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RESEARCH ARTICLE

Daily consumption of red grape cell powder in a dietary dose improves cardiovascular parameters: a double blind, placebo-controlled, randomized study

Nachum Vaisman* and Eva Niv*

The Unit of Clinical Nutrition, Tel Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Consumption of polyphenol-rich food and food ingredient such as grape and grape products improved various cardiovascular parameters. In this study, we investigate the effect of dietary daily consumption of red grape cell powder (RGC) on blood pressure (BP) and flow-mediated dilatation (FMD) as well as on oxidative stress in 50 subjects with prehypertension and mild hypertension. The subjects were randomized into groups that consumed 200, 400 mg RGC or placebo daily for 12 weeks. RGC consumption was associated with an improvement of FMD ($p = 0.013$). There was a significant decrease in lipid peroxidation ($p = 0.013$) after 12 weeks in a combined RGC-treated group. The diastolic BP decreased significantly in the 200 mg RGC group compared to the placebo group ($p = 0.032$). Our results indicate that a daily supplementation, of red grape cell powder, for 12 weeks affects endothelial function, diastolic BP and oxidative stress without any adverse effects.

Keywords

Flow-mediated dilatation, hypertension, lipid peroxidation, red grape cells

History

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Introduction

The World Health Organization (WHO) estimates that there will be about 1.5 billion adults living with high blood pressure (BP) by 2030 (WHO, 2011). Persistent prehypertension (defined as BP of 120–139/80–89 mm/Hg) and more so hypertension (BP of >140/>90 mm/Hg) is one of the risk factors for several diseases and disorders and may contribute significantly to the development of leading factors of death in the Western world such as heart failure and stroke (Huang et al., 2014). In addition, hypertension increases the risk of atherosclerosis (Cheng et al., 2013) and chronic kidney disease (Segura & Ruilope, 2011).

Apart from the obvious need to lower BP, other important goals in the treatment of hypertension are reducing abnormally high lipid peroxidation and controlling the imbalanced anti-oxidant status associated with the disorder (Russo et al., 1998). In addition, hypertensive subjects have been shown to have abnormal endothelium-dependent vascular function as expressed in flow-mediated dilatation (FMD), which may serve as an indicator of several diseases. FMD was highly predictive for coronary artery disease (CAD) with an odds ratio of 1.32 for each percent decrease in FMD (Jambrik et al., 2004; Kuvin et al., 2007). In systemic sclerosis FMD was highly correlated with the progression of the disease and inversely correlated with its duration (Takahashi et al., 2014). FMD is associated with an increased mortality risk in ischaemic advanced chronic heart failure (ACHF) patients (Shechter et al., 2009). Moreover, persistent low FMD despite therapies for heart failure (HF) and atherosclerotic risk factors was a predictor of cardiac events in patients with chronic ischemic HF (Takishima et al., 2012).

Polyphenols are diverse group of antioxidant compounds that occur naturally in fruits, vegetables, olive oil and certain beverages, such as red wine (Sies, 2010). Polyphenols of nutritional interest are commonly divided into three groups: phenolic acids, flavonoids and stilbenes (Tsao, 2010). Consumption of various polyphenol-rich food ingredients, such as grape seed extract, red wine extract, green and black tea and others, has shown to improve different cardiovascular parameters (Crozier et al., 2009; Tangney & Rasmussen, 2013) as well as specific age-associated diseases (Queen & Tollefsbol, 2010). This may be due to the strong anti-oxidative (Pandey & Rizvi, 2009), anti-inflammatory (González et al., 2011), neuro-protective (Panickar & Jang, 2013) and chemopreventive (Gerhauser, 2013) activities associated with polyphenols. The phytoalexin resveratrol (*trans*-3,5,4′-trihydroxystilbene), which is abundant in red wine, has drawn most of the attention of all the polyphenols. This was first recognized in the ''French Paradox'' where a low incidence of cardiovascular diseases was found among the French despite their high-fat diet. This was then attributed to their moderate red wine consumption (Renaud & de Lorgeril, 1992). Since then, however, much evidence has accumulated on biological activities of polyphenols including inhibition of lipid peroxidation, free-radical scavenging, inhibition of platelet aggregation, anti-inflammatory activity and blood pressure lowering effect (BP) (Catalgol et al., 2012; Cottart et al., 2013). Additionally, it was found that resveratrol is involved in energy metabolism and longevity (Timmers et al., 2011; Wood et al., 2004).

*These authors contributed equally to this work.

