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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, f = 93.4%) and DBP (WMD: −1.69 mmHg, 95% CI: −3.12, −0.27, p = .01, f = 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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KEYWORDS
Grape products; Blood pressure; Hypertension; Systematic review; Meta-analysis

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
antioxidants derived from vegetables and fruits.\textsuperscript{[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 mechanisms such as vasodilation and suppressing the ROS production.\textsuperscript{[7,13–15]}

Grape products are listed as one of the excellent sources of plant polyphenolic antioxidant compounds especially for their proanthocyanidins content.\textsuperscript{[16]} There are several studies demonstrating the protective effect of grape products on abnormal metabolic measurements including BP.\textsuperscript{[17,18]} Proanthocyanidins, anthocyanins, flavonols, flavanols, resveratrol, and phenolic acids are phenolic compounds in grape products.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[21]} The Population (aged >18 years old), Intervention (grape and grape products supplementation), Comparison (matched control group), Outcome (blood pressure) (PICO(S) 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 supplantations 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. 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 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. An $I^2$ value $>$50% was considered to indicate substantial heterogeneity between trials. 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
Records identified through database searching: PubMed (186), Scopus (505), and The Cochrane library (234) and Embase (273) (n=1198)

Duplicate Records Excluded: (n=323)

Records screened by title/abstracts (n=875)

Records excluded: 742 unrelated studies 63 animal studies 40 review studies (n=845)

Full-text articles assessed for eligibility (n=30)

Did not reported blood pressure (n=2)

Studies included in qualitative synthesis (n=28)

Studies included in quantitative synthesis (meta-analysis) (n=28)

**Figure 1.** PRISMA flow diagram of study selection process.

reporting. 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 to 52 weeks. The sample size of
| 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     | healthy adults                                   | 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 Sivaprasapillai (A)        | 2009              | USA                 | parallel     | Metabolic Syndrome                              | 18: 7 M, 11 F | 4                     |
| B Sivaprasapillai (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                    |
| J Jiménez                    | 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 1 hypertension                   | 70: 38 M, 32 F | 8                     |
| J Tomé-Cameiro               | 2013              | Spain               | Parallel     | hypertensive patients with coronary artery disease | 22: 22 M     | 52                    |
| G Siassos                    | 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 Lampert                   | 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 |
|-----------|-----------|--------------|-------------|------------|
| 58 ± 9    | 28.4 ± 4.4 | Grape Seed Extract | 2000 mg | control yogurt | 36 | 36 | NR |
| 43 ± 9.16 | 26.5 ± 3.2 | Concord grape juice | 350 ml | Placebo | 21 | 19 | NR |
| 51 ± 8.24 | 25.8 ± 3.29 | 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 | 25.3 ± 2.71 | red grape extract | 173 mg | Placebo | 15 | 18 | |
| 50 ± 13   | 29.3 ± 1.4 | grape juice | 150 ml | without supplementation | 8 | 15 | NR |
| 51 ± 2.4  | 24.2 ± 0.66 | Grape Seed Extract | 200 mg | Placebo | 21 | 20 | |
| 52.9 ± 2  | 24.1 ± 0.62 | Grape Seed Extract | 400 mg | Placebo | 20 | 20 | |
| 35.5 ± 11.8 | 26.1 ± 4.7 | 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    | 36 ± 1.4   | Grape Seed Extract | 150 mg | Placebo | 9 | 9 | NR |
| 47 ± 4    | 37 ± 2.1   | Grape Seed Extract | 300 mg | Placebo | 9 | 9 | |
| 41 ± 13   | 28 ± 3.8   | grape juice | 7 mL/kg/d | Placebo | 30 | 34 | |
| 52.1 ± 8.1 | 52.1 ± 8.1 | grape seed | 1300 mg | Placebo | 50 | 50 | NR |

| | | | | |
|---|---|---|---|---|

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. Of the 190 subjects that underwent actual screening, eighty-four 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. 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.
Table 1. (Continued).

| IG       | CG         | IG       | CG         | Treatment group                  | intervention dose | control | IG | CG | compliance |
|----------|------------|----------|------------|----------------------------------|-------------------|---------|----|----|------------|
| 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 |            |

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.

