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The impact of grape seed extract treatment on blood pressure changes

A meta-analysis of 16 randomized controlled trials

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Abstract

Backgrounds and Objective: Several clinical trials have shown that grape seed extract can reduce blood pressure, but the results are often irreproducible. We therefore sought to systematically evaluate the impact of grape seed extract treatment on the changes of systolic/diastolic blood pressure (SBP/DBP) by meta-analyzing available randomized controlled trials.

Methods: Trial selection and data extraction were completed independently by 2 investigators. Effect-size estimates were expressed as weighted mean difference (WMD) and 95% confidence interval (CI).

Results: Twelve articles involving 16 clinical trials and 810 study subjects were analyzed. Overall analyses found significant reductions for SBP (WMD = −6.077; 95% CI: −10.736 to −1.419; $P = 0.011$) and DBP (WMD = −2.803; 95% CI: −4.417 to −1.189; $P = 0.001$) after grape seed extract treatment. In subgroup analyses, there were significant reductions in younger subjects (mean age < 50 years) for SBP (WMD = −6.049; 95% CI: −10.223 to −1.875; $P = 0.005$) and DBP (WMD = −3.116; 95% CI: −4.773 to −1.459; $P < 0.001$), in obese subjects (mean body mass index ≥ 25 kg/m^2) for SBP (WMD = −4.469; 95% CI: −6.628 to −2.310; $P < 0.001$), and in patients with metabolic syndrome for SBP (WMD = −8.487; 95% CI: −11.869 to −5.106; $P < 0.001$). Further meta-regression analyses showed that age, body mass index, and baseline blood pressure were negatively associated with the significant reductions of SBP and DBP after treatment. There was no indication of publication bias.

Conclusion: Our findings demonstrate that grape seed extract exerted a beneficial impact on blood pressure, and this impact was more obvious in younger or obese subjects, as well as in patients with metabolic disorders. In view of the small sample size involved, we agree that confirmation of our findings in a large-scale, long-term, multiple-dose randomized controlled trial, especially among hypertensive patients is warranted.

Abbreviations: 95% CI = 95% confidence interval, BMI = body mass index, DBP = diastolic blood pressure, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, ROS = reactive oxygen species, SBP = systolic blood pressure, WMD = weighted mean difference.

Keywords: diastolic blood pressure, grape seed extract, meta-analysis, randomized controlled trial, systolic blood pressure

1. Introduction

It is widely recognized that oxidative stress is implicated in the pathogenesis of hypertension.[1,2] Oxidative stress is defined as an excessive production of reactive oxygen species (ROS) that cannot be quenched by antioxidants.[3] Agents that can suppress oxidative stress therefore represent an effective therapeutic option for the management and treatment of hypertension. Overwhelming evidence from in vitro experiments suggests that grape seed extract has an antioxidant property that can protect cells from ROS-mediated DNA damage.[4] This property is mainly determined by polyphenols, especially proanthocyanidins, contained in grape seed extract, which can well interpret the French paradox that refers to the low rate of coronary heart disease mortality in France people despite the diets being rich in saturated fat.[5] Today grape seed extract is commercially available on the market, and it is generally well tolerated when taken by mouth. Several clinical trials have reported a beneficial impact of grape seed extract on blood pressure,[6–8] while others have not.[9,10] Many times the conflicting results may arise from differences in sampling strategy, lifestyle modality, dosage of agents, and treatment duration. To help clarify this issue and explore the potential causes of heterogeneity, we systematically evaluated the impact of grape seed extract treatment on blood pressure changes in a meta-analysis of available randomized controlled trials according to the principles stipulated in the

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HZ, SL, and LL have contributed equally to this work.

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Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see the PRISMA checklist).[11]

2. Methods

2.1. Retrieval strategy

We identified all possible clinical trials that provided the changes of systolic or diastolic blood pressure (SBP or DBP) after grape seed extract treatment by retrieving PubMed and Embase as of November 30, 2015. The keywords included "grape seed" or "grape juice" or "polyphenol" or "proanthocyanidin" or "blood pressure" or "hypertension." Only articles published in English language were considered. The reference lists of major clinical trials and reviews were manually searched for additionally unidentified citations. All retrieved clinical trials were reported to be approved by ethics committees of local hospitals or institutes, and written informed consent was obtained from all study subjects.

