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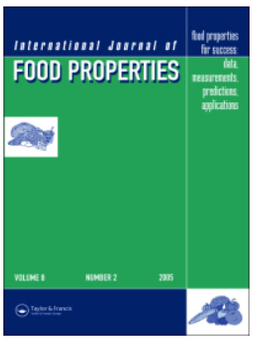

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Effect of grape products on blood pressure: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Previous studies have suggested that grape and its products may possess blood pressure (BP)-lowering properties. Due to inconsistencies in results, we aimed to systematically examine the effect of grape products on BP by conducting a meta-analysis of randomized controlled trials (RCTs). PubMed, Scopus, Web of Science (ISI), and Cochrane Library databases were comprehensively searched until March 2020. Human clinical trials which reported the effect of grape products supplementation on systolic BP (SBP) and diastolic BP (DBP) were included. Data were pooled using a random-effects model and expressed as a weighted mean difference (WMD) with a 95% confidence interval (CI). Twenty-eight studies comprising a total of 1344 subjects were included in our meta-analysis. The overall outcome of the meta-analysis indicates that grape products consumption can significantly reduce SBP (WMD: −3.40 mmHg, 95% CI: −6.55, −0.24, $p = .03$, $I^2 = 93.4\%$) and DBP (WMD: −1.69 mmHg, 95% CI: −3.12, −0.27, $p = .01$, $I^2 = 80.4\%$). This meta-analysis found a moderate and statistically significant reduction for either SBP or DBP with grape products compared with controls. Additional high-quality studies are needed to further evaluate the causal conclusions.

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Grape products; Blood pressure; Hypertension; Systematic review; Meta-analysi

Introduction

Hypertension (HTN), a medical condition when systolic/diastolic BP reaches more than 140/90 mmHg, is one of the primary risk factors for several health problems such as cardiovascular diseases (CVDs), renal failure, and sudden death, affecting approximately one billion individuals worldwide.[1] Using medications and lifestyle changes including dietary supplements, low sodium intake, and exercise are common treatments for HTN.[2] However, there has been a surge of interest to find new agents with BP-modifying properties to be used as adjuncts to low dose antihypertensive drugs in patients who cannot tolerate higher doses.

Recent studies have reported that oxidative stress, the state of overproduction of reactive oxygen species (ROS), can play a crucial role in developing HTN.[3–5] Increasing number of evidences suggest that improvement in systemic antioxidant activity has beneficial effect on reversing deleterious changes in arteries' endothelium and BP.[6,7] Plant polyphenolic compounds are of powerful

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antioxidants derived from vegetables and fruits.[8–12] It has been suggested that a dietary pattern rich in plant polyphenols plays a positive role in prevention or management of HTN through different mechanism such as vasodilation and suppressing the ROS production.[7,13–15]

Grape products are listed as one of the excellent sources of plant polyphenolic antioxidant compounds especially for their proanthocynidins content.[16] There are several studies demonstrating the protective effect of grape products on abnormal metabolic measurements including BP.[17,18] Proanthocyanidins, anthocyanins, flavonols, flavanols, resveratrol, and phenolic acids are phenolic compounds in grape products .[19] Angiotensin-converting enzyme (ACE), is a zinc metalloenzyme; because ACE is a metalloenzyme, phenolic compounds bond with its zinc ion and therefore decrease its activity.[2] Altogether, the hypotensive effect of grape products may be related to the level of prostacyclin and reduction of ACE activity.

A previous meta-analysis of 16 randomized controlled trials (RCTs) by Zhang et al.[20] showed that grape seed extract (GSE) has some benefits in reducing BP especially in younger obese people and patients with metabolic disorders. However that study evaluated only GSE in essence. Due to release of more recent studies and lack of a strong conclusion on the effective dose and type of grape products for improvement in BP control, we aimed to perform this systematic review and meta-analysis to evaluate the effect of grape products on BP.

Methods

This systematic review and meta-analysis was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[21] The Population (aged >18 years old), Intervention (grape and grape products supplementation), Comparison (matched control group), Outcome (blood pressure) (PICOS) model was used and included SBP and DBP measures that were conducted as randomized controlled trials (RCT).

Literature search

Two authors (O.A. and E.Gh.) independently performed a comprehensive literature search with PubMed, Scopus, Web of Science (ISI), and Cochrane Library databases from inception to March 2020. The following keywords were used in all fields as search strategy: ("Grape Seed Extract" OR "Grape seed" OR "Grape juice" OR "Proanthocyanidin" OR "Proanthocyanidins" OR "Grape" OR "Grapes") AND ("Blood pressure" OR "Systolic blood pressure" OR "Diastolic blood pressure" OR "Hypertension") AND ("Intervention" OR "Intervention Study" OR "Intervention Studies" OR "Controlled trial" OR "Randomized" OR "Random" OR "Randomly" OR "Placebo" OR "Clinical trial" OR "Trial" OR "Randomized" controlled trial" OR "Randomized clinical trial" OR "RCT" OR "Blinded" OR "Double blind" OR "Cross-Over Studies" OR "Cross-Over" OR "Cross-Over Study" OR "Parallel" OR "Parallel study" OR "Parallel trial").The search results were limited to English-language publications. In addition, references of selected studies and relevant review articles were screened to identify eligible trials that were not found through the database searches.

Study selection

After removing the duplicates, remained manuscripts were reviewed based on title, abstract, or full text by two authors (O.A. and E.Gh) separately. Finally, studies were included if they met all of the following inclusion criteria: a) Study design: RCTs with either a parallel or crossover design; b) Population: adult participants (aged ≥18 years) (healthy or otherwise); c) Intervention: investigated grape products as an intervention; d) Comparators: placebo or a comparison group were used; and e) Outcomes: including systolic BP (SBP) and diastolic BP (DBP). Studies were excluded if they were animal, in vitro or short-term intervention (less than 1 week). We also excluded studies that had a co-intervention of other supplementations or were duplicate reports from the same trial. During the study

selection process, disagreements between researchers were resolved by face-to-face discussion to achieve consensus.

Data extraction

We recorded study characteristics as follows: first author's last name, publication year; design details, including whether parallel or crossover; study duration; number of participants; daily dose of intervention. Participant characteristics including health status, mean age, mean body mass index (BMI) and baseline SBP and DBP were also recorded. When aforesaid characteristics were not reported in available publications, we contacted the corresponding author to acquire the necessary data. Two of the authors (O.A. and E.Gh) independently performed the data extraction, and disagreements resolved by discussion.