Correspondence: Nachum Vaisman, MD, Unit of Clinical Nutrition, The Tel Aviv Sourasky Medical Center, 6 Wiezmann Street, Tel Aviv 64239, Israel. Tel: +972 3 6974077. Fax: +972 3 6973191. E-mail: Nachumv@Tlvmc.Gov.Il

Specifically, grape and red wine polyphenols were found to be involved in improving vascular function both *in vitro* and in animal models (Fuhrman et al., 2005). However, there are few studies addressing the beneficial effect of grape polyphenols as a food on vascular endothelial function, blood pressure and lipid oxidation for hypertensive subjects.

RGC (Red Grape Cells; Patent application US 2008/0166306a1) is a powder of red grape cells from the fruits of *Vitis Vinifera* L. cultivar commercially grown in disposable bioreactors in order to produce food and functional food. This technology mirrors nature as it does not involve any solvent extraction, genetic modification or synthetic molecular processing, and enables preservation of the active properties of the grapes. RGC consists of the whole matrix of polyphenols and other healthy ingredients naturally existing in red grape as well as in red wine in their natural state. Despite similar total polyphenolic content, the concentration of natural grape resveratrol in RGC is significantly higher than that found in fresh grapes (Azachi et al., 2014). The present study aimed at studying the effect of long-term daily consumption of RGC on BP and FMD as primary outcomes, as well as oxidative stress and different metabolic and biochemical parameters in subjects with prehypertension and mild hypertension.

Materials and methods

The investigational product

RGC powder (Fruitura Bioscience Ltd.) consists of dried red grape cells grown in nutritive liquid solution. Polyphenols and *trans*-resveratrol content in RGC were evaluated by HPLC. RGC powder was dissolved in 80% methanol. The solution was sonicated for 10 min at 30 °C, centrifuged at 16 900 *g* to remove non-soluble matter and filtered through 0.45 μm filter, and the filtrated supernatant was used for analysis. The HPLC quantification was performed using JASCO PU-2089 HPLC system and the operation software ChromNAV (Jasco Inc., Easton, MD). Total phenolic compounds content was evaluated at 280 nm and expressed as epicatechin equivalent. *Trans*-resveratrol content was evaluated at 306 nm based on its characteristic absorption profile, and anthocyanins content was evaluated at 520 nm and expressed as delphinidin equivalent. Total tannins content was evaluated using a colorimetric method as previously described (Giner-Chavez et al., 1997). Daily doses of RGC were provided by Fruitura Bioscience Ltd. packaged in polyethylene containers of either 200 or 400 mg. The placebo consisted of 200 mg of colored maltodextrin powder identical in appearance to the RGC powder. Each container was labeled with the codes A, B or C and packed in aluminium bags with the corresponding codes. All subjects and study personnel were unaware of differences between groups.

LC/MS analysis

Sample preparation and LC–MS analysis for piceid (glycoside-resveratrol) in RGC were performed by an external LAB (Ben-Gurion University of the Negev, Israel; The Jacob Blaustein Institutes for Desert Research). Detection of resveratrol in RGC powder was performed by UPLC-QTOF-MS system equipped with an ESI interface (LC: Waters Acquity UPLC system; Xevo™ QTof Waters MS Technologies, Manchester, UK), operating in both negative and positive ion mode. Chromatographic separation was carried out on an ACQUITY UPLC BEH C18 column (100 mm × 2.1 mm, 1.7 μm).

MassLynx software (Waters) version 4.1 was used for system controlling and data acquisition. The raw data acquired were processed using MarkerLynx application manager (Waters, Manchester, UK). Further multivariate statistical data analyses were performed by the Extended Statistics module of the EZinfo software (Waters Ltd.). Identification was based on the fragmentation pattern of typical standard.

Study design

The study was a randomized, double-blind and placebo-controlled parallel arm study conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Tel Aviv Sourasky Medical Center (TASMC) IRB and registered at clinicaltrials.gov as NCT01146470. Subjects provided written informed consent after explanation of the intervention and possible benefits and side effects. Fifty adults with pre- and Stage 1 hypertension received, in randomized order, the investigational product RGC (oral doses of 200 or 400 mg), or placebo once daily for 12 weeks.

Subjects were instructed to ingest the investigational product with a glass of water 10 min before breakfast. They attended the Unit of Clinical Nutrition at TASMC, Tel Aviv, Israel every 14 ± 3 days for a total of nine visits throughout the study period and were weighed and queried on adverse events at each visit. On each meeting subjects received 14 daily doses. Telephone follow-up was conducted during the weeks when there were no scheduled clinic visits. The subjects were requested not to change their diet (continuing to eat fruit and vegetables as they normally would) or the level of their physical activity for the duration of the study. They were also requested to complete a food diary for three days prior to taking the first dose and prior to the last visit.