52 ± 9 51 ± 10 30.82 ± 5.67 30.58 ± 29.69 Grape Seed Extract 200 mg Placebo 26 22
Sixty six subjects were screened for the study and 34 met the criteria for prehypertension. Two refused to participate in the trial and remaining 32 were randomized.

62.9 ± 7.69 64.5 ± 5.32 25.3 ± 2.36 25.7 ± 2.95 Grape Seed Extract 300 mg Placebo 35 35
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.

60 ± 10 57 ± 10 32.2 ± 5.1 30.5 ± 3.8 grape extract Concord Grape Juice grape seed procyanidins extract 350 mg Placebo 13 9 NR
Of the 190 subjects that underwent actual screening, eighty-four 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.

49.9 ± 9 49.4 ± 3 23.21 ± 4.1 23.21 ± 4.1 Concord Grape Juice grape seed procyanidins extract 240 ml Placebo 26 26 NR

51.33 ± 5.31 49.4 ± 3 25.41 ± 0.8 25.11 ± 0.7 grape seed procyanidins extract 300 mg management plan 35 47 NR

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).

| Treatment group | Intervention | Sample Size | compliance |
|-----------------|--------------|-------------|------------|
| CG | IG | CG | CG | 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 |
| 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 |
| 43.2 ± 3 | 43.2 ± 3 | 24.6 ± 2.5 | 24.6 ± 2.5 | Concord grape juice | 355 ml | Placebo | 25 | 25 |
| 62.3 ± 9.1 | 62.7 ± 7.5 | NR | NR | Grape Seed Extract | 2000 mg | Placebo | 23 | 10 |
| 50.7 ± 10.9 | 51.6 ± 9.4 | 29.7 ± 22.2 | 29.1 ± 21.8 | raisins | 36 g | Regular diet | 28 | 27 |

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. Of the 60 participants enrolled for the trial, 51 were eligible and were randomized to either the control group or the CR intervention group. 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. Importantly no patient drop out of the study nor adverse side effects were noted during the entire clinical trial period. 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.
 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.

Table 1. (Continued).

| Means Age | Means BMI | Intervention | Sample Size | compliance |
|------------|------------|--------------|-------------|------------|
| IG 44 ± 10 | CG 42 ± 10 | grape seed extract | Placebo 12 | 17 |
| IG 34 ± 7 | CG 31 ± 9 | intervention dose 300 mg | | |
| Treatment group | control | IG | CG |
| 25–54 | 20–53 | NR | NR | grape juice raisins | 10 ml/kg/day | Not consume juice | 15 | 13 |
| 30.8 ± 7.5 | 29.8 ± 5.23 | 24.4 ± 2.81 | 24.4 ± 2.99 | 90 g | Regular diet | 22 | 14 |
| 30–70 | 30–70 | 32.93 ± 4.82 | 32.64 ± 4.51 | Grape Powder | 60 g | Placebo | 20 | 20 |