Risk for bias assessment

Two reviewers (O.A. and E.Gh.) independently assessed the quality of each study according to the Cochrane risk of bias.[22] This scale involves of 7 criteria to assess the risk of the bias which are as follows: random sequence, generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Bias is assessed as a judgment (high, low, or unclear) for individual elements, which are interpreted as high risk, low risk and unknown risk, respectively.

Statistical analyses

Data were analyzed using Stata version 12.0 software (StataCorp, College Station, Texas, USA). Blood pressure was measured in mmHg. The effect size of each study was calculated from mean and standard deviation (SD) of the outcomes before and after the intervention and presented as weighted mean difference (WMD) with 95% confidence intervals (CI). If only SD for the baseline and final values was provided, SD for the net changes was assigned based on the Follmann method[23] using a correlation coefficient of 0.5. Where standard error (SE) was only reported, SD was estimated as follows: SD = SE × sqrt (n), where n is the number of participants in each group. Due to the fact that selected RCTs were carried out in different settings, the random-effects model was employed to calculate the overall effect from effect sizes. Heterogeneity was examined using the I-squared (I^2) index.[24] An I^2 value >50% was considered to indicate substantial heterogeneity between trials.[25] To explore the source of heterogeneity, as well as the possible influences of study designs and participant characteristics on combined effect sizes, we further conducted pre-specified subgroup analyses stratified by trial duration, baseline BMI of subjects, type of intervention, health status, and baseline SBP. Sensitivity analysis was also performed to explore the extent to which inferences might depend on a particular trial using the leave-one-out method. Publication bias was assessed by visual inspection of funnel plots and formally complemented by Begg's test, where $P < .10$ was considered evidence of small study effects. All tests were two-sided. P values <0.05 were considered statistically significant, except where otherwise specified.

Results

Study selection

From 1198 provided articles in initial search, 323 duplicated studies excluded. After screening of title and abstract 843 unrelated studies discarded because of primary evaluation of inclusion criteria: unrelated title or abstract (n = 740), animal studies (n = 63) and review studies (n = 40). The remaining 32 studies were screened based on full text for eligibility, 4 studies were excluded due to lack of BP

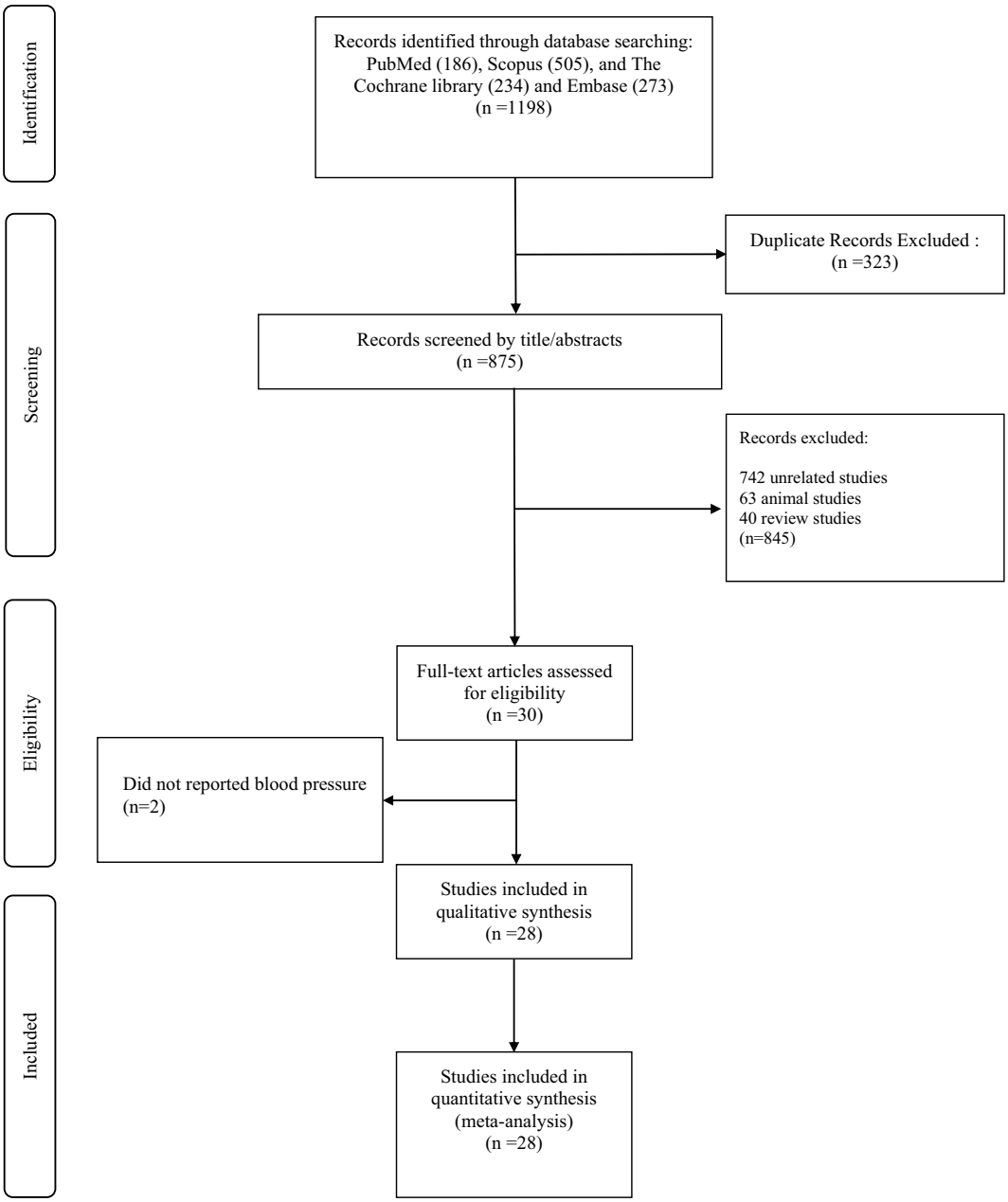


Figure 1. PRISMA flow diagram of study selection process.

reporting.[26,27] Ultimately, 28 studies with 1344 participants were included. The PRISMA flow diagram of search process is illustrated in Figure 1.

Study characteristics

The characteristics of studies included are outlined in Table 1. Included studies were published between 2004 and 2017. The follow-up period ranged from 2[28] to 52[29] weeks. The sample size of

Table 1. Characteristic of included studies in meta-analysis.