2.2. Inclusion/exclusion criteria

Articles were included if they included a randomized clinical trial that compared grape seed extract treatment with the placebo on the changes of SBP and DBP for at least 2 weeks. In case of duplicate publications from the same study group, clinical trial with the larger sample size or more complete information was retained. Conference abstracts and posters were not included as information was insufficient to make a complete evaluation.

2.3. Trial selection

Two authors (GT and HZ) independently assessed the eligibility of each retrieved article by reviewing the title and abstract, and if necessary by reading the full text. In case of any disagreements during selection, a discussion was made between the 2 authors until a consensus was reached.

2.4. Data extraction

The same 2 authors independently extracted relevant data from each eligible article according to the same template enacted by all contributing authors, and then a cross-check was run to minimize typing mistakes. The relevant data of interest included the first author's surname, publication year, study design, treatment duration, sample size, grape seed extract type, age, sex, body mass index (BMI), the means, and standard deviations of SBP and DBP at both baseline and postintervention.

2.5. Statistical analysis

Weighted mean difference (WMD) and 95% confidence interval (95% CI) were calculated to appraise the changes of SBP and DBP from baseline to postintervention using the DerSimonian-Laird-based random-effects model.[12] Between-trial heterogeneity was quantified as the I^2 statistic, a proportion denoting the probability of variability seen between trials due to heterogeneity rather than chance. Possible causes of heterogeneity between trials were explored by both stratified and meta-regression analyses. Publication bias was examined by Begg and Egger tests at a significance level of 5%, as well as by the Begg funnel plots. All statistical analyses were done with the STATA software v12.0 for Windows (StataCorp LP, College Station, TX).

3. Results

3.1. Qualified trials

The flow diagram for the selection process of qualified articles is shown in Fig. 1. The initial retrieval of 2 public databases identified 31 potentially relevant articles, and 12 articles published in English language met our predefined inclusion criteria.[6–10,13–19] Four articles that provided data by the low and high dosages of grape seed extract were treated separately, and therefore 16 clinical trials including 810 study subjects were available for the final analysis.

3.2. Baseline characteristics

The baseline characteristics of 16 clinical trials are presented in Table 1 and Supplementary Table S1, http://links.lww.com/MD/B197. Of 16 clinical trials, 12 followed a parallel design and 5 followed a cross-over design. The dosages of grape seed extract agents taken ranged from 100 to 2000 mg/d. Twelve trials were double-blinded and 4 trials were single-blinded. Seven trials had grape seed extract treatment <8 weeks, and 9 trials ≥8 weeks. Five trials were conducted in Asian countries, 4 in American countries, 4 in European countries, and 2 in Australian countries. The average levels of age, male gender, and BMI were comparable between the treatment and placebo groups (all $P > 0.05$). Of 16 clinical trials, 4 were conducted in patients with pre- and stage 1 hypertension, 4 in healthy subjects, 3 in patients with metabolic syndrome, 2 in hypertensive patients, 2 in women with at least 1 menopausal symptom, and 1 in patients with above-average vascular risk (Supplementary Table S1, http://links.lww.com/MD/B197).

3.3. Overall analysis

Pooling 16 clinical trials together identified significant reductions for SBP (WMD = −6.077; 95% CI: −10.736 to −1.419; $P = 0.011$) and DBP (WMD = −2.803; 95% CI: −4.417 to −1.189; $P = 0.001$) after grape seed extract treatment relative to the placebo, with strong and moderate evidence of heterogeneity ($I^2 = 94.0\%$ and 62.4%), respectively (Fig. 2). There was no indication of publication bias as reflected by both Begg ($P = 0.528$ for SBP and 0.893 for DBP) and Egger ($P = 0.220$ for SBP and 0.132 for DBP) tests, as well as by the visually symmetrical Begg funnel plots in Fig. 3.

3.4. Stratified analysis

To explore potential causes of heterogeneity, we stratified all clinical trials according to age, BMI, study design, randomization, treatment duration, dosage of phenols in grape seed extract, and baseline status of study subjects, respectively (Table 2). After grouping clinical trials by age at a cutoff of 50 years, the effect-size estimates were comparable between the 2 subgroups, while significance was only detected in trials enrolling younger subjects (mean age < 50 years) for both SBP (WMD = −6.049; 95% CI: −10.223 to −1.875; $P = 0.005$) and DBP (WMD = −3.116; 95% CI: −4.773 to −1.459; $P < 0.001$), and heterogeneity was improved, especially for the latter ($I^2 = 34.2\%$). Upon stratification by BMI at a cutoff of 25 kg/m^2, SBP was significantly reduced in trials enrolling subjects with mean BMI ≥ 25 kg/m^2 (WMD = −7.420; 95% CI: −13.870 to −0.970; $P = 0.024$) relative to those with mean BMI < 25 kg/m^2 (WMD = −4.469; 95% CI: −6.628 to −2.310; $P < 0.001$), while the reduction in DBP was slightly