Abbreviations: IG, intervention group; CG, control group; NR, not reported; F, Female; M, Male; NR, not reported.
the included studies ranged from 18\textsuperscript{[17]} to 84\textsuperscript{[30]} participants. The design of all studies was parallel, except for six studies.\textsuperscript{[28,31–35]} Included studies enrolled subjects with cardiovascular disease,\textsuperscript{[29,32,33,36–38]} metabolic syndrome,\textsuperscript{[17,35]} type 2 diabetes mellitus,\textsuperscript{[59–42]} pre and mildly hypertensive subjects,\textsuperscript{[18,30,43]} healthy adults\textsuperscript{[28,31,34,44–51]} and others.\textsuperscript{[52,53]} Selected studies carried out in diverse countries such as USA,\textsuperscript{[17,18,32,33,35,43,44,47]} Japan,\textsuperscript{[45,48]} Spain,\textsuperscript{[29,46]} Greece,\textsuperscript{[28,42,50,52]} Iran,\textsuperscript{[39,40]} Italy,\textsuperscript{[30]} United Kingdom,\textsuperscript{[34]} Tunisia,\textsuperscript{[53]} South Korea,\textsuperscript{[37]} France,\textsuperscript{[38,41]} Denmark,\textsuperscript{[36]} Chile,\textsuperscript{[49]} Brazil,\textsuperscript{[51]} Australia.\textsuperscript{[31]} Some studies enrolled only males\textsuperscript{[29,37,49]} and females\textsuperscript{[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.\textsuperscript{[39]} In addition, various types of grape products supplements have been used in studies, for example: grape extract,\textsuperscript{[29,36,41,46]} grape juice,\textsuperscript{[28,32,34,37,44,47,51]} and grape seed extract,\textsuperscript{[17,18,30,31,38–40,43,45,48,53]} raisins\textsuperscript{[42,50,52]} and others.\textsuperscript{[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.\textsuperscript{[18,32,34,41,42,49,50,52]} Allocation concealment reported in six studies.\textsuperscript{[18,28,32,40,41,45]} Moreover, two trials had high risk of bias regarding blinding of participants and personnel\textsuperscript{[35,44]} and six studies did not provide sufficient information about participants’ blindness.\textsuperscript{[30,42,45,46,49,51]} Only three trials had low risk of bias concerning outcome assessors.\textsuperscript{[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.\textsuperscript{[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                    | U                                     | L                          | L                      |
| AS Hansen        | U                           | U                      | L                   | H                    | L                                     | U                          | L                      |
| AE Banini        | U                           | L                      | L                   | L                    | H                                     | U                          | L                      |
| A Sano           | U                           | L                      | L                   | H                    | L                                     | U                          | L                      |
| JP Jiménez       | U                           | L                      | L                   | H                    | L                                     | U                          | L                      |
| B Sivaprakasapillai | U                        | U                      | L                   | L                    | L                                     | U                          | L                      |
| MM Dohadwala     | L                           | L                      | L                   | L                    | L                                     | U                          | L                      |
| PB Mellen        | U                           | U                      | L                   | L                    | L                                     | U                          | L                      |
| P-Gargari        | U                           | L                      | L                   | L                    | L                                     | U                          | L                      |
| R Krikorian      | U                           | U                      | L                   | H                    | L                                     | U                          | L                      |
| M. Robinson      | U                           | L                      | 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                   | L                    | L                                     | U                          | L                      |
| G Belcaro        | U                           | L                      | L                   | L                    | H                                     | U                          | U                      |
| M Hokayem        | U                           | L                      | L                   | L                    | L                                     | U                          | L                      |
| M Terauchi       | U                           | L                      | L                   | L                    | L                                     | U                          | L                      |
| PT Kanellos 2014 | L                           | U                      | L                   | L                    | U                                     | L                          | L                      |
| I Urquiaga       | L                           | U                      | L                   | L                    | L                                     | U                          | L                      |
| DJ Lamport       | L                           | U                      | L                   | L                    | L                                     | U                          | L                      |
| K Turki          | U                           | U                      | L                   | L                    | L                                     | U                          | L                      |
| AC Kaliara       | L                           | U                      | L                   | L                    | L                                     | U                          | L                      |
| E Park 2016      | L                           | L                      | L                   | L                    | L                                     | L                          | L                      |
| LT Toscana       | H                           | H                      | L                   | L                    | L                                     | U                          | L                      |
| PT Kanellos 2017 | L                           | U                      | L                   | L                    | L                                     | L                          | L                      |
| Q Duclos         | U                           | U                      | L                   | L                    | H                                     | L                          | 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/m²) (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.](image)
Table 3. Subgroup analyses of grape intake on blood pressure.

| Subgroup analyses of grape intake on SBP level | NO | WMD (95%CI) | P within group | P heterogeneity | I² |
|-----------------------------------------------|----|-------------|----------------|----------------|----|
| 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 (−3.47, 2.509) | 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/m²)                           |    |             |                |                |     |
| 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/m²)                           |    |             |                |                |     |
| 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.
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/m² (WMD: −3.34 mmHg, 95% CI: −5.81, −0.87, p = .008) and baseline BMI >30 kg/m² (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/m².

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. [58] 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
Figure 4. Funnel plots for SBP, and DBP.
angiotensin-II, which is a vasoconstrictor. Phenolic compounds deactivate metal ions by its chelation ability. Because ACE is a metalloenzyme, phenolic compounds bond with its zinc ion and therefore decrease its activity. 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/m². Larger, better designed trials, that specifically include hypertensive subjects, are required to verify our results in the future.