Fifty volunteer subjects were recruited into the study. Volunteers' eligibility criteria included ages of 35–70 years; BMI less than 40.0 kg/m^2, systolic BP (SBP) $\leq$ 154 mmHg and diastolic BP (DBP) up to 93 mmHg. Exclusion criteria included: breastfeeding or pregnancy, history of milk allergy (as the study product could contain traces of casein), consumption of anti-hypertensive medications or antioxidant food supplements (excluding probiotic agents and fibers ingested for less than two weeks before entering the study), a history of cardiovascular disorders, renal disorders, intestinal disorders, hepatic disease, malignant or autoimmune diseases or other metabolic diseases. Baseline blood tests indicative of abnormalities in hepatic, renal or thyroid functions or abnormal blood counts caused exclusion. Other exclusion criteria included: alcohol or drug abuse, documented psychiatric problems or neurological disorders, habitual smoking within two years prior to the study, and consumption of phosphodiesterase 5 inhibitors and unusual eating habits or following an active regimen of weight loss/gain.

Blood pressure

BP and vital signs were measured after resting quietly in a supine position for 15 min. SBP and DBP were measured four times, one minute apart, and the last three measurements were averaged. If the difference between measurements was higher than 5 mmHg, the whole process was repeated after another 5 min rest.

Blood sampling procedure

Blood was drawn for the following parameters at baseline and during the 12 weeks study. The tests included complete blood count (CBC), C reactive protein (CRP), insulin, glucose, glycosylated hemoglobin (HbA1C), urea, creatinine, uric acid, glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), low-density lipoprotein (LDL), high-density lipoproteins (HDL), cholesterol, triglycerides, total bilirubin, transferrin, ferritin, sodium, potassium, chloride, magnesium, phosphor, zinc, albumin, iron and thyroid-stimulating

hormone (TSH) were measured during screening and at the end of the study. Glucose, urea, uric acid, GOT, GPT, GGT, ALP, LDL, HDL, cholesterol and triglycerides were also measured at 6 weeks during the course of treatment. Lipid peroxidation was measured using the thiobarbituric acid reactive substances (TBARS) and the lipid peroxide assays as described by Fuhrman et al. (2005) after an overnight fast. All clinical laboratory measurements were performed by the TASMC laboratories except for the oxidative stress parameters measurements which were performed by the Lipid Research Laboratory at the Rambam Medical Center, Haifa, Israel.

Flow-mediated dilatation

Endothelial function was inferred from FMD according to the guidelines of the International Brachial Artery Reactivity Task Force (Corretti et al., 2002). FMD was assessed by measuring the change in the brachial artery diameter during reactive hyperemia following transient forearm occlusion using a high-frequency (7.5 MHz) linear-array transducer (AlokaProSound 4000, Tokyo, Japan) and expressed as percent FMD compared with baseline. FMD was determined as the average diameter of quadruplicate measurements and expressed as a percentage change relative to the diameter before the cuff inflation reflected endothelium-independent vasodilatation.

Statistical analysis

All measured variables were listed individually and, if appropriate, tabulated by descriptive statistics. For descriptive statistics, summary tables were provided giving sample size, absolute and relative frequency by study group, and sample size, arithmetic mean, standard deviation, median, minimum and maximum by study group for means of continuous variables. After checking for normal distribution, an ANOVA model was applied for testing the significance of the difference in the changes between study groups. The paired *t*-test or Signed Rank test (as appropriate) was applied for testing the significance of the changes from baseline within each study group. Student's *t*-test or the non-parametric Rank sum test (as appropriate) tested the significance of the difference in quantitative parameters (changes and relative changes) between the study groups. The Chi-square test or Fisher's Exact test (as appropriate) assessed the significance of the difference for categorical variables (% subjects with positive change) between the study groups. The RGC treatment groups were then combined and Student's *t*-test and the non-parametric Wilcoxon Rank Sum test were used to study the differences between the placebo and treatment groups. All the tests were two-tailed, and significance was set at $p < 0.05$. All analyses were performed with the SAS® version 9.1.3 (SAS Institute, Cary, NC).

Results

Investigational product

The RGC and placebo used in this intervention were supplied by Bioharvest Ltd. RGC's total polyphenol content was 56 mg/g, total catechins (epicatechin equivalent) 13 mg/g, total anthocyanins 6.7 mg/g (delphinidin equivalent), resveratrol 15 mg/g and 33.6 mg/g dry weight condensed tannins. The composition and phytochemical characterization were described previously in Azachi et al. (2014).

Study subjects

Disposition of subjects data sets analyzed

Fifty (35 males and 15 females) subjects were enrolled and randomized into the study. Of these, 46 subjects (92%) completed the study (one subject withdrew prematurely due to adverse events, and three subjects withdrew their informed consent for participating in the trial), their characteristics and baseline results are shown in Table 1.

All subjects (45 subjects), except one who completed the study, were included in the efficacy analysis. This subject was excluded from all analyses as he continued treatment with a concomitant medication which can affect study parameters tested in this article.

