American Dietetic Association

RESEARCH

Review

The Effect of Grape Seed Extract on Cardiovascular Risk Markers: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Recent animal studies have suggested that grape seed extract has beneficial effects on the cardiovascular system. Randomized trials in human beings have yielded conflicting results. The objective of this systematic review was to assess the effect of grape seed extract on changes in blood pressure, heart rate, lipid levels, and C-reactive protein (CRP) levels. We searched MEDLINE (January 1, 1950, through October 31, 2010), Agricola (January 1, 1970, through October 31, 2010), Scopus (January 1, 1996, through October 31, 2010), and the Cochrane Central Register of Controlled Trials (through October 31, 2010) for randomized controlled trials in human beings of grape seed extract reporting efficacy data on at least one of the following end points: systolic or diastolic blood pressure, heart rate, total cholesterol, low-density or high-density lipoprotein cholesterol, triglycerides, or CRP. A manual search of references from primary and review articles was performed to identify additional relevant trials. For all endpoints except CRP, the mean change in each parameter from baseline was treated as a continuous variable and the effect size was calculated as the weighted mean difference between the means in the grape seed extract and control groups. Data on CRP were pooled as a standardized mean difference. Nine randomized, controlled trials (N=390) met the inclusion criteria, and a meta-analysis was conducted. Upon meta-analysis, grape seed extract significantly lowered systolic blood pressure (weighted mean difference −1.54 mm Hg (95% confidence interval −2.85 to −0.22, $P=0.02$]), and heart rate (weighted mean difference −1.42 bpm (95% confidence interval −2.50 to −0.34, $P=0.01$]). No significant effect on diastolic blood pressure, lipid levels, or CRP was found. No statistical heterogeneity was observed for any analysis ($I^2<39\%$ for all). Egger's weighted regression statistic suggested low likelihood of publication bias in all analysis ($P>0.05$ for all), except for the effect on diastolic blood pressure ($P=0.046$). Based on the currently available literature, grape seed extract appears to significantly lower systolic blood pressure and heart rate, with no effect on lipid or CRP levels. Larger randomized, double-blinded trials evaluating different dosages of grape seed extract and for longer follow-up durations are needed.

J Am Diet Assoc. 2011;111:1173-1181.

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Manuscript accepted: March 2, 2011.

0002-8223/$36.00

doi: 10.1016/j.jada.2011.05.015

Coronary artery disease is the leading cause of death worldwide (1). Prevention centers on the modifiable risk factors, which include decreasing lipid levels, addressing obesity and hypertension, smoking cessation, and making healthy dietary modifications. The so-called French Paradox refers to the observation that subjects in France experience a relatively low incidence of coronary artery disease, despite high saturated fat consumption (2). It has been suggested that France's high red wine consumption is a primary factor in this trend (3). Epidemiologic studies have demonstrated that flavonoids, which are highly concentrated in red wine, are inversely related with mortality from coronary heart disease (4). Grape seed extract is commercially available and is prepared from the seed of grapes. Grape seed extract contains a high concentration of proanthocyanidins, a class of polyphenol flavonoid complexes, and are known to possess the strongest antioxidant effect among polyphenols contained in red wine (5,6). Oral grape seed extract is typically available as 50- or 100-mg capsules or tablets, and can be obtained at pharmacies and grocery stores without physician prescription. Grape seed extract is also found in wine, with red wines having substantially more than white wines (177 mg/L compared to 8.75 mg/L) (6). There is a growing body of research showing that grape seed extract may have beneficial effects on the cardiovascular system. Several randomized controlled trials in human beings have been conducted to evaluate the effects of grape seed extract on different cardiovascular risk markers; however, these studies have yielded conflicting results. In addition, most of these trials included modest sample sizes with low power to detect differences in effect.

To better characterize the relation between grape seed extract and changes in different cardiovascular markers,

1	grape seed.mp.[a]
2	grape seed extract.mp.
3	grape seed polyphenols.mp.
4	grape seed proanthocyanidins.mp.
5	1 or 2 or 3 or 4
6	limit 5 to humans [Limit not valid in CCTR,[b] AGRICOLA; records were retained]
7	random$.[c]mp.
8	6 and 7

Figure 1. Search strategy utilized in Medline to identify eligible randomized controlled trials of grape seed extract. [a]mp=search all fields of citations. [b]CCTR=Cochrane controlled trial register. [c]$=truncated word search.

including blood pressure, heart rate, lipid levels, and C-reactive protein (CRP) levels, we conducted a systematic review and meta-analysis of randomized controlled trials.