Author	Publication years	Country	Study Design	Participant	Sample (Sex)	Trial Duration (Week)
PM Clifton	2004	Australia	crossover	healthy adults	36. 24 M, 12 F	4
YK Park	2004	South Korea	Parallel	hypertensive	40; 40 M	8
AS Hansen (A)	2005	Denmark	Parallel	cardiovascular disease	35: 16 M, 19 F	4
AS Hansen (B)	2005	Denmark	Parallel	cardiovascular disease	33: 15 M, 18 F	4
AE Banini	2006	USA	Parallel	healthy adults	23: 11 M, 12 F	4
A Sano (A)	2007	Japan	parallel	healthy adults	41: 20 M, 21 F	12
A Sano (B)	2007	Japan	parallel	healthy adults	40: 19 M, 21 F	12
JP Jiménez	2008	Spain	Parallel	healthy adults	43: 16 M, 27 F	16
B Sivaprakasapillai (A)	2009	USA	parallel	Metabolic Syndrome	18: 7 M, 11 F	4
B Sivaprakasapillai (B)	2009	USA	parallel	Metabolic Syndrome	18: 7 M, 11 F	4
MM Dohadwala	2010	USA	crossover	stage 1 hypertension	64: 44 M, 20 F	8
PB Mellen	2010	USA	crossover	Cardiovascular Disease	50: 25 M, 25 F	4
P-Gargari	2011	Iran	parallel	Type 2 Diabetic	48	8.6
R Krikorian	2012	USA	Parallel	healthy adults	21: 11 M, 10 F	16
M. Robinson	2012	USA	Parallel	Pre-Hypertension	32: 15 M, 17 F	8
S Abedini	2012	Iran	parallel	Type 2 Diabetic	48: 6 M, 42 F	8
RT Ras	2013	France	parallel	pre- and stage I hypertension	70: 38 M, 32 F	8
J Tomé-Carneiro	2013	Spain	Parallel	hypertensive patients with coronary artery disease	22: 22 M	52
G Siasos	2013	Greece	crossover	Healthy Smokers	26: 10 M, 16 F	2
G Belcaro (A)	2013	Italy	parallel	healthy, pre and mildly hypertensive subjects	82: 45 M, 37 F	16
G Belcaro (B)	2013	Italy	parallel	healthy, pre and mildly hypertensive subjects	84: 51 M, 33 F	16
M Hokayem	2013	France	Parallel	Type 2 Diabetic	38: 18 M, 20 F	8
M Terauchi (A)	2014	Japan	parallel	healthy adults	61 F. 61	8
M Terauchi (B)	2014	Japan	parallel	healthy adults	59 F. 59	8
PT Kanellos	2014	Greece	Parallel	Type 2 Diabetic	48: 25 M, 23 F	24
I Urquiaga	2015	Chile	Parallel	healthy adults	38: 38 M	16
DJ Lamport	2016	United Kingdom	crossover	mothers of preteen children	25: 25 F	12
K Turki	2016	Tunisia	parallel	Chronic kidney disease	33: 19 M, 14 F	25
AC Kaliora	2016	Greece	Parallel	patients with NAFLD	55: 23 M, 32 F	24
E Park	2016	USA	parallel	pre-hypertension	29: 15 m, 14 F	6
LT Toscano	2017	Brazil	Parallel	healthy adults	28 M/F	4
PT Kanellos	2017	Greece	Parallel	Healthy Smokers	36: 27 M, 9 F	4
Q Duclos	2017	USA	crossover	Metabolic Syndrome	20: 12 M, 8 F	4

Continued

Table 1. (Continued).

Means Age		Means BMI		Intervention		Sample Size		compliance	
IG	CG	IG	CG	Treatment group	intervention dose	control	IG	CG	Twelve women and twenty-four men completed the study and one additional woman missed the last phase of treatment. Six subjects withdrew after commencement and 6 withdrew prior to commencement.
58 ± 9	58 ± 9	28.4 ± 4.4	28.4 ± 4.4	Grape Seed Extract	2000 mg	control yogurt	36	36	NR
43 ± 9.16	46 ± 8.71	26.5 ± 3.2	26.2 ± 2.61	Concord grape juice	350 ml	Placebo	21	19	NR
51 ± 8.24	53 ± 8.48	25.8 ± 3.29	24.6 ± 2.54	red grape extract	346 mg	Placebo	17	18	A total of 74 subjects were included in the study. One female subject dropped out due to digestion problems unrelated to the study. Furthermore, four subjects were excluded (one male did not show up for blood sampling, one male was noncompliant with respect to alcohol rules, one female subject had elevated C-reactive protein in plasma at baseline, and one female took vitamin C for 3 days during intervention). Data from the remaining 69 completers were used for the present paper.
53 ± 7.74	53 ± 8.48	25.3 ± 2.71	24.6 ± 2.54	red grape extract	173 mg	Placebo	15	18	
50 ± 13	56 ± 7.5	29.3 ± 1.4	27.5 ± 1.4	grape juice	150 ml	without supplementation	8	15	NR
51 ± 2.4	53.2 ± 2.1	24.2 ± 0.66	24.4 ± 0.59	Grape Seed Extract	200 mg	Placebo	21	20	Of the 190 subjects that underwent actual screening, eightyfour subjects were eligible for the study. Of these, ten subjects were randomly excluded and four subjects were assigned to be spare subjects to allow for some dropout before the start of the intervention.
52.9 ± 2	53.2 ± 2.1	24.1 ± 0.62	24.4 ± 0.59	Grape Seed Extract	400 mg	Placebo	20	20	
35.5 ± 11.8	34.6 ± 12.4	26.1 ± 4.7	22.7 ± 2.4	grape antioxidant dietary fiber	7.5 g	without supplementation	34	9	No subject reported any adverse effect derived from the intake of GADF and all participants concluded the trial. Only two subjects reported slight episodes of constipation.
45 ± 3	46 ± 3	36 ± 1.4	36 ± 2.4	Grape Seed Extract	150 mg	Placebo	9	9	NR
47 ± 4	46 ± 3	37 ± 2.1	36 ± 2.4	Grape Seed Extract	300 mg	Placebo	9	9	
41 ± 13	44 ± 11	28 ± 3.8	28 ± 3.9	grape juice	7 mL/kg/d	Placebo	30	34	Nineteen subjects withdrew or were terminated from the study, mostly by patient preference. One subject withdrew while drinking grape juice after developing diarrhea that may have been related to the study intervention.
52.1 ± 8.1	52.1 ± 8.1	NR	NR	grape seed	1300 mg	Placebo	50	50	NR

(*Continued*)

Table 1. (Continued).