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**References**

[1] Kearney, P. M.; Whelton, M.; Reynolds, K.; Muntner, P.; Whelton, P. K.; He, J. Global Burden of Hypertension: Analysis of Worldwide Data. *Lancet (London, England)*. 2005, 365(9455), 217–223. DOI: 10.1016/S0140-6736(05)17741-1.

[2] Al Shukor, N.; Van Camp, J.; Gonzales, G. B.; Staljanssens, D.; Struijs, K.; Zotti, M. J.; Raes, K.; Smagghe, G. Angiotensin-converting enzyme inhibitory effects by plant phenolic compounds: a study of structure activity relationships. *J Agric Food Chem.* 2013 Dec 4;61(48):11832-9. doi: 10.1021/jf404641v. Epub 2013 Nov 21. PMID: 24219111.

[3] Pisoschi, A. M.; Pop, A. The Role of Antioxidants in the Chemistry of Oxidative Stress: A Review. *Eur. J. Med. Chem.* 2015, 97, 55–74.
[25] Borenstein, M.; Hedges, L. V.; Higgins, J. P.; Rothstein, H. R. Introduction to Meta-analysis; Chichester, UK: John Wiley & Sons, 2011.

[26] Evans, M.; Wilson, D.; Guthrie, N. A Randomized, Double-blind, Placebo-controlled, Pilot Study to Evaluate the Effect of Whole Grape Extract on Antioxidant Status and Lipid Profile. *J. Funct. Foods.* 2014, 7, 680–691. DOI: 10.1016/j.jff.2013.12.017.

[27] Zunino, S. J.; Peerson, J. M.; Freytag, T. L.; Breksa, A. P.; Bonnel, E. L.; Woodhouse, L. R.; Storms, D. H. Dietary grape powder increases IL-1β and IL-6 production by lipopolysaccharide-activated monocytes and reduces plasma concentrations of large LDL and large LDL-cholesterol particles in obese humans. *Br J Nutr.* 2014 Aug 14;112(3):369-80. doi: 10.1017/S0007114514000890. Epub 2014 May 15. PMID: 24832727.

[28] Siasos, G.; Tousoulis, D.; Kokkou, E.; Oikonomou, E.; Kollia, M.-E.; Verveniotis, A.; Gouliopoulos, N.; Zisimos, K.; Plastiras, A.; Maniatis, K.; et al. Favorable Effects of Concord Grape Juice on Endothelial Function and Arterial Stiffness in Healthy Smokers. *Am. J. Hypertens.* 2014, 27(1), 38–45.

[29] Tomé-Carneiro, J.; Larrosa, M.; Yáñez-Gascón, M. J.; Dávalos, A.; Gil-Zamorano, J.; González-V, Garcia-Almagro, F. J.; Ruiz Ros, J. A.; Tomás-Barberán, F. A.; Espin, J. C.; et al. One-year Supplementation with a Grape Extract Containing Resveratrol Modulates Inflammatory-related microRNAs and Cytokines Expression in Peripheral Blood Mononuclear Cells of Type 2 Diabetes and Hypertensive Patients with Coronary Artery Disease. *Pharmacol. Res.* 2013, 72, 69–82. DOI: 10.1016/j.phrs.2013.03.011.

[30] Belcaro, G.; Ledda, A.; Hu, S.; Cesaroni, M. R.; Feragalli, B.; Dugall, M. Grape Seed Procyanidins in Pre-and Mild Hypertension: A Registry Study. In *Evidence-Based Complementary and Alternative Medicine, 2013*; pp 2013.

[31] Clifton, P. M. Effect of Grape Seed Extract and Quercetin on Cardiovascular and Endothelial Parameters in High-Risk Subjects. *J Biomed Biotechnol.* 2004; 2004(5):272–278. doi: 10.1155/S1110724304403088. PMID: 15577189; PMCID: PMC1082891.