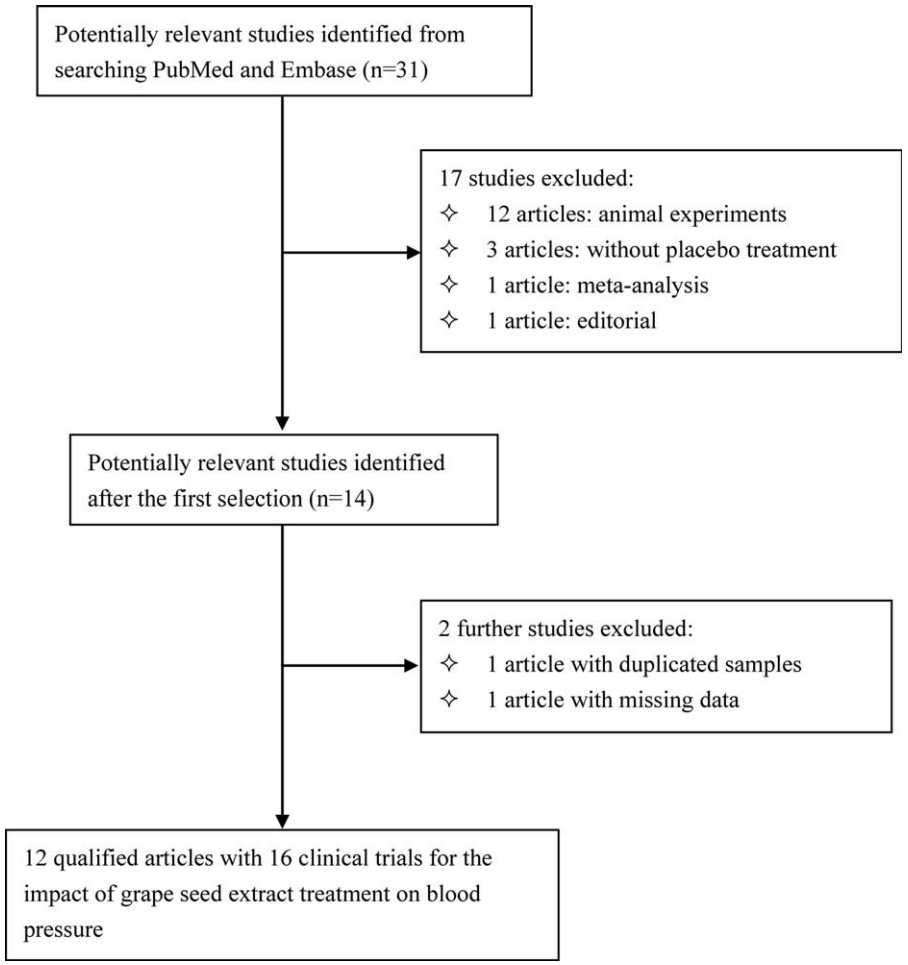

Figure 1. Flow diagram of search strategy and study selection.

Table 1

Baseline characteristics of all clinical trials in this meta-analysis.

