

Effect of Grape Seed Extract on Blood Pressure in Subjects with Pre-Hypertension

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Abstract: Pre-hypertension affects approximately 31% of the adult population of the United States over the age of 18 years. It is defined in the 7th report of the Joint National Committee (JNC - 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as a systolic blood pressure of 120-139 mmHg or a diastolic blood pressure of 80-89 mmHg. JNC-7 also recommended that individuals considered to be prehypertensive require health-promoting lifestyle modifications to prevent cardiovascular disease. This study was undertaken to determine whether a grape seed extract (GSE) which is a nutraceutical containing vasodilator phenolic compounds lowers blood pressure in subjects with pre-hypertension. The subjects were randomized into a placebo or an experimental group (GSE at a dose of 300 mg/day) and treated for 8 weeks. Serum lipids and blood glucose were measured at the beginning of the study and at the end. The blood pressure was recorded using an ambulatory monitoring device at the start of the treatment period and at the end. Both the systolic and diastolic blood pressures were significantly lower after treatment with GSE. Treatment with the placebo had no effect on blood pressure. There were no significant changes in serum lipids or blood glucose values. These findings suggest that GSE could be used as a nutraceutical in a lifestyle modification program for patients with pre-hypertension.

Keywords: Grape seed extract, pre-hypertension, human, polyphenolics.

INTRODUCTION

Hypertension affects approximately 60% of adults in the United States [1] and remains a major cause of morbidity and mortality. Despite the availability of numerous antihypertensive medications, control of blood pressure to optimal levels remains inadequate in most patients. In people over the age of 18 years, the prevalence of pre-hypertension alone in the U.S. is 31% [1]. It is defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in its Seventh Report (JNC 7) [2] as a systolic blood pressure between 120 and 139 mmHg or a diastolic blood pressure between 80 and 89 mmHg. Current guidelines recommend that these individuals should be managed by lifestyle modifications which include exercise, weight management, salt restriction and consumption of a diet rich in fruits and vegetables [2].

There is evidence that such a regimen which includes vegetables and fruits coupled with a low fat intake has a beneficial effect on blood pressure [3]. It has been suggested that this effect is at least in part due to the presence of phenolic compounds in the plant products [4]. These compounds have also been shown to have vasodilator effects [5-7]. Of all the phenolic compounds, those derived from grape seeds appear to have received the most attention, possibly because of their involvement with the French Paradox [8].

Previous studies completed in our laboratory have shown that extracts derived from grape seeds causes an endothelium dependent relaxation in rings of the rabbit aorta that is mediated by nitric oxide. This process is initiated by phosphorylation of nitric oxide synthase through the PI3K/Akt pathway. Inhibition of this pathway also abolishes the endothelium dependent relaxation and up-regulates nitric oxide synthase in human umbilical vein endothelial cells [9]. In humans, the extract was also found to lower blood pressure in patients diagnosed with the metabolic syndrome [10]. A similar effect has also been demonstrated with a freeze dried product of grapes in people with the metabolic syndrome [11].

The investigation reported here was undertaken to test the hypothesis that a well characterized extract of grape seeds lowered blood pressure in subjects with pre-hypertension. The trial was a single center, double blind, placebo controlled, parallel arm study which lasted 8 weeks. The study was approved by the Internal Review Board of the University of California.

METHODS

The study was conducted on a convenience sample of 66 adults (age 25-80 years) who were screened for pre-hypertension. Those with average day time blood pressures which met the JNC 7 criteria for pre-hypertension (systolic blood pressures between 120 and 139 mmHg or diastolic blood pressures between 80 and 89 mmHg) were enrolled in the trial after obtaining written consent. The exclusion criteria were as follows: smokers (abstinence for < 1 year), clinical

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evidence of coronary artery, pulmonary, gastro intestinal or renal disease, consumption of prescription medications and vitamin preparations.

