; *MAP*: Kendall's Tau with continuity correction= 0.07; z= 0.42; two-tailed p=

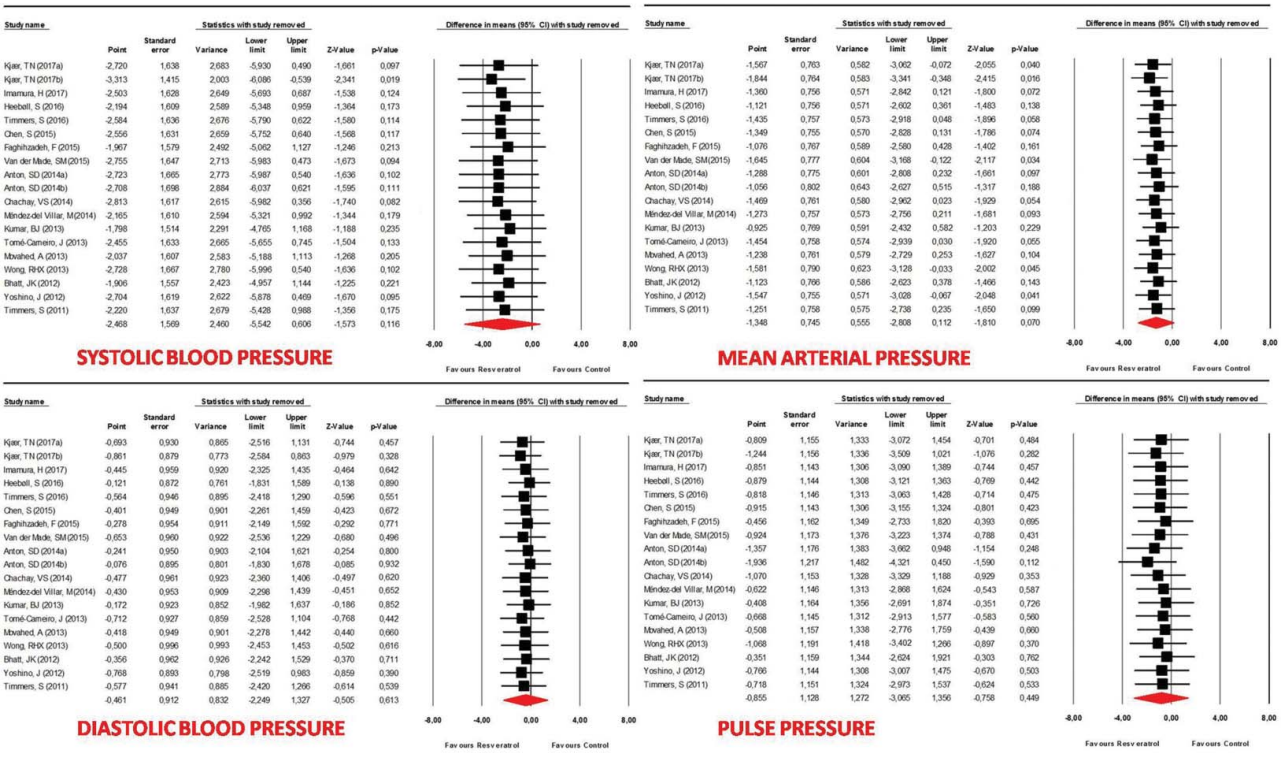

Figure 3. Plot showing leave-one-out sensitivity analysis.

Table 3. *P*-values referring to WMDs between subgroups of studies stratified by resveratrol daily dose (> or ≤ the median dosage), duration of treatment (> or ≤3 months), and presence of type 2 diabetes or non-alcoholic fatty liver disease as inclusion criteria.

	SISTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE	MEAN ARTERIAL PRESSURE	PULSE PRESSURE
Type 2 diabetes	0.006	0.276	0.043	0.007
NAFLD	0.616	0.087	0.182	0.833
Daily dosage> 300 mg	0.707	0.013	0.690	0.350
Treatment period> 3 months	0.783	0.389	0.271	0.355

CI= Confidence Interval; NAFLD= Non-Alcoholic Fatty Liver Disease; WMD= Weighted Mean Difference.

0.67; *PP*: Kendall's Tau with continuity correction= −0.05; *z*= 0.28; two-tailed *p*= 0.78) (Figure 7). Correction of the asymmetries using Duval & Tweedie "trim and fill" method yielded potentially missing studies for SBP [1 missing study on the right-side of the funnel plot, adjusted effect size= −1.82 (95% CI: −4.97, 1.34) mmHg], MAP [2 missing studies on the left-side of the funnel plot, adjusted effect size= −2.07 (95% CI: −3.48, −0.66) mmHg] and PP [7 missing studies on the right-side of the funnel plot, adjusted effect size= 2.31 (95% CI: 0.38, 4.23) mmHg] and no missing studies for DBP [adjusted effect size= −0.46 (95% CI: −2.25, 1.33) mmHg].