[32] Dohadwala, M. M.; Hamburg, N. M.; Holbrook, M.; Kim, B. H.; Duess, M.-A.; Levi, A.; Titat, M.; Chung, W. B.; Vincent, F. B.; Caiano, T. L.; et al. Effects of Concord Grape Juice on Ambulatory Blood Pressure in Prehypertension and Stage 1 Hypertension. *Am. J. Clin. Nutr.* 2010, 92(5), 1052–1059.

[33] Mellen, P. B.; Daniel, K. R.; Brosnihan, K. B.; Hansen, K. J.; Herrington, D. M. Effect of Muscadine Grape Seed Supplementation on Vascular Function in Subjects with or at Risk for Cardiovascular Disease: A Randomized Crossover Trial. *J. Am. Coll. Nutr.* 2010, 29(5), 469–475. DOI: 10.1080/07317724.2010.10719883.

[34] Lampert, D. J.; Lawton, C. L.; Merat, N.; Jamson, H.; Myrissa, K.; Hofman, D.; Chadwick, H. K.; Quadt, F.; Wightman, J. D.; Dye, L.; et al. Concord Grape Juice, Cognitive Function, and Driving Performance: A 12-wk, Placebo-controlled, Randomized Crossover Trial in Mothers of Preteen Children. *Am. J. Clin. Nutr.* 2016, 103(3), 775–783.

[35] Duclos, Q.; Effects of A Standardized, Freeze-Dried Grape Powder in Adults with Metabolic Syndrome. 2017.

[36] Hansen, A. S.; Markmann, P.; Dragsted, L.; Nielsen, L.-L. F.; Nielsen, S.; Grenbaek, M. Effect of Red Wine and Red Grape Extract on Blood Lipids, Haemostatic Factors, and Other Risk Factors for Cardiovascular Disease. *Eur. J. Clin. Nutr.* 2005, 59(3), 449–455. DOI: 10.1038/sj.ejcn.1602107.

[37] Park, Y. K.; Kim, J. S.; Kang, M. H. Concord Grape Juice Supplementation Reduces Blood Pressure in Korean Hypertensive Men: Double-blind, Placebo Controlled Intervention Trial. *Biofactors.* 2004, 22(1–4), 145–147. DOI: 10.1002/biof.5520220128.

[38] Ras, R. T.; Zock, P. L.; Zebregs, Y. E.; Johnston, N. R.; Webb, D. J.; Draijer, R. Effect of Polyphenol-rich Grape Seed Extract on Ambulatory Blood Pressure in Subjects with Pre- and Stage I Hypertension. *Br. J. Nutr.* 2013, 110(12), 2234–2241. DOI: 10.1017/S000711451300161X.

[39] Pourghassem-Gargari, B.; Abedini, S.; Baebei, H.; Aliasgarzadeh, A.; Pourabdollahi, P. Effect of Supplementation with Grape Seed (Vitis Vinifera) Extract on Antioxidant Status and Lipid Peroxidation in Patient with Type II Diabetes. *J. Med. Plant Res.* 2011, 5(10), 2029–2034.

[40] Abedini, S.; Pourghassem Gargari, B.; Baebei, H.; Aliasgarzadeh, A.; Pourabdollahi, P. Effect of Supplementation with Grape Seed Extract (Vitis Vinifera) on Serum Lipid Profiles in Patient with Type 2 Diabetes. *Iranian J. Endocrinol. Metabol.* 2013, 15(1), 59–66.

[41] Hokayem, M.; Blond, E.; Vidal, H.; Lambert, K.; Meugnier, E.; Feillet-Coudray, C.; Coudray, C.; Pesenti, S.; Lutyon, C.; Lambert-Porcheron, S.; et al. Grape Polyphenols Prevent Fructose-induced Oxidative Stress and Insulin Resistance in First-degree Relatives of Type 2 Diabetic Patients. *Diabetes Care.* 2013, 36(6), 1454–1461.

[42] Kanellos, P. T.; Kaliora, A. C.; Tentolouris, N. K.; Argiva, V.; Perrea, D.; Kalogeropoulos, N.; Kountouri, A. M.; Karathanos, V. T. A pilot, randomized controlled trial to examine the health outcomes of raisin consumption in patients with diabetes. Nutrition. 2014 Mar;30(3):358-64. doi: 10.1016/j.nut.2013.07.020. Epub 2013 Nov 18. PMID: 24262513.