								Sample size		Age, y		Male		BMI, kg/m^2	
Author	Year	Blind	Country	Design	Duration, wk	GSE type	GSE dosage, mg/d	TG	PG	TG	PG	TG	PG	TG	PG
Clifton	2004	Double	Australia	Cross-over	4	Polyphenols	2000	35	35	58.0	58.0	0.686	0.686	28.4	28.4
Park	2004	Double	Korea	Parallel	8	Polyphenols	885	21	19	43.0	46.0	1.000	1.000	26.5	26.2
Ward	2005	Double	Australia	Parallel	6	Polyphenols	1000	16	18	61.3	63.6	0.750	0.778	27.7	29.3
Sano (low)	2007	Single	Japan	Parallel	12	Proanthocyanidin	200	21	20	51.0	53.2	0.476	0.500	24.2	24.4
Sano (high)	2007	Single	Japan	Parallel	12	Proanthocyanidin	400	20	20	52.9	53.2	0.450	0.500	24.1	24.4
Sivaprakasapillai (low)	2009	Double	USA	Parallel	4	Meganatural BP	150	9	9	45.0	46.0	0.444	0.333	36.0	36.0
Sivaprakasapillai (high)	2009	Double	USA	Parallel	4	Meganatural BP	300	9	9	47.0	46.0	0.444	0.333	37.0	36.0
Dohadwala	2010	Double	USA	Cross-over	8	Polyphenols	1172	64	64	43.0	43.0	0.688	0.688	28.0	28.0
van Mierlo	2010	Double	The Netherland	Cross-over	6	Polyphenols	800	35	35	31.4	31.4	1.000	1.000	23.2	23.2
Barona	2012	Double	Colombia	Cross-over	4	Polyphenols	267	24	24	51.3	51.3	1.000	1.000	NR	NR
Belcaro (low)	2013	Single	Italy	Parallel	16	Enovita	150	37	47	49.9	49.4	0.486	0.596	25.2	25.1
Belcaro (high)	2013	Single	Italy	Parallel	16	Enovita	300	35	47	51.3	49.4	0.622	0.596	25.4	25.1
Ras	2013	Single	The Netherland	Parallel	8	Meganatural BP	300	35	35	62.9	64.5	0.543	0.543	25.3	25.7
Siasos	2014	Double	Greece	Cross-over	2	Polyphenols	981	26	26	26.3	26.3	0.385	0.385	23.2	23.2
Terauchi (low)	2014	Double	Japan	Parallel	8	Proanthocyanidin	100	32	29	49.2	49.8	0.000	0.000	21.4	21.4
Terauchi (high)	2014	Double	Japan	Parallel	8	Proanthocyanidin	200	30	29	49.8	49.8	0.000	0.000	21.3	21.4

BMI = body mass index, GSE = grape seed extract, NR = not reported, PG = placebo group, TG = treatment group.