Means Age		Means BMI		Intervention		Sample Size		compliance	Twelve women and twenty-four men completed the study and one additional woman missed the last phase of treatment. Six subjects withdrew after commencement and 6 withdrew prior to commencement.
IG	CG	IG	CG	Treatment group	intervention dose	control	IG	CG	
30–65	30–65	31 ± 6	30 ± 4	grape seed extract	200 mg	Placebo	26	22	NR
78 ± 5	75 ± 6	NR	NR	Concord Grape Juice	355 ml	Placebo	10	11	NR
50 ± 2.5	54 ± 3	NR	NR	Grape Seed Extrac	300 mg	Placebo	16	16	Sixty six subjects were screened for the study and 34 met the criteria for pre hypertension. Two refused to participate in the trial and remaining 32 were randomized.
52 ± 9	51 ± 10	30.82 ± 5.67	30.58 ± 29.69	Grape Seed Extract	200 mg	Placebo	26	22	Out of 60 patients, 12 samples (8 in the drug group and 4 in the placebo group) were excluded from the study due to non-return to the laboratory. Forty-eight patients (26 patients, 22 placebo) completed the study.
62.9 ± 7.69	64.5 ± 5.32	25.3 ± 2.36	25.7 ± 2.95	Grape Seed Extract	300 mg	Placebo	35	35	Of the 190 subjects that underwent actual screening, eightyfour subjects were eligible for the study. Of these, ten subjects were randomly excluded and four subjects were assigned to be spare subjects to allow for some dropout before the start of the intervention.
60 ± 10	57 ± 10	32.2 ± 5.1	30.5 ± 3.8	grape extract	350 mg	Placebo	13	9	NR
26.34 ± 4.93	26.34 ± 4.93	23.21 ± 4.1	23.21 ± 4.1	Concord Grape Juice	240 ml	Placebo	26	26	NR
49.9 ± 9	49.4 ± 3	25.2 ± 0.73	25.11 ± 0.7	grape seed procyanidins extract	150 mg	management plan	35	47	NR
51.33 ± 5.31	49.4 ± 3	25.41 ± 0.8	25.11 ± 0.7	grape seed procyanidins extract	300 mg	management plan	37	47	
49.7 ± 8.49	48.4 ± 8.48	29.3 ± 2.68	29.1 ± 2.96	Grape Polyphenols	2000 mg	Placebo	20	18	Five subjects were enrolled but dropped out for difficulties during blood withdrawal (one PCB) or for personal reasons (two PCB and two PP) not linked to secondary effects regarding study protocol.
49.2 ± 5.3	49.8 ± 5.2	21.4 ± 3	21.4 ± 2.6	grape seed proanthocyanidin extract	100 mg	Placebo	32	29	A total of 96 middle-aged women were enrolled in the study and randomized to the low-dose group (n = 33), highdose group (n = 32), or placebo group (n = 31); of these, 91 (95%) completed the 8-week study
49.8 ± 4.7	49.8 ± 5.2	21.3 ± 2.6	21.4 ± 2.6	grape seed proanthocyanidin extract	200 mg	Placebo	30	29	

(*Continued*)

Table 1. (Continued).

Means Age		Means BMI		Intervention		Sample Size		compliance	Twelve women and twenty-four men completed the study and one additional woman missed the last phase of treatment. Six subjects withdrew after commencement and 6 withdrew prior to commencement.
IG	CG	IG	CG	Treatment group	intervention dose	control	IG	CG	
63.7 ± 6.3	63 ± 8.5	30.5 ± 4.4	30.4 ± 5.5	raisins	36 g	Regular diet	26	22	Of the 60 participants enrolled for the trial, 51 were eligible and were randomized to either the control group or the CR intervention group.
44.5 ± 9.3	43.1 ± 8.4	29.1 ± 3.9	27.9 ± 3.5	Wine grape pomace flour	20 g	without supplementation	25	13	Thirty-eight participants completed the protocol: 13 controls and 25 subjects in the intervention group. After the initial randomization, three participants in the control group quit the study: one underwent a programmed cholecystectomy; another needed medical treatment that involved anti inflammatory drugs to treat pain, and a third did not want to repeat blood tests. In the intervention group, six participants dropped out of the study: one had to undergo kidney surgery, two disliked blood sampling, and three declined to consume WGPF. Although the withdrawal, no statistical differences in baseline measurements were found between groups. Also, some participants reported side effects during the period when they consumed WGPF: 7, exhibited increased intestinal gas; 2, heartburn; 2, slight episodes of constipation, 7, regularization of intestinal transit; 6, softer stools; 3, increased appetite; 2, dyspepsia; 2, gastroesophageal reflux.
43.2 ± 3	43.2 ± 3	24.6 ± 2.5	24.6 ± 2.5	Concord grape juice	355 ml	Placebo	25	25	NR
62.3 ± 9.1	62.7 ± 7.5	NR	NR	Grape Seed Extract	2000 mg	Placebo	23	10	Importantly no patient drop out of the study nor adverse side effects were noted during the entire clinical trial period.
50.7 ± 10.9	51.6 ± 9.4	29.7 ± 22.2	29.1 ± 21.8	raisins	36 g	Regular diet	28	27	By the end of the trial, 4 out of 27 patients in Control and 1 out of 23 in Currant arm gave personal reasons for dropping out. In addition, 2 patients in Control and 4 patients in Currant arm were ineligible, as 5 modified lipid lowering treatment and one started antimetabolite treatment during the trial. By the end of the study, 21 patients in the Control arm and 23 in the Currant arm were eligible for analysis

(*Continued*)

Table 1. (Continued).

Means Age		Means BMI		Intervention		Sample Size		compliance	Twelve women and twenty-four men completed the study and one additional woman missed the last phase of treatment. Six subjects withdrew after commencement and 6 withdrew prior to commencement.
IG	CG	IG	CG	Treatment group	intervention dose	control	IG	CG	
44 ± 10	42 ± 10	34 ± 7	31 ± 9	grape seed extract	300 mg	Placebo	12	17	total of thirty-six subjects were recruited into the study; twenty-nine subjects completed 6 weeks of GSE or Placebo (n 12 and n 17, respectively) and twenty-eight subjects completed the entire study, including the 4 week no beverage follow-up period (one subject from the Placebo group was lost to follow-up)
25–54	20–53	NR	NR	grape juice	10 ml/kg/day	Not consume juice	15	13	NR
30.8 ± 7.5	29.8 ± 5.23	24.4 ± 2.81	24.4 ± 2.99	raisins	90 g	Regular diet	22	14	To allow for a 10% dropout rate over the 4 weeks, a total sample of no< 36 participants was required.
30–70	30–70	32.93 ± 4.82	32.64 ± 4.51	Grape Powder	60 g	Placebo	20	20	Of the remaining 23 participants, three dropped while on study

Abbreviations:IG, intervention group; CG, control group; NR, not reported; F, Female; M, Male; NR, not reported.