Tolerability and safety of resveratrol consumption

Resveratrol was fairly well-tolerated and no serious adverse events (AEs) occurred among most of the eligible trials. 4 RCTs (Chachay et al. 2014; Anton et al. 2014; Heebøll et al. 2016; Kjær et al. 2017; Ornstrup et al. 2014). reported mild com-

Table 4. . Subgroup analyses stratified by resveratrol daily dose (> or ≤ the median dosage), duration of treatment (> or ≤3 months), and presence of type 2 diabetes or non-alcoholic fatty liver disease as inclusion criteria.

		SISTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE	MEAN ARTERIAL PRESSURE	PULSE PRESSURE
Type 2 diabetes					
YES	Number of considered studies:	5	5	5	5
	WMD	−8.8 mmHg	−2 mmHg	−4.2 mmHg	−6.5 mmHg
	95% CI	(−12.5, −5) mmHg	(−4.7, 0.7) mmHg	(−7.4, −1.1) mmHg	(−11.2, −1.8) mmHg
	p-value	<0.001	0.152	0.008	0.006
	I^2	31.3%	0%	0%	0%
NO	Number of considered studies:	12	12	12	12
	WMD	−0.5 mmHg	−0.03 mmHg	−0.6 mmHg	0.8 mmHg
	95% CI	(−3.6, 2.6) mmHg	(−2.3, 2.2) mmHg	(−2.2, 1.1) mmHg	(−1.7, 3.3) mmHg
	p-value	0.754	0.982	0.508	0.547
	I^2	50.4%	59.8%	40.4%	2.9%
NAFLD					
YES	Number of considered studies:	4	4	4	4
	WMD	−4.2 mmHg	−3.3 mmHg	−3.7 mmHg	−1.4 mmHg
	95% CI	(−11.6, 3.3) mmHg	(−6.3, −0.3) mmHg	(−7.3, 0.04) mmHg	(−7, 4.2) mmHg
	p-value	0.271	0.034	0.052	0.623
	I^2	56.9%	26.5%	27.6%	0%
NO	Number of considered studies:	13	13	13	13
	WMD	−2.1 mmHg	0.2 mmHg	−0.9 mmHg	−0.8 mmHg
	95% CI	(−5.5, 1.4) mmHg	(−1.8, 2.2) mmHg	(−2.5, 0.7) mmHg	(−3.2, 1.7) mmHg
	p-value	0.239	0.825	0.257	0.539
	I^2	64.6%	51.8%	41.3%	28%
Daily dosage≥ 300 mg					
YES	Number of considered studies:	9	9	9	9
	WMD	−2.5 mmHg	−2.2 mmHg	−2.4 mmHg	0.1 mmHg
	95% CI	(−4.9, −0.04) mmHg	(−4, −0.5) mmHg	(−4.4, −0.4) mmHg	(−2.9, 3.2) mmHg
	p-value	0.047	0.012	0.021	0.933
	I^2	46.1%	45.3%	0%	31.7%
NO	Number of considered studies:	9	9	9	9
	WMD	−1.7 mmHg	0.8 mmHg	−0.2 mmHg	−2 mmHg
	95% CI	(−7.2, 3.8) mmHg	(−0.8, 2.5) mmHg	(−3.5, 3.2) mmHg	(−5.2, 1.3) mmHg
	p-value	0.541	0.328	0.924	0.230
	I^2	74%	42.6%	58%	2.9%
Treatment period≥ 3 months					
YES	Number of considered studies:	10	10	10	10
	WMD	−2.1 mmHg	−0.9 mmHg	−1.4 mmHg	−0.01 mmHg
	95% CI	(−6.4, 2.1) mmHg	(−3.7, 1.8) mmHg	(−4.3, 1.5) mmHg	(−2.9, 2.8) mmHg
	p-value	0.327	0.510	0.332	0.993
	I^2	65.9%	65.2%	53.7%	28.7%
NO	Number of considered studies:	7	7	7	7
	WMD	−3 mmHg	0.5 mmHg	−0.7 mmHg	−2.1 mmHg
	95% CI	(−7.6, −1.6) mmHg	(−1.3, 2.4) mmHg	(−3, 1.6) mmHg	(−5.7, 1.4) mmHg
	p-value	0.200	0.573	0.568	0.232
	I^2	59.7%	0%	0%	0%

CI= Confidence Interval; NAFLD= Non-Alcoholic Fatty Liver Disease; WMD= Weighted Mean Difference.