[43] Robinson, M.; Lu, B.; Edirisinghe, I.; Kappagoda, C. Effect of Grape Seed Extract on Blood Pressure in Subjects with Pre-hypertension. *J. Pharm. Nutr. Sci.* 2012, 2(2), 155–159.

[44] Banini, A. E.; Boyd, L. C.; Allen, J. C.; Allen, H. G.; Sauls, D. L. Muscadine Grape Products Intake, Diet and Blood Constituents of Non-diabetic and Type 2 Diabetic Subjects. *Nutrition.* 2006, 22(11–12), 1137–1145. DOI: 10.1016/j.nut.2006.08.012.
[45] Sano, A.; Uchida, R.; Saito, M.; Shioya, N.; Komori, Y.; Tho, Y.; Hashizume, N. Beneficial effects of grape seed extract on malondialdehyde-modified LDL. J Nutr Sci Vitaminol (Tokyo). 2007 Apr; 53(2):174-82. doi: 10.3177/ jnsv.53.174. PMID: 17616006.

[46] Jiménez, J. P.; Serrano, J.; Tabernerio, M.; Arranz, S.; Díaz-Rubio, M. E.; García-Diz, L.; Goñi, I.; Saura-Calixto, F. Effects of grape antioxidant dietary fiber in cardiovascular disease risk factors. Nutrition. 2008 Jul-Aug; 24(7-8):646-53. doi: 10.1016/j.nut.2008.03.012. Epub 2008 May 15. PMID: 18485668.

[47] Krikorian, R.; Boesplug, E. L.; Fleck, D. E.; Stein, A. L.; Wightman, J. D.; Shidler, M. D.; Sadat-Hossieny, S.; et al. Concord Grape Juice Supplementation and Neurocognitive Function in Human Aging. J. Agric. Food Chem. 2012, 60(23), 5736–5742.

[48] Terauchi, M.; Horiguchi, N.; Kajiyama, A.; Akiyoshi, M.; Owa, Y.; Kato, K.; Kubota, T.; et al. Effects of Grape Seed Proanthocyanidin Extract on Menopausal Symptoms, Body Composition, and Cardiovascular Parameters in Middle-aged Women: A Randomized, Double-blind, Placebo-controlled Pilot Study. Menopause. 2014, 21(9), 990–996.

[49] Urquiaga, I.; D’Acuña, S.; Pérez, D.; Dicenta, S.; Echeverría, G.; Rigotti, A.; Leighton F. Wine Grape Pomace Flour Improves Blood Pressure, Fasting Glucose and Protein Damage in Humans: A Randomized Controlled Trial. Biol. Res. 2015, 48(1), 49.

[50] Kanellos, P. T.; Kaliora, A. C.; Protogerou, A. D.; Tentoulouris, N.; Perrea, D. N.; Karathanos, V. T. The Effect of Raisins on Biomarkers of Endothelial Function and Oxidant Damage: an Open-label and Randomized Controlled Intervention. Food Res. Int. 2017, 102, 674–680. DOI: 10.1016/j.foodres.2017.09.061.

[51] Lydiane Tavares Toscano, Alexandre Sérgio Silva, Luciana Tavares Toscano, Renata Leite Tavares, Aline Camarão Telles Bisoto, Adriano Costa de Camargo, Câssia Surama Oliveira da Silva, Maria da Conceição Rodrigues Gonçalves, Ferreidoon Shahidi. Phenolics from Purple Grape Juice Increase Serum Antioxidant Status and Improve Lipid Profile and Blood Pressure in Healthy Adults under Intense Physical Training. J. Funct. Foods. 2017, 33, 419–424. DOI: 10.1016/j.jff.2017.03.063.

[52] Kaliora, A. C.; Kokkinos, A.; Diolintzi, A.; Stoupaki, M.; Giousari, A.; Kanellos, P. T.; Dedoussis, G. V. Z.; Vlachogiannakos, J.; Revenas, C.; Ladas, S. D.; et al. The Effect of Minimal Dietary Changes with Raisins in NAFLD Patients with Non-significant Fibrosis: A Randomized Controlled Intervention. Food Funct. 2016, 7(11), 4533–4544.