After baseline biochemical and hematological parameters were measured, all subjects commenced a two-week placebo run-in period. During this period they were fitted with an ambulatory blood pressure measuring system to confirm the diagnosis of pre-hypertension. (Model SE-25S; Sein Electronics, Koyang, South Korea). This system has been evaluated using a protocol approved by the British Hypertension Society (www.tiba.medical.com). It was programmed to record the blood pressure every hour for 12 hours after waking up. At the end of two weeks, the subjects had a second ambulatory blood pressure measurement (12 hour) and were randomized subsequently to receive a capsule containing either a placebo (Maltodextrin) or a grape seed extract (300 mg) daily. The grape seed extract used in this study was Meganatural BP® (Polyphenolics Inc. Fresno, California). The subjects were advised to maintain their usual level of activity and diet. The latter was monitored by examining a 4-day food diary which was completed at the start and at the end of the study. After a further 8 weeks, a final ambulatory blood pressure was recorded and blood was drawn for measurement of biochemical and hematological parameters. In each instance, the average of 12 values was taken as the mean day time blood pressure.

The distribution of phenolic compounds in the grape seed extract is shown in Table 1. The ORAC value of the compound was 16,810 μmol Trolox equivalents/g. The average degree of polymerization is 2.3. (These details are archived with reference [9]). In a previous study, administration of this grape seed extract (300 mg) (n=5) resulted in a 10-fold increase in plasma catechin levels from a baseline value of 2.0 ± 4 after 90 minutes. There were no significant changes in subjects given placebo capsules [10].

Fasting blood samples were collected for the following measurements at the start of the study and at the end: hemoglobin, white cell count with differential, serum lipids, chemistry panel, blood glucose, plasma insulin, and oxidized low-density lipoprotein (Ox-LDL). The Ox-LDL concentration in plasma was measured using an mAb-4E6-based enzyme-linked Immunosorbent assay (Mercodia, Uppsala, Sweden). The analysis was undertaken by Shiel Laboratories, New York.

Statistical Analysis

The primary endpoints were the mean day-time systolic and diastolic blood pressures. Secondary endpoints were the changes in serum lipids and oxidized LDL. Baseline values in the 2 groups were compared using a t test. A p value of 0.05 with an associated power of 0.08 was taken to indicate statistical significance.

RESULTS

Sixty six subjects were screened for the study and 34 met the criteria for pre-hypertension. Two refused to participate in the trial and remaining 32 were randomized. The baseline clinical data are given in Table 2. There were no significant differences in the baseline parameters in these subjects.

At the end of 8 weeks both systolic and diastolic blood pressures in the group receiving GSE were significantly lower than those in the placebo group. These findings are summarized in Table 2. There were also no changes in body weight, blood counts, serum electrolytes and chemistry and glucose values during the course of the study.

There were also no changes in the serum total, LDL and HDL cholesterol values in both groups. An interim analysis was performed on the oxidized LDL values after 8 subjects in each group had completed the study.

Table 1: Composition of the Grape Seed Extract (n = 8). Original Data Archived with Ref [9]
<http://www.ciinsci.org/cs/114/cs1140331add.htm>

Total Phenol content (gallic acid equivalents (g/100g))	93.9 \pm 0.9
Epicatechin gallate terminal units (%)	0%
Epicatechin gallate extension units (%)	5.7 \pm 0.6
Monomers (%) *	9.1 \pm 1.2
Oligomers (%) *	68.7 \pm 1.2
Polymers (%) *	22.3 \pm 0.6
Catechin and epicatechin by weight (%)	9.9 \pm 0.6

*Determined by reverse-phase HPLC using peak area.

Table 2: Baseline Clinical Data

	Placebo	GSE
Age (yr)	54±3	50±2.5
Male/female	6/10	9/7
Total cholesterol (mg/dl)	204±9	200±10
LDL (mg/dl)	134±9	128±9
HDL (mg/dl)	48 ±3	55±4
Triglycerides (mg/dl)	100±12	146±18
Oxidized LDL (mU/l) (n=8)	43.3±3	41.2±3

It was found that the baseline values were similar in both groups (Table 1) and there were no significant changes after two months in either group. These interim measurements were done without compromising the blinded status of the study. No additional measurements of oxidized LDL were undertaken on the other subjects.