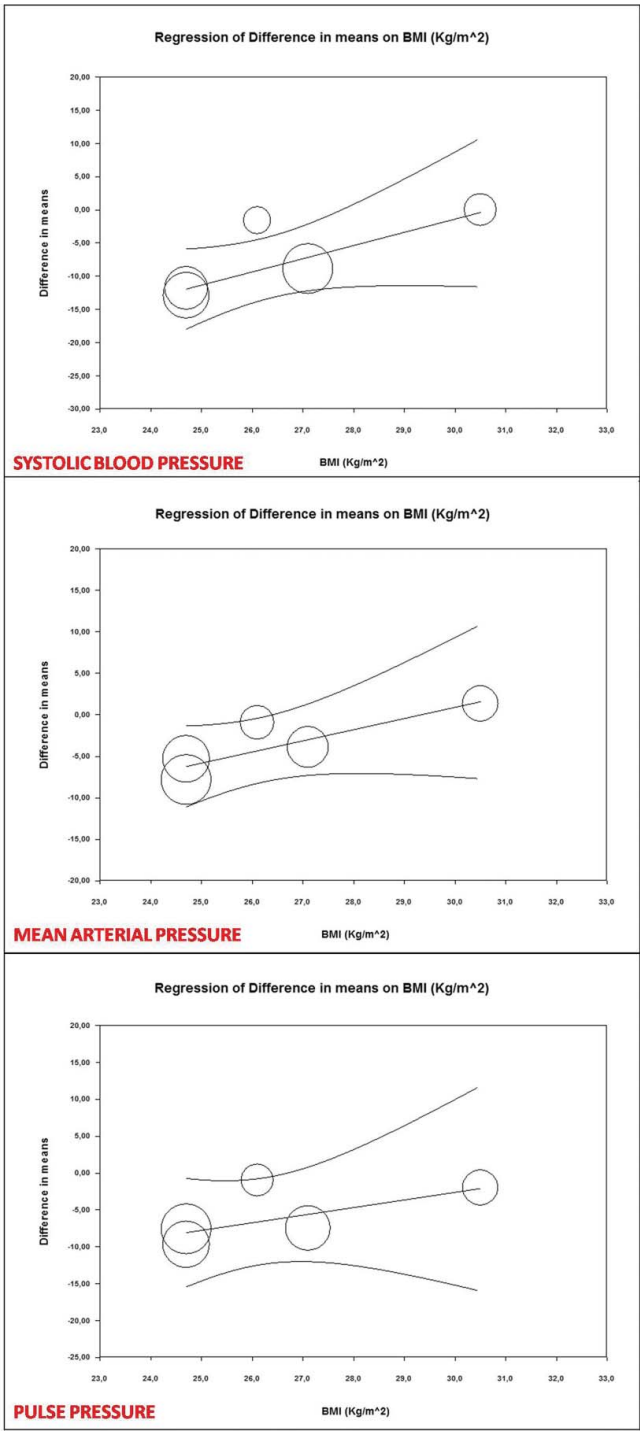

Figure 4. Meta-regression bubble plots of the association between mean changes in SBP, MAP and PP and mean baseline BMI in subset of trials with diabetes as inclusion criterion. The size of each circle is inversely proportional to the variance of change.