METHODS

Data Sources

We conducted a systematic search of MEDLINE (January 1, 1950, through October 31, 2010), Agricola (January 1, 1970, through October 31, 2010), Scopus (January 1, 1996, through October 31, 2010), and the Cochrane Central Register of Controlled Trials (through October 31, 2010) to identify literature evaluating grape seed extract on cardiovascular risk markers. All databases were searched using the following medical subject headings and text key words: grape seed extract, polyphenols, and proanthocyanidins. The complete MEDLINE search strategy is provided in Figure 1. Results were limited to randomized trials in human subjects. No language restrictions were imposed, and duplicate citations were removed. A manual search of references of primary and review articles was performed to identify additional relevant studies. When applicable, efforts were made to contact investigators for clarification or additional required data.

Study Selection

Studies were included if they were randomized controlled trials of grape seed extract in human participants that reported efficacy data (suitable for calculation of change from baseline) on at least one of the following a priori endpoints: systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, low-density (LDL) or high-density lipoprotein (HDL) cholesterol, triglycerides, or CRP. Studies had to expose patients to the intervention for a minimum of 2 weeks to be included. Both parallel and crossover trials were eligible for inclusion. Crossover trials without a washout period were included, as long as the duration of intervention met or exceeded 2 weeks. This cutoff was arrived at based on commonly accepted guidelines for dietary clinical trials evaluating surrogate cardiovascular endpoints and the ~72-hour half-life of grape seed extract proanthocyanidins (assuming three to five half-lives required to clear drug from the body) (7). In trials with more than one published report on the same study population, the most recent publication was selected for analysis, although previous publications were reviewed to supplement for missing data, where applicable. Using an accepted methodology, trials evaluating multiple treatment arms (low- or high-dose grape seed extract) were included by entering each pairwise comparison into the meta-analysis as a separate trial, but with the repeated control group's sample size divided out evenly among the comparisons.

Data Abstraction

Using a predefined data-abstraction tool, three investigators (H.H.H.F., D.A.L., J.E.D.) independently recorded data for each included trial. Any disagreements were resolved through discussion with a fourth investigator (C.I.C.). As summarized in the Table, the following information from each included trial was recorded: author identification, year of publication, total sample size, study design, description of study population, exclusion criteria, follow-up period, grape seed extract daily dose (product, if known), and diet and lifestyle modifications during intervention. The validated Jadad score was used in a nonblinded fashion to assess the methodologic quality of included trials. The Jadad scale assesses inherent controllers of bias by assessing randomization, double-blinding, and patient withdrawals. These individual components were assessed and an aggregate score was calculated for each included trial (0=weakest, 5=strongest). Trials scoring <3 were deemed to have lower methodologic quality, in which points are given for each satisfied criterion (8). Trials with scores <3 were considered to have lower methodologic quality. For each study, baseline and last reported blood pressure, heart rate, lipid, and CRP values were recorded, along with measurements of variance. For two studies in which data were solely provided in graphical form, Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) was used to estimate numerical values for the endpoints in question.

Data Analysis

The outcomes of interest in this meta-analysis were overall changes in systolic and diastolic blood pressure, heart rate total, LDL, and HDL cholesterol, triglycerides, and CRP. For all endpoints except CRP, the mean change in each parameter from baseline was treated as a continuous variable and the weighted mean difference was calculated as the difference between the means in the grape seed extract and control groups. Data on CRP were pooled as a standardized mean difference (mean difference between treatment and control groups divided by pooled standard deviation) and 95% confidence interval because the outcome measure included both CRP and high-sensitivity CRP values. Regardless of endpoint, within parallel trials, net changes were calculated as the difference (grape seed extract minus control) of the changes (follow-up minus baseline) in the mean values (also referred to as the change score). For crossover trials, net changes were calculated as the mean difference in values at the end of the grape seed extract and control periods. Vari-