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File: ■ Grape (*Vitis vinifera*, Vitaceae) Seed Extract
■ Blood Pressure
■ Meta-analysis

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RE: Meta-analysis Reports that Grape Seed Extract Reduces Blood Pressure in Some Groups

Zhang H, Liu S, Li L, et al. The impact of grape seed extract treatment on blood pressure changes: A meta-analysis of 16 randomized controlled trials. *Medicine (Baltimore)*. August 2016;95(33):e4247. doi: 10.1097/MD.0000000000004247.

Oxidative stress contributes to the development of hypertension, and grape (*Vitis vinifera*, Vitaceae) seed extract can help reduce oxidative stress damage. Some clinical trials have shown that grape seed extract (GSE) can reduce blood pressure (BP), but the effect is not consistent. This meta-analysis evaluated the impact of GSE on systolic and diastolic blood pressure (SBP and DBP, respectively) by analyzing available randomized controlled trials.

Database and literature searches identified randomized clinical trials published in English that compared effects of GSE treatment and placebo on SBP and DBP with a treatment period of at least two weeks. A total of 16 clinical trials including 810 subjects were included in the final analysis, derived from 12 publications, four of which included two doses of GSE that were separately analyzed. Of the 16 clinical trials, 11 followed a parallel design and five followed a crossover design; 11 were double-blinded and five were single-blinded; and seven had GSE treatment < 8 weeks and nine had GSE treatment ≥ 8 weeks. [Note: These numbers are inconsistently stated in the paper and derived from the summary table.] Dosages of GSE ranged from 100 to 2000 mg/d. Trials were conducted in Asia, America, Europe, Australia, and Colombia. Four of the clinical trials were conducted in patients with prehypertension and stage 1 hypertension, two in patients with hypertension, three in patients with metabolic syndrome, one in patients with "above-average vascular risk," two in women with menopausal symptoms, and four in healthy subjects.

Overall analyses found significant reductions for SBP (weighted mean difference [WMD] relative to placebo = −6.077 mmHg; 95% confidence interval [CI], −10.736 to −1.419; P = 0.011) and DBP (WMD = −2.803 mmHg; 95% CI, −4.417 to −1.189; P = 0.001) after GSE treatment, with strong and moderate evidence of heterogeneity (I^2 = 94.0% and 62.4%, respectively), respectively. To find potential causes of heterogeneity, subgroup

analyses were performed. Grouping by age, although the WMD in SBP was almost identical in studies enrolling younger subjects (mean age < 50 years) versus older subjects, BP reductions were statistically significant only in studies with younger subjects for both SBP (WMD = −6.049 mmHg; P = 0.005) and DBP (WMD = −3.116 mmHg; P < 0.001), and heterogeneity was improved. Reduction in SBP was greater in trials whose subjects had an average body mass index [BMI] ≥ 25 kg/m^2 (WMD = −7.420 mmHg; P = 0.024), though still statistically significant in trials with subjects having a mean BMI < 25 kg/m^2 (WMD = −4.469 mmHg; P < 0.001). Heterogeneity improved in trials with lower BMIs for both SBP (I^2 = 0.0%) and DBP (I^2 = 21.0%).

Grouping by study design, BP was reduced in parallel trials (SBP: WMD = −8.045 mmHg; P = 0.006 and DBP: WMD = −3.791 mmHg; P < 0.001) but not in crossover trials. Greater BP reductions were seen in single-blinded trials (SBP: WMD = −14.111 mmHg; P = 0.001 and DBP: WMD = −5.418 mmHg; P < 0.001) versus double-blinded trials (SBP: WMD = −3.969 mmHg; P < 0.001 and DBP: WMD = −1.831 mmHg; P = 0.009). Reductions in BP were greater in longer trials (≥ 8 weeks) (SBP: WMD = −7.708 mmHg; P = 0.019 and DBP: WMD = −4.347 mmHg; P < 0.001) than in shorter trials (< 8 weeks). Significant reductions in SBP (WMD = −9.051 mmHg; P = 0.001) and DBP (WMD = −4.637 mmHg; P < 0.001) were observed only in trials using lower GSE dosages (< 800 mg/d of phenolic compounds).

Grouping according to subject baseline status showed significant SBP reduction in patients with metabolic syndrome (WMD = −8.487 mmHg; P < 0.001), patients with pre- and stage 1 hypertension (WMD = −10.811 mmHg; P = 0.028), and subjects with "others" health status (menopausal or "above-average vascular risk"; WMD = −5.369 mmHg; P < 0.001), but not in perfectly healthy subjects or in patients with full-blown hypertension. Patterns of reduction in DBP were similar, with significant effects only in studies of patients with pre- and stage 1 hypertension (WMD = −3.791 mmHg; P = 0.011) or "others" (WMD = −4.284 mmHg; P = 0.011).

To further explore heterogeneity, mean age, male gender, BMI, and baseline SBP and DBP "between the treatment and placebo groups" were incorporated in a meta-regression model. Significant negative associations with reduced SBP and DBP after GSE treatment were found for age (regression coefficient: −0.126 and −0.056; P = 0.005 and 0.003, respectively), BMI (regression coefficient: −0.232 and −0.099; P = 0.008 for both), baseline SBP (regression coefficient: −0.050 and −0.022; P = 0.004 and 0.002, respectively), and baseline DBP (regression coefficient: −0.082 and −0.037; P = 0.002 for both).

The authors of this meta-analysis believe it is the largest such analysis to evaluate the effect of GSE on BP. This meta-analysis found that GSE treatment had a beneficial effect on both SBP and DBP, whereas a previous smaller meta-analysis showed a significant change only in SBP.[1] Differences in study design, randomization, and baseline BP were possible causes of heterogeneity. Interestingly, low GSE dosages showed more effect on BP than high dosages. This unexpected finding is attributed to study design, as nine of ten low-dose trials followed a parallel design, while four of six high-dose trials used a crossover design. Parallel trials showed reduced BP, while no changes were noted in crossover trials. Parallel trials also had a significantly longer duration of GSE treatment compared to crossover trials (mean 9.3 weeks versus 4.8 weeks, respectively), and studies with longer treatment times showed better effects. Greater reduction in BP after GSE treatment was seen in studies enrolling subjects with

higher baseline BP, though no significant effects were seen in patients with hypertension. The authors comment, "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." Indeed, larger and longer clinical trials are required to quantify the effects of GSE more precisely. Future meta-analyses should also consider the total phenolic content of GSE products as a possible influence on effect size.

—*Alexis Collins, MS*

Reference

[1]Feringa HH, Laskey DA, Dickson JE, Coleman CI. The effect of grape seed extract on cardiovascular risk markers: a meta-analysis of randomized controlled trials. *J Am Diet Assoc*. 2011;111(8):1173-1181.

Referenced article can be accessed at http://journals.lww.com/md-journal/Fulltext/2016/08160/The_impact_of_grape_seed_extract_treatment_on.6.aspx.