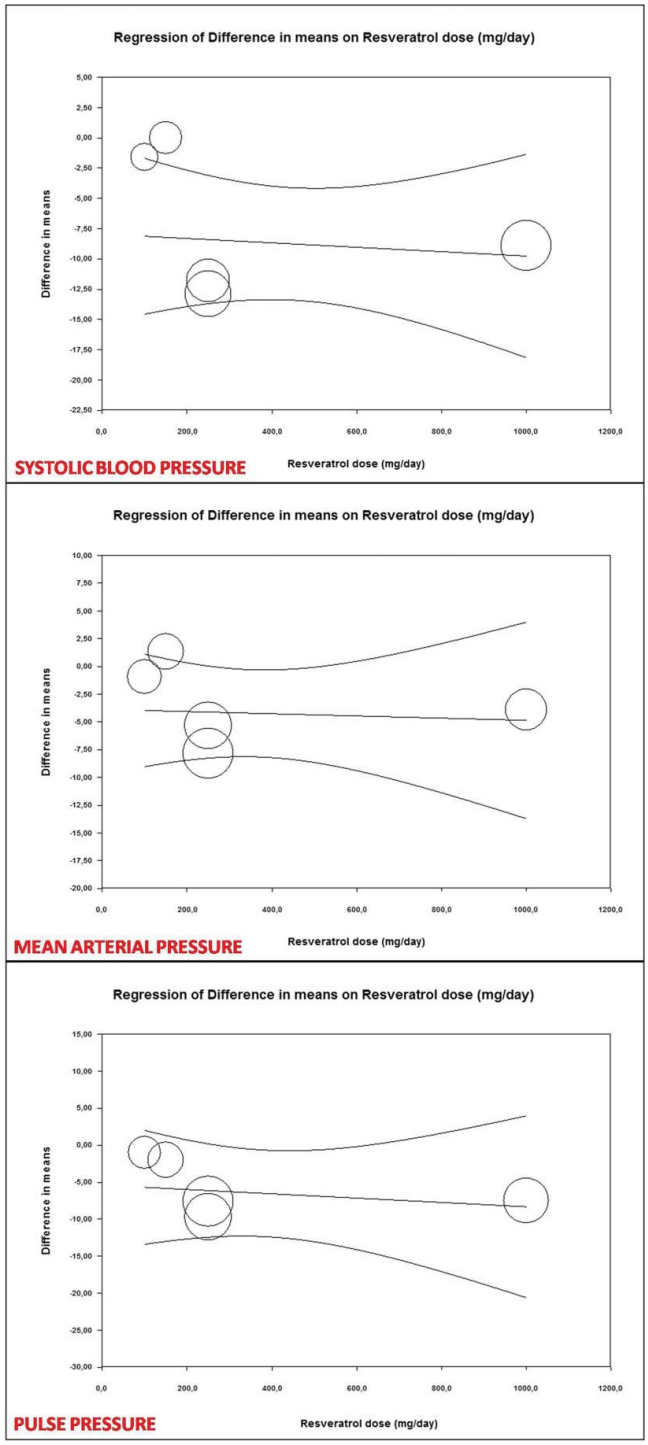

Figure 5. Meta-regression bubble plots of the association between mean changes in SBP, MAP and PP and resveratrol daily dose in subset of trials with diabetes as inclusion criterion. The size of each circle is inversely proportional to the variance of change.

plaints of the gastrointestinal tract, which were described as an increased frequency of bowel movements and loose stools, especially occurring during the first 3–4 weeks of treatment. (Chachay et al. 2014; Ornstrup et al. 2014). One month after randomization, one patient receiving resveratrol at high dose (1000 mg daily) developed a transient itchy skin rash which resolved 14 days after having stop taking it. (Ornstrup et al. 2014). Other AEs were rare and unlikely related with resveratrol treatment. A serious case of febrile leukopenia and thrombocytopenia after 10 days of supplementation was reported in one study. (Heebøll et al. 2016). The trial conducted by Anton et al. found that participants receiving the higher dose of resveratrol (1000 mg/day) had slightly lower haemoglobin levels, lower mean corpuscular haemoglobin concentration levels and higher alkaline phosphatase levels than baseline. (Anton et al. 2014). However, lower doses of resveratrol did

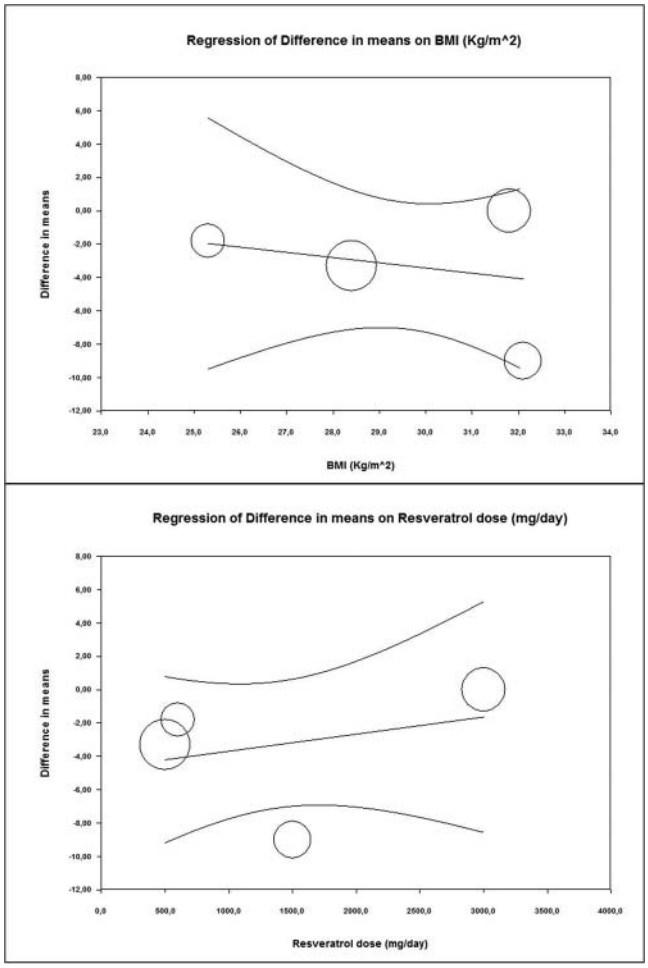

Figure 6. Meta-regression bubble plots of the association between mean changes in SBP and mean baseline BMI (above) and resveratrol daily dosage (below) in subset of trials with presence of NAFLD as inclusion criterion. The size of each circle is inversely proportional to the variance of change.