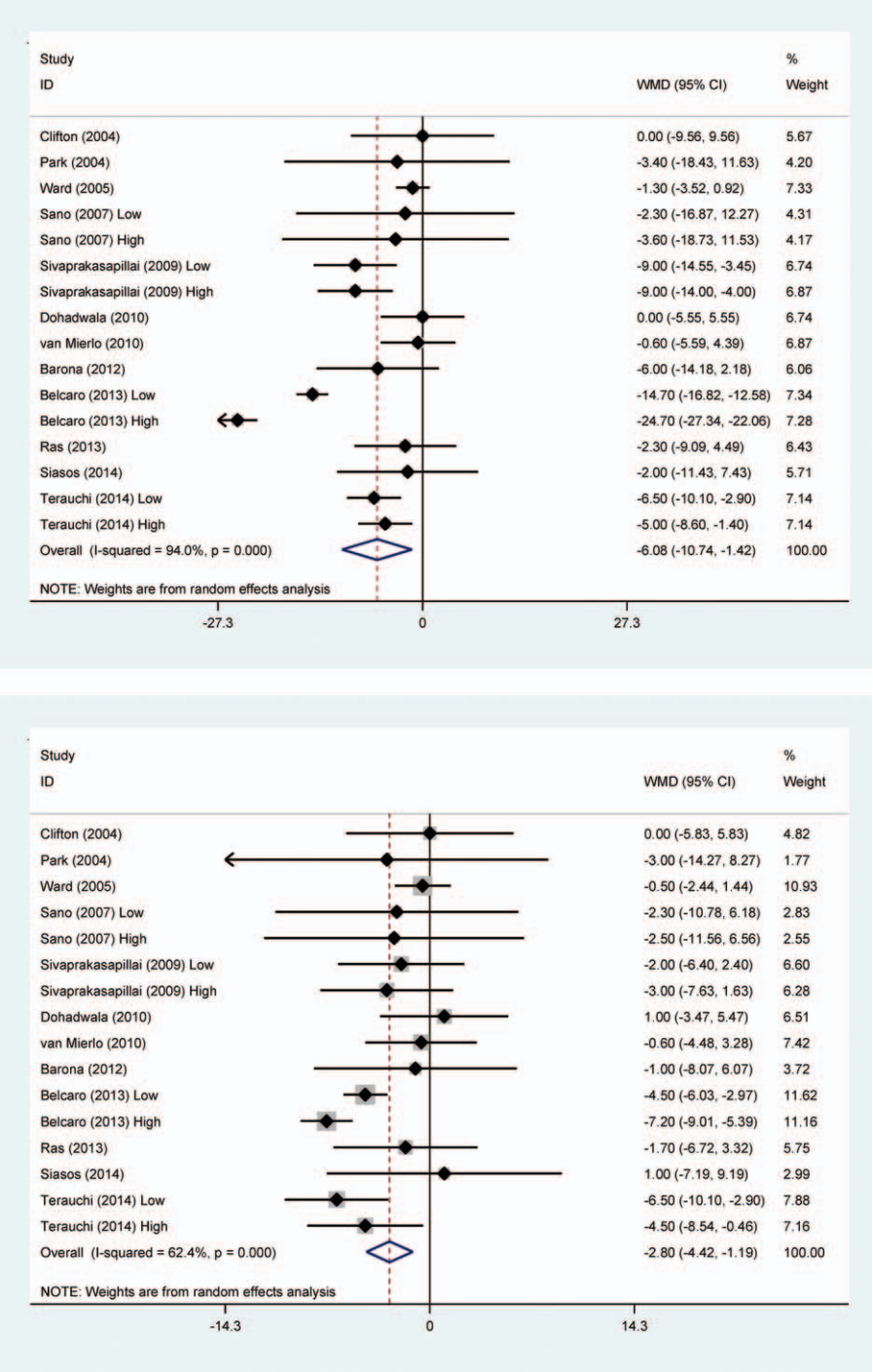

Figure 2. Forest plots of systolic (the upper) and diastolic (the lower) blood pressure after grape seed extract treatment.

obvious in trials with lower mean BMI (WMD = −3.351; 95% CI: −5.744 to −0.959; $P = 0.006$). There was improved heterogeneity in trials with lower mean BMI for both SBP ($I^2 = 0.0\%$) and DBP ($I^2 = 21.0\%$).

According to the study design, blood pressure was remarkably reduced in parallel trials (for SBP: WMD = −8.045; 95% CI: −13.750 to −2.340; $P = 0.006$ and for DBP: WMD = −3.791; 95% CI: −5.605 to −1.978; $P < 0.001$), and no material changes were noted in cross-over trials (Table 2). In addition, grape seed extract treatment resulted in greater reductions in blood pressure in single-blinded trials (for SBP: WMD = −14.111; 95% CI: −22.537 to −5.686; $P = 0.001$ and for DBP: WMD = −5.418; 95% CI: −7.568 to −3.267; $P < 0.001$) than in double-blinded trials (for SBP: WMD = −3.969; 95% CI: −5.995 to −1.942; $P <$ 0.001 and for DBP: WMD = −1.831; 95% CI: −3.195 to −0.467; $P = 0.009$).

The reductions in blood pressure were more obvious in long-duration trials (≥8 weeks) (for SBP: WMD = −7.708; 95% CI:

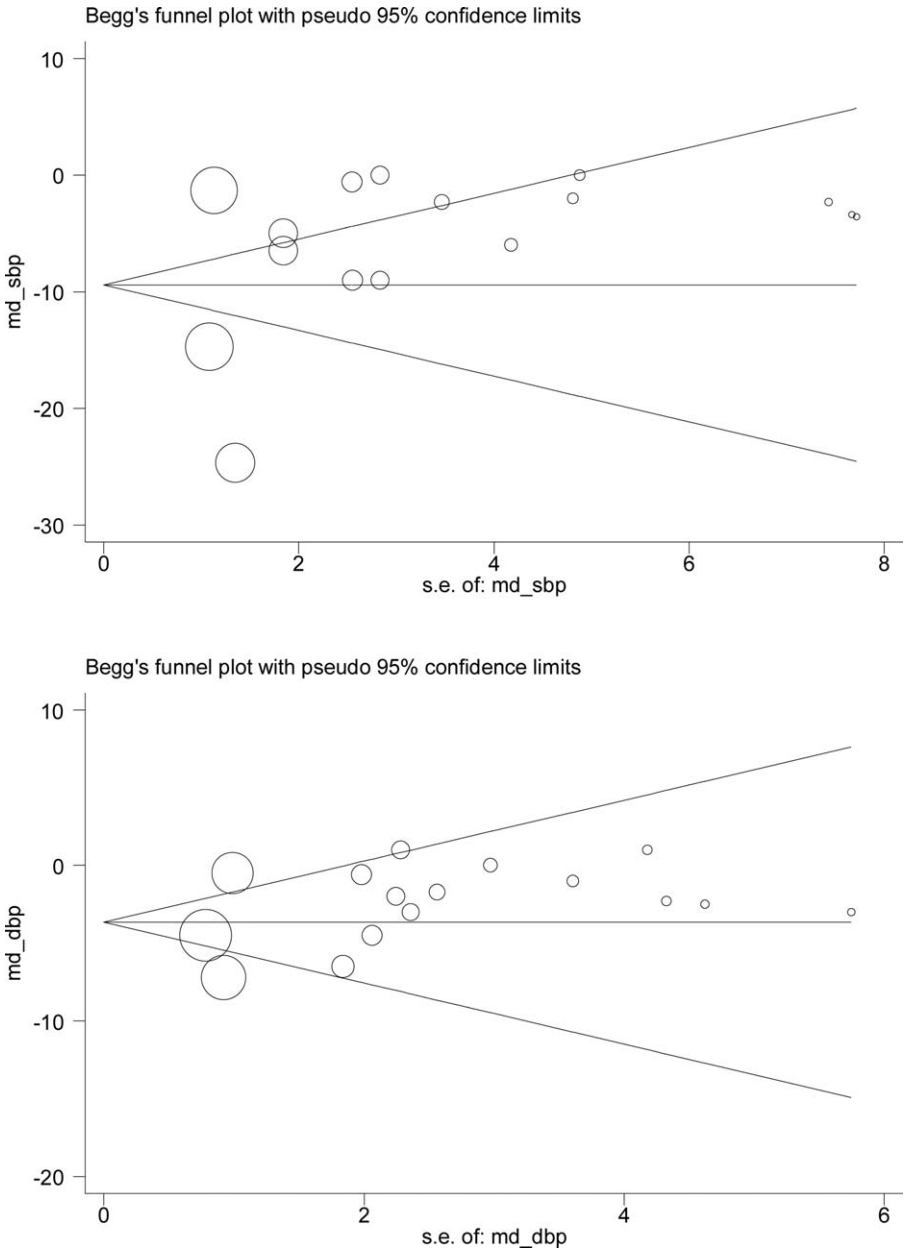

Figure 3. Begg funnel plots of systolic (the upper) and diastolic (the lower) blood pressure after grape seed extract treatment.

−14.154 to −1.262; $P=0.019$ and for DBP: WMD = −4.347; 95% CI: −6.163 to −2.531; $P<0.001$) relative to short-duration trials (<8 weeks) (Table 2). Regarding the dosage of phenols in grape seed extract, it was noted that SBP (WMD = −9.051; 95% CI: −14.415 to −3.686; $P=0.001$) and DBP (WMD = −4.637; 95% CI: −6.032 to −3.242; $P<0.001$) were significantly reduced in trials with low dosage (<800 mg/d) relative to trials with high dosage (≥800 mg/d). Finally, according to the baseline status of study subjects, the reduction in SBP was strikingly significant in patients with metabolic syndrome (WMD = −8.487; 95% CI: −11.869 to −5.106; $P<0.001$), and was marginal in patients with pre- and stage 1 hypertension (WMD = −10.811; 95% CI: −20.454 to −1.168; $P=0.028$). Similarly, DBP was significantly reduced by 3.791 mm Hg in patients with pre- and stage 1 hypertension (WMD = −3.791; 95% CI: −6.716 to −0.866; $P=0.011$). No significance was observed in healthy subjects and hypertensive patients.

3.5. Meta-regression analysis

To account for heterogeneity from another point of view, we incorporated the mean values of age, male gender, BMI, baseline SBP, and baseline DBP between the treatment and placebo groups in a meta-regression model. There were significant negative associations with reduced SBP and DBP after grape seed extract treatment for age (regression coefficient: −0.126 and −0.056; $P=0.005$ and 0.003, respectively) and BMI (regression coefficient: −0.232 and −0.099; $P=0.008$ and 0.008, respectively), as well as for baseline SBP (regression coefficient: −0.050 and −0.022; $P=0.004$ and 0.002, respectively) and baseline DBP

Table 2

Stratified analyses of GSE treatment on blood pressure changes.