the included studies ranged from 18[17] to 84[30] participants. The design of all studies was parallel, except for six studies.[28,31–35] Included studies enrolled subjects with cardiovascular disease,[29,32,33,36–38] metabolic syndrome,[17,35] type 2 diabetes mellitus,[39–42] pre and mildly hypertensive subjects,[18,30,43] healthy adults[28,,31,,34,,44–51] and others.[52,53] Selected studies carried out in diverse countries such as USA, [17,18,32,33,35,43,44,47] Japan,[45,48] Spain,[29,46] Greece,[28,42,50,52] Iran,[39,40] Italy,[30] United Kingdom,[34] Tunisia,[53] South Korea,[37] France,[38,41] Denmark,[36] Chile,[49] Brazil,[51] Australia.[31] Some studies enrolled only males[29,,37,,49] and females [,34,48] and the rest of included studies involved both genders. Also one study did not provide information on the gender of the people being treated.[39] In addition, various types of grape products supplements have been used in studies, for example: grape extract, [29,36,41,46] grape juice, [28,32,34,37,44,47,51] and grape seed extract, [17,18,30,31,38–40,43,45,48,53] raisins [,42,50,52] and others .[33,35,49]

Quality assessment

Details of quality assessment are described in Table 2. Random allocation of participants was mentioned in all included trials, but only eight studies have mentioned the method of randomization, and they had low risk.[18,32,34,41,42,49,50,52] Allocation concealment reported in six studies.[18,28,32,40,41,45] Moreover, two trials had high risk of bias regarding blinding of participants and personnel [,35,44] and six studies did not provide sufficient information about participants' blindness.[30,42,45,46,49,51] Only three trials had low risk of bias concerning outcome assessors.[29,40,50] Selective reporting and incomplete outcome data considered as low risk in all trials. Twelve studies showed low risk based on other sources of bias.[29,35,36,39–42,44,46,49,50,52]

Table 2. Quality assessment.

Study	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
PM Clifton	U	U	L	H	L	U	L
YK Park	U	U	L	H	L	U	L
AS Hansen	U	U	L	L	L	U	L
AE Banini	U	U	L	L	H	U	L
A Sano	U	L	L	H	U	U	L
JP Jiménez	U	U	L	L	U	U	L
B Sivaprakasapillai	U	U	L	H	L	U	L
MM Dohadwala	L	L	L	H	L	U	L
PB Mellen	U	U	L	H	L	U	L
P-Gargari	U	U	L	L	L	U	L
R Krikorian	U	U	L	H	L	U	L
M. Robinson	U	U	L	H	L	U	L
S Abedini	U	L	L	L	L	L	L
RT Ras	U	U	L	H	L	U	L
J Tomé-Carneiro	U	U	L	L	L	L	L
G Siasos	U	L	L	H	L	U	L
G Belcaro	U	U	L	H	U	U	L
M Hokayem	L	L	L	L	L	U	L
M Terauchi	U	U	L	H	L	U	L
PT Kanellos 2014	L	U	L	L	U	U	L
I Urquiaga	L	U	L	L	U	U	L
DJ Lamport	L	U	L	H	L	U	L
K Turki	U	U	L	H	L	U	L
AC Kaliora	L	U	L	L	L	U	L
E Park 2016	L	L	L	H	L	U	L
LT Toscano	H	H	L	H	U	U	L
PT Kanellos 2017	L	U	L	L	L	L	L
Q Duclos	U	U	L	L	H	H	L

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

Effect of grape products on systolic blood pressure

The effect of grape products supplementation on SBP was investigated in 28 trials with 33 arms (772 cases and 729 control subjects). Overall, meta-analysis indicated that SBP decreased significantly following grape products supplementation (WMD: −3.40 mmHg, 95% CI: −6.55, −0.24, $p = .03$). Due to a significant heterogeneity between studies ($I^2 = 93.4\%$, $p < .001$) (Figure 2), subgroup analyses were performed based on baseline SBP, duration of intervention, intervention type, health status, and baseline BMI. Between-study heterogeneity was decreased or disappeared after subgroup analysis by baseline SBP, intervention type, health status, and baseline BMI. However, after classifying the studies, the results remained significant only in the following subsets: baseline SBP ≥130 (WMD: −5.89 mmHg, 95% CI: −10.76, −1.01, $p = .02$), trial duration<12 weeks (WMD: −2.88 mmHg, 95% CI: −5.18, −0.570, $p = .01$), grape seed extract (WMD: −6.57 mmHg, 95% CI: −10.80, −2.34, $p = .002$), healthy subjects (WMD: −2.17 mmHg, 95% CI: −4.24, −0.11, $p = .039$), metabolic syndrome (WMD: −7.09 mmHg, 95% CI: −11.16, −3.02, $p = .001$), pre and mildly hypertensive subjects (WMD: −14.37 mmHg, 95% CI: −21.85, −6.89, $p < .001$) and baseline BMI >30 (kg/m^2) (WMD: −5.62 mmHg, 95% CI: −9.14, −2.17, $p = .001$) (Table 3).