not significantly result in similar alterations of these haematochemical parameters, as previously found by Yoshino et al. (Yoshino et al. 2012)

Discussion

At the best of our knowledge, the current systematic review and meta-analysis is the first one to comprehensively analyse evidences from RCTs on the efficacy of supplementation with resveratrol on BP. In particular, a previous meta-analysis of Liu et al. (Liu et al. 2015). included only six trials for a total of 247 subjects, while we included 17 trials with 681 subjects. The one of Sahbekar et al. (Sahebkar et al. 2015). was more comprehensive compared with the one of Liu et al. but focused on trials reporting the effect of resveratrol on hsCRP, thus excluding the ones reporting data on BP but without hsCRP, otherwise included in our meta-analysis. Moreover, both meta-analyses meta-analysed data on SBP and DBP, but not on MAP and PP, as we did. Indeed, the present analysis provides several items to be discussed.

First, it demonstrates favourable, though not significant, BP lowering effects of resveratrol on SBP, MAP and PP, whilst no relevant effect was observed with regard to DBP. This may have at least, in part, potentially important clinical implications, since recent sets of International guidelines have strengthened the need of achieving the recommended therapeutic BP targets, mostly for SBP ($\leq$140 mmHg) in order to reduce hypertension-related morbidity and mortality (Antza et al. 2017). Despite the availability of different pharmacological drugs and molecules, observational studies have showed persistently low rates of BP control, mostly in Western countries, thus highlighting the need of using other and integrated approach to reduce BP levels and achieve effective BP control. These considerations may promote a more extended use of resveratrol in hypertensive patients for ameliorating the effectiveness of a given antihypertensive strategy.

Secondly, our data show a more pronounced BP lowering effect in those patients at high cardiovascular risk, such as those with diabetes and metabolic abnormalities or obesity. In view of the high prevalence of these conditions in general hypertensive populations and in view of the detrimental role in enhancing the risk of coronary events and stroke in diabetic patients with high BP levels (Newmann et al. 2017), our findings may suggest a potential way to improve BP control rates and reduce the risk of hypertension-related complications in hypertensive patients with diabetes. Moreover, the insulin-sensitivity improving effect of resveratrol, that contribute to its blood pressure improving effect, could also have a positive impact on diabetes control (Zhu et al. 2017).

Thirdly, considerations on tolerability of the resveratrol administration may also have important clinical implications, since it is well known that hypertension is an asymptomatic clinical condition in which adherence and persistence on prescribed antihypertensive medications is relatively low after 6–12 months (Burnier 2017). Discontinuation rates may be even higher in presence of adverse events or drug reactions, (Burnier 2017). so that the lack of any clinical relevant side effects with resveratrol, also when used at high or very high dosages, can be of potential clinical usefulness.

Finally, the clinical effectiveness of resveratrol-based therapy in lowering systolic BP levels has been observed across a wide spectrum of age classes included in the selected RCTs. This aspect should be taken in consideration, mostly when treating elderly or very elderly patients with isolated systolic hypertension, which is commonly observed in the clinical practice, especially in view of the recently increased average life expectancy, worldwide. (Rochlani et al. 2017). Resveratrol might be used both in fit elderly patients for improving stricter BP control, as recommended by current guidelines, as well as in frail elderly, in whom conservative BP control has been proposed for the frequent concomitant presence of additional clinical conditions and comorbidities.

It is then noteworthy that similar effects on BP have been observed also with other natural antioxidant compounds as quercetin (Serban et al. 2016): it would be interesting in the next future to investigate if the contemporary use of resveratrol and other similar natural molecules could further improve its effect on BP.

Potential limitations

Certainly, our meta-analysis has some limitations. Firstly, among the eligible RCTs was found a moderate and marginally