Subgroups	Trials (no.)	SBP		DBP	
		WMD; 95% CI; *P*	I^2, %	WMD; 95% CI; *P*	I^2, %
Age, y					
<50	9	−6.049; −10.223 to −1.875; 0.005	86.2	−3.116; −4.773 to −1.459; <0.001	34.2
≥50	7	−6.051; −16.931 to 4.830; 0.276	96.8	−2.436; −5.777 to 0.905; 0.153	78.4
BMI, kg/m^2					
<25	6	−4.469; −6.628 to −2.310; <0.001	0.0	−3.351; −5.744 to −0.959; 0.006	21.0
≥25	10	−7.420; −13.870 to −0.970; 0.024	95.9	−2.565; −4.668 to −0.461; 0.017	73.2
Study design					
Cross-over	5	−1.242; −4.260 to 1.776; 0.420	0.0	0.028; −2.323 to 2.380; 0.981	0.0
Parallel	11	−8.045; −13.750 to −2.340; 0.006	95.4	−3.791; −5.605 to −1.978; <0.001	65.3
Randomization					
Double-blinded	12	−3.969; −5.995 to −1.942; <0.001	43.4	−1.831; −3.195 to −0.467; 0.009	15.4
Single-blinded	4	−14.111; −22.537 to −5.686; 0.001	92.9	−5.418; −7.568 to −3.267; <0.001	50.1
Treatment duration, wk					
<8	7	−4.074; −7.283 to −0.865; 0.013	57.5	−0.851; −2.273 to 0.571; 0.241	0.0
≥8	9	−7.708; −14.154 to −1.262; 0.019	94.5	−4.347; −6.163 to −2.531; <0.001	50.7
Phenols in GSE, mg/d					
<800	10	−9.051; −14.415 to −3.686; 0.001	93.1	−4.637; −6.032 to −3.242; <0.001	30.2
≥800	6	−1.077; −2.895 to 0.740; 0.245	0.0	−0.302; −1.820 to 1.215; 0.696	0.0
Baseline status					
Healthy	4	−1.209; −5.275 to 2.856; 0.560	0.0	−0.813; −3.865 to −2.238; 0.601	0.0
Pre- and stage 1 hypertension	4	−10.811; −20.454 to −1.168; 0.028	96.7	−3.791; −6.716 to −0.866; 0.011	79.6
Hypertension	2	−1.345; −3.538 to 0.849; 0.230	0.0	−0.572; −2.284 to 1.340; 0.558	0.0
Metabolic syndrome	3	−8.487; −11.869 to −5.106; <0.001	0.0	−2.226; −5.133 to 0.682; 0.133	0.0
Others	3	−5.369; −7.831 to −2.907; <0.001	0.0	−4.284; −7.599 to −0.968; 0.011	42.3

95% CI = 95% confidence interval, BMI = body mass index, DBP = diastolic blood pressure, GSE = grape seed extract, SBP = systolic blood pressure, WMD = weighted mean difference.

(regression coefficient: −0.082 and −0.037; $P = 0.002$ and 0.002, respectively).

4. Discussion

The key finding of this study was that grape seed extract exerted a beneficial impact on blood pressure, and this impact was more obvious in younger or obese subjects, as well as in patients with metabolic disorders. Moreover, study design, randomization, and baseline blood pressure were identified as the possible causes of heterogeneity. As far as we know, this is to date the largest meta-analysis that has evaluated the relationship between grape seed extract treatment and blood pressure changes.

In a previous meta-analysis by Feringa et al,[20] grape seed extract was reported to significantly reduce SBP by 1.54 mm Hg, but no material change was noted for DBP, which was likely due to the relatively small sample size. With the accumulation of data from subsequent clinical trials, we therefore conducted an updated meta-analysis that involved 16 trials and 810 study subjects, and our findings demonstrated the apparently beneficial impact of grape seed extract on both SBP and DBP. The biological mechanisms underlying this benefit so far remain largely speculative. It is widely recognized that grape seed extract, a polyphenolic compound, contains antioxidants that can help prevent cell damage caused by free radicals. Experimental data have indicated that grape seed extract could lead to an endothelium-dependent relaxation in rabbit aorta.[21] Moreover, Lopez-Sepulveda et al[22] found that polyphenols in red wine were able to improve endothelial function of large vessels in female spontaneously hypertensive rats by enhancing nitric oxide bioactivity and lowering blood pressure. Further experiments by Wallerath et al suggested that resveratrol, a polyphenolic phytoalexin in red wine, could enhance the expression and activity of endothelial nitric oxide synthase in human umbilical vein endothelial cells,[23] possibly through the activation of PI3K/Akt pathway.[21] These findings potentially contribute to a better understanding of the mechanism of grape seed extract treatment and blood pressure regulation.