[53] Turki, K.; Charradi, K.; Boukhalfa, H.; Belhaj, M.; Limam, F.; Aouani, E. Grape Seed Powder Improves Renal Failure of Chronic Kidney Disease Patients. Excli J. 2016, 15, 424. DOI: 10.17179/excli2016-363.

[54] Woerdeman, J.; Poelgeest, E.; Ket, J.; Eringa, E.; Serné, E.; Smulders, Y. Do Grape Polyphenols Improve Metabolic Syndrome Components? A Systematic Review. Eur. J. Clin. Nutr. 2017, 71(12), 71. DOI: 10.1038/ ejcn.2016.227.

[55] Li, S.-H.; Zhao, P.; Tian, H.-B.; Chen, L.-H.; Cui, L.-Q. Effect of Grape Polyphenols on Blood Pressure: A Meta-analysis of Randomized Controlled Trials. PloS One. 2015, 10(9), e0137665. DOI: 10.1371/journal. pone.0137665.

[56] MacDonald, J.; MacDougall, J.; Hogben, C. The Effects of Exercise Duration on Post-exercise Hypotension. J. Human Hypertens. 2000, 14(2), 125–129. DOI: 10.1038/sj.jhh.1000953.

[57] Nassiri-Asl, M.; Hosseinzadeh, H. Review of the Pharmacological Effects of Vitis Vinifera (Grape) and Its Bioactive Constituents: An Update. Phytother Res. 2016, 30(9), 1392–1403. DOI: 10.1002/trp.5644.

[58] Granato, D.; Md, M. C.; Fogliano, V.; Ruth, S. Effects of Geographical Origin, Varietal and Farming System on the Chemical Composition and Functional Properties of Purple Grape Juices: A Review. Trends Food Sci. Technol. 2016, 52, 31–48. DOI: 10.1016/j.tifs.2016.03.013.

[59] Dusman, E.; Almeida, I. V.; Pinto, E. P.; Lucchetta, L.; Vicentini, V. E. P. Influence of Processing and Storage of Integral Grape Juice (Vitis Labrusca L.) On Its Physical and Chemical Characteristics, Cytotoxicity, and Mutagenicity in Vitro. Gene. Mol. Res. GMR. 2017, 16(2), 2. DOI: 10.4238/gmr16029670.

[60] Edirisinghe, I.; Burton-Freeman, B.; Tissa Kappagoda, C. Mechanism of the Endothelium-dependent Relaxation Evoked by a Grape Seed Extract. Clinical Sci. 2008, 114(4), 331–337. DOI: 10.1042/CS20070264.

[61] Wallerath, T.; Deckert, G.; Ternes, T.; Anderson, H.; Li, H.; Witte, K.; Förstermann, U. Resveratrol, a Polyphenolic Phytoalexin Present in Red Wine, Enhances Expression and Activity of Endothelial Nitric Oxide Synthase. Circulation. 2002, 106(13), 1652–1658.

[62] M. Quiñones, L. Guerrero, S. Fernández-Vallinas, Z. Pons, L. Arola, A. Alexandre, B. Muguera. Involvement of Nitric Oxide and Procyanidin in the Antihypertensive Effect of Low-molecular-weight Procyanidin Rich Grape Seed Extract in Male Spontaneously Hypertensive Rats. J. Funct. Foods. 2014, 6, 419–427. DOI: 10.1016/j. jff.2013.11.008.

[63] Levin, R.; Weksler, B.; Marcus, A.; Jaffe, E. Prostacyclin Production by Endothelial Cells, 1984; pp 228–247. Springer, Netherlands.

[64] Guy, J. L.; Lambert, D. W.; Warner, F. J.; Hooper, N. M.; Turner, A. J. Membrane-associated Zinc Peptidase Families: Comparing ACE and ACE2. Biochim. Biophys. Acta. 2005, 1751(1), 2–8. DOI: 10.1016/j. bbapap.2004.10.010.

[65] Hider, R.; Liu, Z.; Khodr, H. Metal Chelation of Polyphenols. Methods Enzymol. 2001, 335, 190–203.