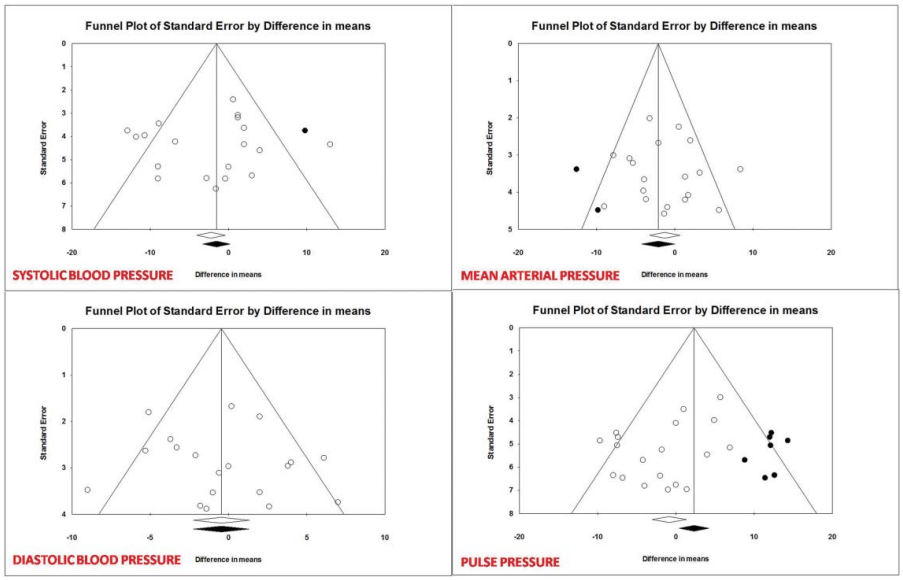

Figure 7. Funnel plot detailing publication biases in the studies included in the meta-analysis.

significant heterogeneity which may be due to differences in the intervention duration, sample size and daily dose of resveratrol. For this reason, we performed the random effects analysis, which is a suitable method in the presence of heterogeneity studies. Remarkably, the significance of estimated pooled effect size on SBP was not biased by any single study overall.

Then, since no dose-escalation study has yet been carried out to determine the optimal dose of resveratrol to improve DBP, it is unclear if the doses used in the included trials are sufficient to elicit a sizable effect in DBP in clinical setting, even if they are clearly enough to improve SBP. Moreover, the resveratrol bioavailability after oral administration is usually poor in humans, because of the massive biotransformation phenomena occurring in the liver microsomes and intestine and the relative metabolites are much less active or completely inactive (Walle et al. 2004; Walle 2011). On the other side, the development of new drug delivery systems intended to enhance its bioavailability could dramatically increase its plasma level and, presumably, its efficacy (Amri et al. 2012; Sergides et al. 2016). However, since no direct comparison between different resveratrol formulation has been yet carried out, it was impossible to carry out a specific subanalysis to understand if these approach are more effective than the use of standard resveratrol.

Another potential limitation is the methodology applied for measuring BP levels in the selected RCTs, which was mostly based on the use of mercury sphygmomanometer. Since the accuracy of this method in detecting systolic/diastolic BP levels is lower than other oscillometric devices, further clinical studies based on proper assessment of clinic BP levels are needed to support the main findings of our analysis.

Conclusions

In conclusion, the favourable effect of resveratrol emerging from the current meta-analysis suggests the possible use of this nutraceutical as active compound in order to promote cardiovascular health, mostly when used in high dose and in diabetic patients. However, further well-designed trials are needed to confirm whether longer-term resveratrol supplementation might significantly improve BP by decreasing DBP other than SBP.

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References

Anton, S. D., C. Embry, M. Marsiske, X. Lu, H. Doss, C. Leeuwenburgh, and T. M. Manini. 2014. Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. *Experimental Gerontology* 57:181–7.

Antza, C., I. Doundoulakis, S. Stabouli, and V. Kotsis. 2017. Comparison among recommendations for the management of arterial hypertension issued by last US, Canadian, British and European Guidelines. *High Blood Pressure & Cardiovascular Prevention* 2017 Nov 1. doi: 10.1007/s40292-017-0236-x. [Epub ahead of print]

Amri, A., J. C. Chaumeil, S. Sfar, and C. Charrueau. 2012. Administration of resveratrol: What formulation solutions to bioavailability limitations? *Journal of Controlled Release* 158:182–93;

Bhatt, J. K., S. Thomas, and M. J. Nanjan. 2012. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutrition Research* 32:537–41.

Borenstein, M., L. Hedges, J. Higgins, and H. Rothstein. 2005. Comprehensive meta-analysis version 3. Englewood, NJ. *Biostatistics* 2005:104.

Borghi, C., and A. F. Cicero. 2017. Nutraceuticals with a clinically detectable blood pressure-lowering effect: A review of available randomized clinical trials and their meta-analyses. *British Journal of Clinical Pharmacology* 83:163–171.

Burnier, M. 2017. Drug adherence in hypertension. *Pharmacological Research* 125:142–149.

Chachay, V. S., G. A. Macdonald, J. H. Martin, J. P. Whitehead, T. M. O'Moore-Sullivan, P. Lee, M. Franklin, K. Klein, P. J. Taylor,

M. Ferguson, et al. 2014. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. *Clinical Gastroenterology and Hepatology* 12:2092–103.e1–6.

Chen, S., X. Zhao, L. Ran, J. Wan, X. Wang, Y. Qin, F. Shu, Y. Gao, L. Yuan, Q. Zhang, and M. Mi. 2015. Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Digestive and Liver Disease* 47:226–32.

Cicero, A. F., F. Fogacci, and A. Colletti. 2017a. Food and plant bioactives for reducing cardiometabolic disease risk: an evidence based approach. *Food and Function* 8:2076–2088.