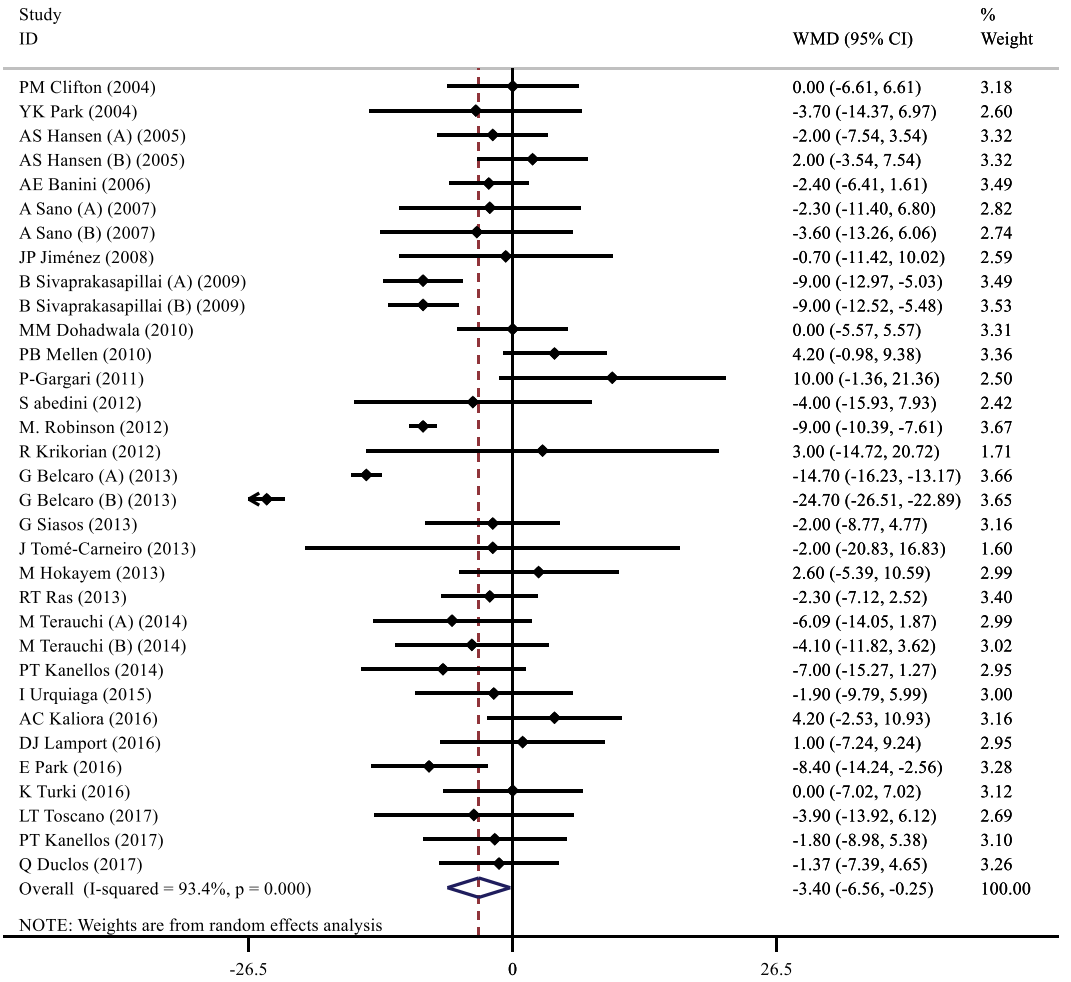


Figure 2. Forest plot of the effects of grape products on SBP.

Table 3. Subgroup analyses of grape intake on blood pressure.

	NO	WMD (95%CI)	P within group	P heterogeneity	I^2
Subgroup analyses of grape intake on SBP level.					
Overall effect	33	−3.40 (−6.55, −0.24)	**0.035**	<0.001	93.4%
Baseline SBP (mmHg)					
≥130	13	−5.89 (−10.76, −1.01)	**0.018**	<0.001	95.9%
<130	20	−1.92 (−3.97, 0.13)	0.067	0.018	44.1%
Trial duration (week)					
<12	21	−2.88 (−5.18, −0.570	**0.014**	<0.001	74.7%
≥12	12	−4.80 (−10.96, 1.35)	0.127	<0.001	94.7%
Intervention type					
Grape Seed Extract	15	−6.57 (−10.80, −2.34)	**0.002**	<0.001	95.2%
Raisin	3	−1.18 (−7.45, 5.09)	0.712	0.113	54.1%
Grape juice	7	−1.56 (−4.12, 0.98)	0.229	0.961	0.0%
Grape extract	5	0.31 (−2.97, 3.60)	0.852	0.839	0.0%
Other types	3	0.91 (−3.14, 4.96)	0.660	0.276	22.4%
Health status					
Type 2 diabetes	4	0.08 (−7.06, 7.24)	0.981	0.088	54.2%
Healthy	13	−2.17 (−4.24, −0.11)	**0.039**	0.997	0.0%
Other	2	2.19 (−2.66, 7.04)	0.377	0.397	0.0%
Cardiovascular disease	7	0.10 (−2.19, 2.40)	0.931	0.558	0.0%
Metabolic syndrome	3	−7.09 (−11.16, −3.02)	**0.001**	0.075	61.4%
Pre and mildly hypertensive	4	−14.37 (−21.85, −6.89)	**<0.001**	<0.001	98.4%
Baseline BMI (kg/m^2)					
18.5–24.9	7	−2.65 (−5.64, 0.34)	0.083	0.942	0.0%
25–29.9	13	−3.60 (−9.70, 2.49)	0.247	<0.001	96.5%
>30	8	−5.65 (−9.14, −2.17)	**0.001**	0.037	53.1%
Subgroup analyses of grape intake on DBP level.					
Overall effect	33	−1.69 (−3.12, −0.27)	**0.019**	<0.001	80.4%
Baseline DBP (mmHg)					
<85	29	−1.36 (−3.02, 0.29)	0.106	<0.001	76.4%
≥85	4	−3.72 (−6.80, −0.64)	**0.018**	<0.001	88.7%
Trial duration (week)					
<12	21	−1.03 (−2.97, 0.89)	0.294	<0.001	81.8%
≥12	12	−3.31 (−5.39, −1.23)	**0.002**	<0.001	69.2%
Intervention type					
Grape Seed Extract	15	−3.83 (−5.33, −2.34)	**<0.001**	<0.001	73.7%
Raisin	3	−0.88 (−7.99, 6.23)	0.808	0.005	81.5%
Grape juice	7	−0.20 (−2.21, 1.81)	0.843	0.463	0.0%
Grape extract	5	1.42 (−0.59, 3.43)	0.166	0.589	0.0%
Other types	3	1.68 (−0.50, 3.86)	0.132	0.392	0.0%
Health status					
Type 2 diabetes	4	−1.49 (−5.66, 2.66)	0.481	0.032	65.8%
Healthy	13	−1.68 (−3.31, −0.05)	**0.043**	0.338	10.7%
Other	2	2.61 (−1.61, 6.85)	0.226	0.270	17.8%
Cardiovascular disease	7	0.91 (−0.61, 2.43)	0.242	0.465	0.0%
Metabolic syndrome	3	−1.15 (−3.88, 1.56)	0.405	0.125	51.8%
Pre and mildly hypertensive	4	−6.26 (−8.22, −4.30)	**<0.001**	<0.001	84.3%
Baseline BMI (kg/m^2)					
18.5–24.9	7	−3.34 (−5.81, −0.87)	**0.008**	0.287	18.7%
25–29.9	13	−0.80 (−3.04, 1.42)	0.478	<0.001	85.5%
>30	8	−2.24 (−4.11, −0.37)	**0.019**	0.137	36.6%

Abbreviations: NO, number of effect sizes; CI, confidence interval; WMD, weighted mean differences; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Effect of grape products on diastolic blood pressure

The effect of the grape products supplementation on DBP was examined in 33 arms from 28 studies (772 cases and 729 control subjects). Overall, current meta-analysis revealed significant effects of grape products on DBP (WMD: −1.69 mmHg, 95% CI: −3.12, −0.27, p = .01). There was significant heterogeneity among studies (I^2 = 80.4%, p < .001) (Figure 3). Subgroup analysis based on intervention type, health status, and baseline BMI was decreased or disappeared between-study heterogeneity.