DISCUSSION

This study was undertaken to test the hypothesis that polyphenolic compounds found in grape seed lowers blood pressure in people with pre-hypertension. It was a follow up to a previous study which showed that these compounds lowered blood pressure in people who met the diagnostic criteria for the metabolic syndrome. Both these conditions affect nearly half the adult population of the United States and the current recommendations of the National Cholesterol Education Program [12] and the JNC-7 [2] are that the majority of these patients should be managed by encouraging them to undertake lifestyle changes which address weight management, physical activity, reducing the intake of salt and dietary/nutritional changes. The latter includes the consumption of two cups of fruit and 2½ cups of vegetables per day for a reference 2,000-calorie intake. It has been suggested that fruits and vegetables, particularly those with higher polyphenolic content such as grapes, strawberry,

blueberry and pomegranate, influence multiple biological mechanisms which could have favorable effects on human health due to their ability to modulate oxidative and inflammatory stress in peripheral tissues [13-16].

Grape seeds contain approximately 3000 mg of phenols/kg of fresh weight made up principally of monomeric flavan-3-ols (which includes among other compounds (+) catechin and (-) epicatechin), oligomeric proanthocyanidins and polymeric condensed tannins [17]. The extract used in the present study contained significant quantities of oligomers and no terminal gallate units (see methods). This particular extract has been shown to produce an endothelium dependent relaxation in rings of the rabbit aorta in-vitro [9]. The endothelium dependent relaxation evoked by the extract is mediated by the activation of the PI3K/Akt signalling pathway, resulting in the phosphorylation of eNOS through a redoxsensitive mechanism [18]. Removal of the antioxidant activity from the extract by methylation of the hydroxy groups abolished the endothelium dependent relaxation induced by the grape seed extract [9].

Based upon this evidence, a small placebo controlled clinical trial was undertaken in patients with the metabolic syndrome to determine whether this grape seed extract lowered the blood pressure. This study showed that the extract when administered orally

Table 3: Changes in Blood Pressure (mmHg)

	GRAPE SEED EXTRACT 300 mg/day (n = 16)		PLACEBO (n = 16)	
	SBP	DBP	SBP	DBP
Start	133 ± 2	79 ± 2	132 ± 2	79 ± 2
2 months	125 ± 2	74 ± 2	133 ± 2	82 ± 2
p	<0.001	<0.003	0.8	0.03
Power at p<05	>0.9	>0.85	NS	0.5

at a dose of 300 mg daily resulted in a significant reduction in blood pressure. The extract also appeared to reduce the concentration of oxidized LDL particularly when the baseline values were greater than 60 mg/l. In addition the plasma also showed evidence of absorption of polyphenolic compounds. A recently reported study by Barona *et al.* [11] showed that consumption of a freeze dried powder of grape products also resulted in a reduction of blood pressure in patients who had the metabolic syndrome. The subjects consumed sufficient quantities of the powder to yield approximately 266 mg of phenols.

In the present study we examined the effect of the extract on blood pressure in people with pre-hypertension as defined by the Joint National Committee. In this placebo controlled study, there was a significant reduction in both systolic and diastolic blood pressures. There was no effect on oxidized LDL. However, unlike in the patients with the metabolic syndrome who participated in the previous study [10], all the subjects in the in the present study had plasma oxidized LDL values that were less than 50 mU/l.

LIMITATIONS

Several studies have shown that the consumption of appropriate quantities of fruit and vegetables in the United States falls far short of current recommendation (e.g. [19]). Nutraceutical supplementation could provide a means of addressing some of the health problems that stem from an inappropriate diet in the short and medium term such as hypertension and obesity. The studies described in this paper are essentially small trials that attempt to prove the concept that polyphenolic compounds present in grape seed are prototypes of biologically active compounds commonly found in fruits and vegetable which could form the non-pharmaceutical basis for managing pre-hypertension. It is recognized that larger placebo controlled long-term trials (conducted extending over several years) are required to determine whether these compounds reduce the number of people transitioning from pre-hypertension to overt hypertension.

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