Cicero, A. F., A. Colletti, G. Bajraktari, O. Descamps, D. M. Djuric, M. Ezhov, Z. Fras, N. Katsiki, M. Langlois, G. Latkovskis, et al. 2017b. Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Archives of Medical Science* 13: 965–1005.

Cicero, A. F., and A. Colletti. 2015. Nutraceuticals and blood pressure control: results from clinical trials and meta-analyses. *High Blood Pressure and Cardiovascular Prevention* 22:203–13.

Duval, S., and R. Tweedie. 2000. Trim and fill: a simple funnel−plot–based method of testing and adjusting for publication bias in meta−analysis. *Biometrics* 56:455–63.

Faghihzadeh, F., P. Adibi, and A. Hekmatdoost. 2015. The effects of resveratrol supplementation on cardiovascular risk factors in patients with non-alcoholic fatty liver disease: a randomised, double-blind, placebo-controlled study. *British Journal of Nutrition* 114:796–803.

Fogacci, F., A. F. G. Cicero, G. Derosa, M. Rizzo, M. Veronesi, and C. Borghi. 2017. Effect of pistachio on brachial artery diameter and flow-mediated dilatation: a systematic review and meta-analysis of randomized, controlled-feeding clinical studies. *Critical Reviews in Food Science and Nutrition* 30:0.

Follmann, D., P. Elliott, I. Suh, and J. Cutler. 1992. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 45:769–73.

Heebøll, S., M. Kreuzfeldt, S. Hamilton-Dutoit, M. Kjær Poulsen, H. Stødkilde-Jørgensen, H. J. Møller, N. Jessen, K. Thorsen, Y. Kristina Hellberg, S. Bønløkke Pedersen, et al. 2016. Placebo-controlled, randomised clinical trial: high-dose resveratrol treatment for non-alcoholic fatty liver disease. *Scandinavian Journal of Gastroenterology* 51:456–64.

Higgins, J., S. Green. 2010. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0. 2. 2009*. Chichester, UK, John Wiley and Sons Ltd.

Hozo, S. P., B. Djulbegovic, and I. Hozo. 2005. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 5:13.

Imamura, H., T. Yamaguchi, D. Nagayama, A. Saiki, K. Shirai, and I. Tatsuno. 2017. Resveratrol ameliorates arterial stiffness assessed by cardio-ankle vascular index in patients with Type 2 diabetes mellitus. *International Heart Journal* 58:577–583.

Kumar, B. J., and N. M. Joghee. 2013. Resveratrol supplementation in patients with type 2 diabetes mellitus: a prospective, open label, randomized controlled trial. *International Research Journal of Pharmacy* 4:245–249.

Kjær, T. N., M. J. Ornstrup, M. M. Poulsen, H. Stødkilde-Jørgensen, N. Jessen, J. O. L. Jørgensen, B. Richelsen, and S. B. Pedersen. 2017. No beneficial effects of resveratrol on the metabolic syndrome: a randomized placebo-controlled clinical trial. *The Journal of Clinical Endocrinology and Metabolism* 102:1642–1651.

Li, H., N. Xia, and U. Förstermann. 2012. Cardiovascular effects and molecular targets of resveratrol. *Nitric oxide* 26:102–10.

Liu, Y., W. Ma, P. Zhang, S. He, and D. Huang. 2015. Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials. *Clinical Nutrition* 34: 27–34.

Méndez-del Villar, M., M. González-Ortiz, E. Martínez-Abundis, K. G. Pérez-Rubio, and R. Lizárraga-Valdez. 2014. Effect of resveratrol administration on metabolic syndrome, insulin sensitivity, and insulin secretion. *Metabolic Syndrome and Related Disorders* 12:497–501.

Moher, D., A. Liberati, J. Tetzlaff, and D. G. Altman, P. R. I. S. M. A. Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *The BMJ* 339:b2535.

Movahed, A., I. Nabipour, X. Lieben Louis, S. J. Thandapilly, L. Yu, M. Kalantarhormozi, S. J. Rekabpour, and T. Netticadan. 2013. Antihyperglycemic effects of short term resveratrol supplementation in type 2 diabetic patients. *Evidence-Based Complementary and Alternative Medicine* 2013:851267.

Newman, J. D., A. Z. Schwartzbard, H. S. Weintraub, I. J. Goldberg, and J. S. Berger. 2017. Primary prevention of cardiovascular disease in diabetes mellitus. *Journal of the American College of Cardiology* 70:883–893.

Ornstrup, M. J., T. Harsløf, T. N. Kjær, B. L. Langdahl, and S. B. Pedersen. 2014. Resveratrol increases bone mineral density and bone alkaline phosphatase in obese men: a randomized placebo-controlled trial. *The Journal of Clinical Endocrinology and Metabolism* 99:4720–9.