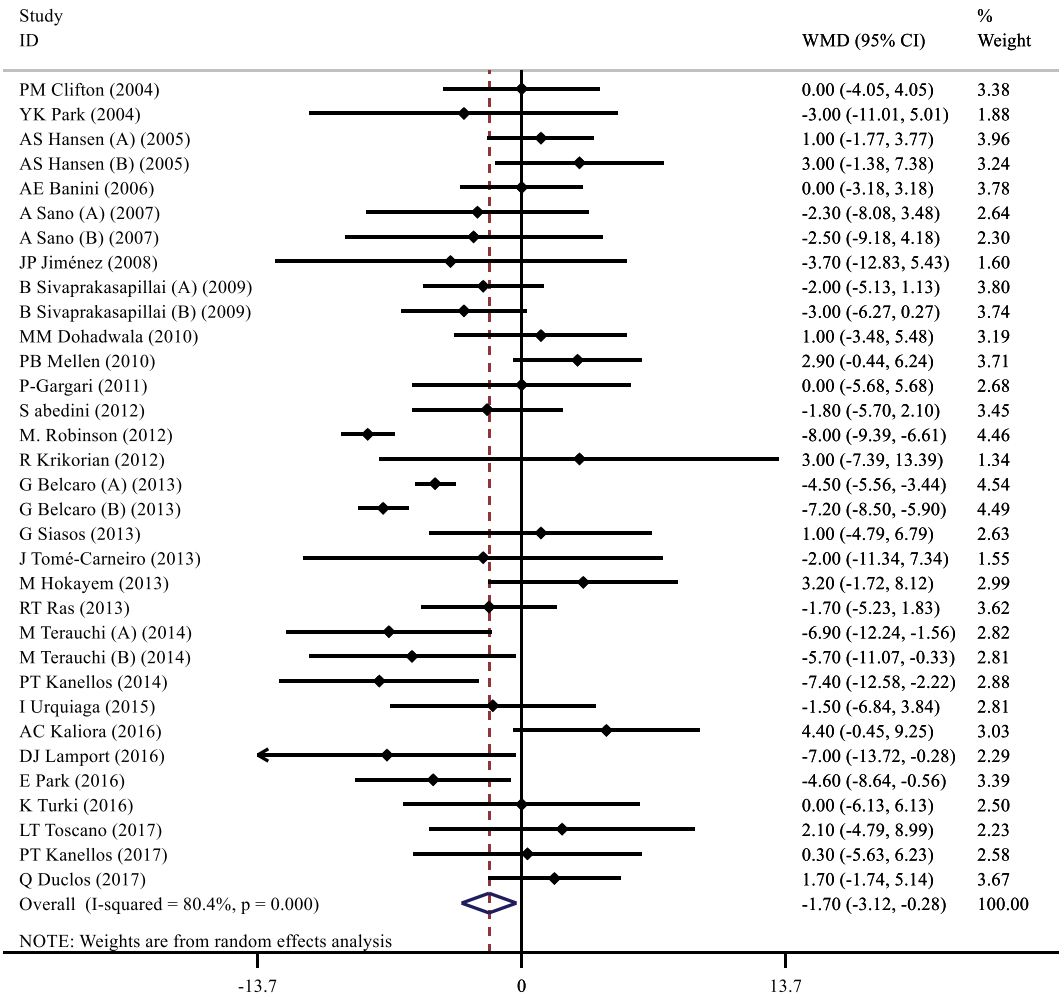


Figure 3. Forest plot of the effects of grape products on DBP.

However, after classifying the studies, the results remained significant only in the following subsets: baseline DBP ≥85 mmHg (WMD: −3.72 mmHg, 95% CI: −6.80, −0.64, p = .01), trial duration ≥12 weeks (WMD: −3.31 mmHg, 95% CI: −5.39, −1.23, p = .002), grape seed extract (WMD: −3.83 mmHg, 95% CI: −5.33, −2.34, p < .001), healthy subjects (WMD: −1.68 mmHg, 95% CI: −3.31, −0.05, p = .04), pre and mildly hypertensive subjects (WMD: −6.26 mmHg, 95% CI: −8.22, −4.30, p < .001), baseline BMI 18.5–24.9 kg/m^2 (WMD: −3.34 mmHg, 95% CI: −5.81, −0.87, p = .008) and baseline BMI >30 kg/m^2 (WMD: −2.24 mmHg, 95% CI: −4.11, −0.37, p = .02) (Table 3).

Sensitivity analysis

To discover the influence of each single study on the combined effect size, we removed each trial from the analysis, step by step. We found that after removing the Sivaprakasapillai (A) (WMD: −3.18 mmHg, 95% CI: −6.45, 0.08), Sivaprakasapillai (B) (WMD: −3.17 mmHg, 95% CI: −6.46, 0.10), Park (WMD: −3.22 mmHg, 95% CI: −6.46, 0.01), Belcaro (A) (WMD: −2.92 mmHg, 95% CI: −6.39, 0.54) and

Robinson (WMD: −3.10 mmHg, 95% CI: −6.75, 0.53) studies for SBP and Belcaro (A) (WMD: −1.54 mmHg, 95% CI: −3.14, 0.06) study for DBP the statistical results were changed to insignificant.

Publication bias

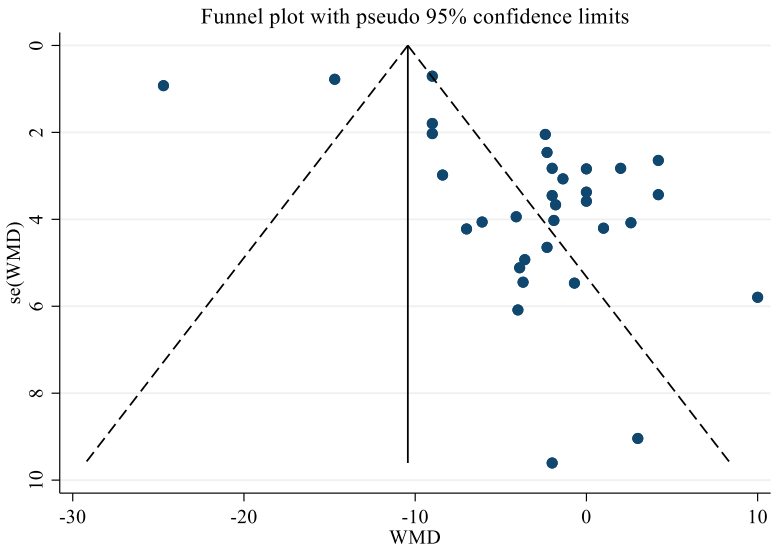
Visual inspection of funnel plots delivered no evidence for publication bias in studies involved in the current meta-analysis (Figure 4). The results of the Begg's test were SBP (P = .19) and DBP (P = .54).