More importantly, we extended previous results and found that the beneficial impact of grape seed extract on blood pressure was more evident in clinical trials enrolling younger or obese subjects. On one hand, it is generally believed that older persons have greater exposure to environmental triggers for elevated blood pressure than the younger.[24] With aging, it has been postulated that the effectiveness of grape seed extract on blood pressure regulation may be less obvious in the presence of these triggers. This proposition was substantiated in our age-stratified analysis. On the other hand, there is a wide recognition that obesity is an independent risk factor for cardiovascular diseases, including hypertension.[25,26] Moreover, obese people tend to have higher blood pressure than lean people,[27] which might be a possible explanation for the more evidence impact of grape seed extract on blood pressure, especially SBP, in clinical trials enrolling subjects with mean BMI ≥ 25 kg/m^2 than those with lower mean BMI in our stratified analysis.

Another finding in this meta-analysis that deserves discussion is that the low-dose phenols were observed to have a more favorable impact on blood pressure than the high-dose phenols. This observation is counterintuitive based on current knowledge about the relationship between grape seed extract and blood pressure. After serious analyses, we found that study design was behind this counterintuitive observation, as 9 of 10 trials using low-dose phenols followed a parallel design compared with 4 of 6 trials using high-dose phenols in a cross-over design. Actually in

this meta-analysis, blood pressure was remarkably reduced in parallel trials, while no material changes were noted in cross-over trials. For this reason, it is easy to interpret the apparent paradox between low-dose and high-dose phenols. Moreover, it is also worth noting that the parallel trials (range: 4–16 weeks, mean: 9.3 weeks) had a significantly longer duration of grape seed extract treatment than the cross-over trials (range: 2–8 weeks, mean: 4.8 weeks), which might explain the nonsignificant reduction in blood pressure for cross-over trials. Indeed, the impact of long-term treatment with grape seed extract on blood pressure is significantly better than that of short-term treatment in our stratified analysis. However, it is important to note that the longest duration of treatment in this meta-analysis was 16 weeks, which might not be enough to unravel the health benefits conferred by grape seed extract.

Besides study design, randomization was identified as another possible cause of heterogeneity in this meta-analysis. This underlying reason for the confounding effect of randomization is the unbalanced statistical power between the single-blinded (4 trials: 247 subjects) and double-blinded (12 trials: 668 subjects) clinical trials. As with all meta-analyses, heterogeneity is an unavoidable issue in most cases.[28] Exploring possible causes of heterogeneity is critical for the interpretation of pooled estimates. In this meta-analysis, we adopted both stratified and regression analyses, and importantly found that the efficacy of grape seed extract treatment may be dependent on baseline blood pressure levels, as higher blood pressure at baseline was linked to a greater reduction in blood pressure after grape seed extract treatment. However, our stratified analyses identified that grape seed extract can reduce blood pressure significantly in patients with metabolic syndrome, as well as in patients with pre- and stage 1 hypertension, while no significance was noted in healthy subjects and hypertensive patients. Considering the limited number of trials enrolling hypertensive patients and the confounding effect of antihypertensive medications, it is critical to examine the impact of grape seed extract treatment on blood pressure changes among hypertensive patients. Nevertheless, the current findings led us to propose that the beneficial impact of grape seed extract on blood pressure was more obvious in patients with metabolic disorders.

There are some limitations in this meta-analysis. First, because all eligible articles were only retrieved from the English-language literature and the "grey" literature was not covered, it remains a possibility of selection bias. However, as reflected by our Begg and Egger tests, there was no indication of publication bias. Second, in spite of exhaustive stratified and meta-regression analyses, there are still other unexplained causes of heterogeneity. Third, given the relatively small sample sizes, especially in stratified analyses, more and larger clinical trials are warranted to quantify the effect-size estimates reliably.

In conclusion, our findings demonstrate that grape seed extract can exert a beneficial impact on blood pressure, and this impact was more obvious in younger or obese subjects, as well in patients with metabolic disorders. In view of above limitations, this meta-analysis emphasizes the need for confirmation of our findings in a large-scale, long-term, multiple-dose randomized controlled trial, especially among hypertensive patients.

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