Rochlani, Y., M. H. Khan, and W. S. Aronow. 2017. Managing hypertension in patients aged 75 years and older. *Current Hypertension Reports* 19:88.

Sahebkar, A., M. Pirro, M. Banach, D. P. Mikhailidis, S. L. Atkin, and A. F. G. Cicero. 2017. Lipid-lowering activity of artichoke extracts: A systematic review and meta-analysis. *Critical Reviews in Food Science and Nutrition* 13:1–8.

Sahebkar, A., Ž. Reiner, L. E. Simental-Mendía, G. Ferretti, and A. F. Cicero. 2016. Effect of extended-release niacin on plasma lipoprotein(a) levels: A systematic review and meta-analysis of randomized placebo-controlled trials. *Metabolism* 65:1664–1678.

Sahebkar, A., C. Serban, S. Ursoniu, N. D. Wong, P. Muntner, I. M. Graham, D. P. Mikhailidis, M. Rizzo, J. Rysz, L. S. Sperling, G. Y. Lip, and M. Banach, Lipid and Blood Pressure Meta-analysis Collaboration Group. 2015. Lack of efficacy of resveratrol on C-reactive protein and selected cardiovascular risk factors–Results from a systematic review and meta-analysis of randomized controlled trials. *International Journal of Cardiology* 189: 47–55.

Serban, M. C., A. Sahebkar, A. Zanchetti, D. P. Mikhailidis, G. Howard, D. Antal, F. Andrica, A. Ahmed, W. S. Aronow, P. Muntner, G. Y. Lip, I. Graham, N. Wong, J. Rysz, and M. Banach, Lipid and Blood Pressure Meta−analysis Collaboration (LBPMC) Group. 2016. Effects of quercetin on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Journal of the American Heart Association* 5: pii: e002713.

Sergides, C., M. Chirilă, L. Silvestro, D. Pitta, and A. Pittas. 2016. Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers. *Experimental and Therapeutic Medicine* 11:164–170.

Sirtori, C. R., A. Arnoldi, and A. F. Cicero. 2015. Nutraceuticals for blood pressure control. *Annals of Medicine* 47:447–56.

Sosnowska, B., P. Penson, and M. Banach. The role of nutraceuticals in the prevention of cardiovascular disease. 2017. *Cardiovascular Diagnosis and Therapy* 7(Suppl 1):S21–S31.

Tomé-Carneiro, J., M. Gonzálvez, M. Larrosa, M. J. Yáñez-Gascón, F. J. García-Almagro, J. A. Ruiz-Ros, F. A. Tomás-Barberán, M. T. García-Conesa, and J. C. Espín. 2013. Grape resveratrol increases serum adiponectin and downregulates inflammatory genes in peripheral blood mononuclear cells: a triple-blind, placebo-controlled, one-year clinical trial in patients with stable coronary artery disease. *Cardiovascular Drugs and Therapy* 27:37–48.

Timmers, S., M. de Ligt, E. Phielix, T. van de Weijer, J. Hansen, E. Moonen-Kornips, G. Schaart, I. Kunz, M. K. Hesselink, V. B. Schrauwen-Hinderling, et al. 2016. Resveratrol as add-on therapy in subjects with well-controlled type 2 diabetes: a randomized controlled trial. *Diabetes Care* 39:2211–2217.

Timmers, S., E. Konings, L. Bilet, R. H. Houtkooper, T. van de Weijer, G. H. Goossens, J. Hoeks, S. van der Krieken, D. Ryu, S. Kersten, et al. 2011. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metabolism* 14:612–22.

van der Made, S. M., J. Plat, and R. P. Mensink. 2015. 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* 10:e0118393.

Walle, T., F. Hsieh, M. H. DeLegge, J. E. Oatis Jr, and U. K. Walle. 2004. High absorption but very low bioavailability of oral

resveratrol in humans. *Drug Metabolism and Disposition* 32:1377–82. Epub 2004 Aug 27;

Walle, T. 2011. Bioavailability of resveratrol. *Annals of the New York Academy of Sciences* 2011;1215:9–15.

Wong, R. H., N. M. Berry, A. M. Coates, J. D. Buckley, J. Bryan, I. Kunz, and P. R. Howe. 2013. Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults. *Journal of Hypertension* 31:1819–27.

Yoshino, J., C. Conte, L. Fontana, B. Mittendorfer, S. Imai, K. B. Schechtman, C. Gu, I. Kunz, F. Rossi Fanelli, B. W. Patterson, et al. 2012. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. *Cell Metabolism* 16:658–64.

Zhu, X., C. Wu, S. Qiu, X. Yuan, and L. Li. 2017. Effects of resveratrol on glucose control and insulin sensitivity in subjects with type 2 diabetes: systematic review and meta-analysis. *Nutrition and Metabolism* 14:60.