Discussion

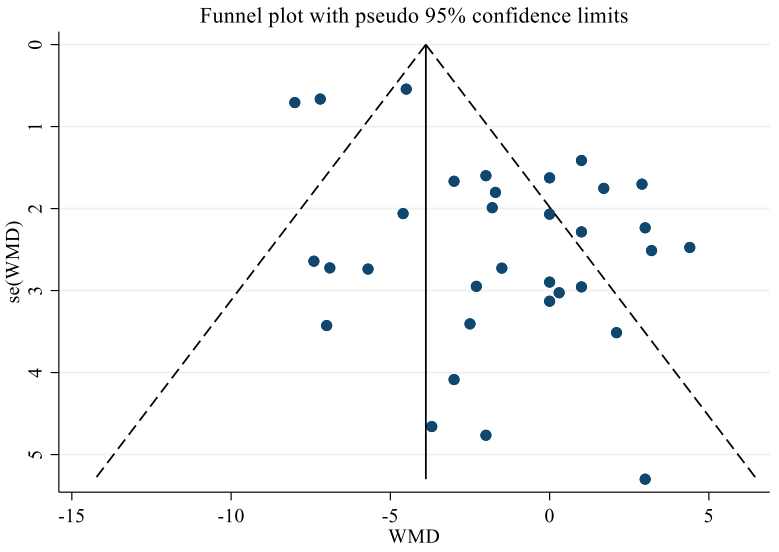
As far as we know, this is the first quantitative review evaluating the effects of grape products such as grape extract, grape juice, grape seed extract, and raisins on BP parameters including SBP and DBP. In the current systematic review and meta-analysis of 28 clinical trials were published between 2004 and 2017, we found that grape products supplementation in a period of 2 to 52 weeks intervention, significantly reduced SBP and DBP levels. In the subgroup analysis, we investigated a significant reduction in both SBP and DBP levels when baseline SBP ≥130 mmHg and DBP ≥85 mmHg, when grape seed extract was administered, in healthy subjects and participants with baseline BMI >30 kg/m^2.

In line with our results, a systematic review of 39 studies that assessed the effects of grape polyphenols on metabolic syndrome components, exhibited that seven studies found a significant decrease in BP indices, but only one was of high quality.[54] Another meta-analysis of 10 clinical trials published in 2015 found a significant reduction in SBP by 1.48 mmHg after grape polyphenol intake. Contrarily, there were no significant changes in DBP levels in the grape polyphenols group as compared to controls.[55] It should be noted, mentioned meta-analysis had a small sample size leading to unsteady approximates of therapeutic effects and also restricted the capacity of randomization to lessen the possible effect of confounding factors. A further review of 16 RCTs and 810 study subjects which evaluated the impact of grape seed extract supplementation on the BP parameters, found a significant reduction in SBP and DBP levels.[20] However, in mentioned review, because of retrieving all included articles from the English-language literature, it remained a possibility of selection bias. Furthermore, there were relatively small sample sizes in stratified analysis. Some published clinical trials demonstrated that various grape products supplementation improved BP indices [,42,48–50] whereas the other trials did not.[29,36,45] In agreement with our findings, a study indicated that phenolic compounds from purple grape juice improved BP parameters, upon receiving supplementation (10 mg/kg/day) for 28 days. This study found a significant decrease in SBP by 5.3 mmHg, while there were no significant changes in DBP levels and mean BP.[51] As can be noted, because participants in mentioned study were normotensive and exercise practitioners, the ability of exercise training in reducing BP led to the absence of a hypotensive effect on diastolic component.[56] Altogether, different biological activity of grape products contributed to dissimilarities in the results explained here. Differences in the context of grape varieties, geographical and botanical grape's origin and, production process affect the biological activity of grape extracts.[57–59]

Grape is a phenol-rich fruit. Proanthocyanidins, anthocyanins, flavonols, flavanols, resveratrol, and phenolic acids are Phenolic compounds in grape.[19] Several polyphenolic compound of grape and its antioxidants prevent cell damage due to free radicals.[60] Stimulation and promotion of the release of NO, resulting in the vasorelaxation, might be the main cause of hypotensive effect of grape polyphenols.[55] In addition, polyphenols endothelial function could be increased by nitric oxide bioactivity and eventually lowering BP. Resveratrol could enhance the expression and activity of eNOS, possibly through the activation of PI3K/Akt pathway.[6,61] Low-molecular-weight procyanidin-rich grape seed extract (LM-GSPE) administration to rats increased 6-keto-prostaglandin F1α (PGF1α) plasma levels, relaxed SHR aorta rings, and finally exhibited antihypertensive effect.[62] PGF1α, a stable metabolite of prostacyclin, is an important vasodilator endothelial factor.[63] Angiotensin-converting enzyme (ACE), a zinc metalloenzyme, converts angiotensin-I into



SBP



DBP

Figure 4. Funnel plots for SBP, and DBP.

angiotensin-II, which is a vasoconstrictor.[64] Phenolic compounds deactivate metal ions by its chelation ability.[65] Because ACE is a metalloenzyme, phenolic compounds bond with its zinc ion and therefore decrease its activity.[2] Altogether, the hypotensive effect of grape products may be related to the level of prostacyclin and reduction of ACE activity, which are influenced by phenolic compounds. However, additional confirmation needed.

Despite the interesting findings of the current meta-analysis, many potential limitations should be addressed. First, grape products supplementation was used in different dosages and various types. Second, variable and wide duration of intervention led to the bias in our meta-analysis. Third, subjects involved in included studies had different physiological status and various age groups. And fourth, lifestyle modifications during the intervention of grape products were not reported in a large number of included articles. Dissimilar lifestyle modifications and diets may affect the impact of grape polyphenols on BP. In addition, the present study was not registered in the International Prospective Register of Systematic Reviews (PROSPERO), which may be a limitation as well. However, this review and meta-analysis was designed and performed according to the Cochrane guidelines. Although, our study has important strengths. All studies included in our review were high quality, well-designed, randomized, double-blinded trials. Furthermore, using Begg's test, there was no publication bias for SBP and DBP. In addition, majority of considered studies permitted a complete subgroup analysis contributing to determine plausible sources of heterogeneity.

Conclusion

Conclusively, our results exhibited that grape products administration improved BP parameters including SBP and DBP levels, and this effect was more obvious in healthy subjects, as well as in subjects with baseline BMI >30 kg/m^2. Larger, better designed trials, that specifically include hypertensive subjects, are required to verify our results in the future.

Disclosure statement

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