Blood pressure efficacy analysis parameters were performed on 41 subjects. One subject was excluded on basis of continuing taking a concomitant medication as mention above and the additional four subjects had only one measurement of SBP, DBP or both above the inclusion criteria for BP during the screening visits.

According to the study design only half of the subjects, from each treatment group, were tested for FMD. Thirty-five subjects were included for the lipid peroxides parameter due to technical problems.

Efficacy evaluation

No significant differences were observed between baseline values across all treatment groups, except for the body mass index (BMI) that was higher in the 200 mg group compared with the two other study groups due to one outlier result (Table 1).

No changes were found between or within groups in the hematological and chemical parameters measured at baseline and at the end of the study (Table 3).

Table 2 displays the measurements at the end of 12 weeks of treatment and the changes from baseline of the main study parameters. A significant difference on DBP was detected between the 200 mg RGC group and the placebo group ($p = 0.032$). While no significant treatment effect on SBP was detected in any of the groups, there was a reduction of

Table 1. Baseline clinical characteristics.

Parameter	RGC 200 mg	RGC 400 mg	Placebo	*p* Value
Males (%)	60.0	77.8	70.6	0.539
Age, mean ± SD (years)	58.5 ± 7.9	57.6 ± 7.2	56.4 ± 7.0	0.715
Age, range (years)	45.3–69.6	41.7–70.0	42.2–66.1	
Height (cm)	172.6 ± 9.2	173.7 ± 8.3	173.7 ± 7.5	0.905
Weight (kg)	88.6 ± 15.0	80.0 ± 13.1	79.7 ± 14.2	0.145
Body mass index (kg/m^2) mean ± SD	29.7 ± 3.0	26.4 ± 3.0	26.3 ± 4.1	0.021
Systolic blood pressure (mmHg) mean ± SD (*n*)	130.3 ± 7.1 (9)	132.1 ± 9.5 (17)	135.8 ± 7.5 (15)	0.31
Diastolic blood pressure (mmHg) mean ± SD (*n*)	82.5 ± 5.6 (9)	82.9 ± 8.5 (17)	80.1 ± 6.5 (15)	0.522
Lipid peroxides (nmol/ml) mean ± SD (*n*)	580.3 ± 45.3 (7)	590.2 ± 51.9 (14)	600.0 ± 40.8 (14)	0.647
Flow-mediated dilatation, mean ± SD (*n*)	5.00 ± 3.51 (6)	1.45 ± 1.02 (8)	4.51 ± 4.59 (9)	0.184

Values are expressed as mean ± SD.

Table 2. Experimental values after 12 weeks of treatment.

Parameter	RGC 200 mg	RGC 400 mg	Placebo	*p* Values: RGC 200 mg versus 400 mg	*p* Values: RGC 200 mg versus placebo	*p* Values: RGC 400 mg versus placebo
Systolic blood pressure, mmHg (*n*)	126.7 ± 10.0 (9)	133.6 ± 6.8 (17)	134.3 ± 8.5 (15)			
Change from baseline, mmHg (*n*)	−3.67 ± 8.96 (9)	0.05 ± 9.40 (17)	−1.46 ± 6.47 (15)			
p Value for change from baseline	0.254	0.981	0.397	0.2855	0.5333	0.6114
Diastolic blood pressure, mmHg (*n*)	78.3 ± 12.1 (9)	84.3 ± 7.1 (17)	82.8 ± 7.1 (15)			
Change from baseline, mmHg (*n*)	−4.18 ± 8.96 (9)	1.43 ± 8.02 (17)	2.74 ± 5.30 (15)			
p Value for change from baseline	0.199	0.474	0.065	0.0729	0.0320	0.6178
Lipid peroxides (*n*)	550.3 ± 41.5 (7)	558.8 ± 32.5 (14)	600.0 ± 48.3 (14)			
Change from baseline (*n*)	−30.0 ± 48.2 (7)	−31.4 ± 56.0 (14)	0.0 ± 51.9 (14)			
p Value for change from baseline	0.150	0.056	1.000	0.9539	0.2300	0.1262
Flow-mediated dilatation, % (*n*)	6.13 ± 3.45 (6)	3.59 ± 2.69 (8)	4.74 ± 3.35 (9)			
Change from baseline, mmHg (*n*)	1.57 ± 3.65 (6)	2.14 ± 1.82 (8)	0.77 ± 2.99 (9)			
p Value for change from baseline	0.341	0.013	0.464	0.7135	0.5987	0.3321

Values are expressed as mean ± SD.

3.67 ± 8.9 mmHg between baseline and end of treatment in the 200 mg RGC group (p = NS).

FMD was studied in six subjects from the 200 mg arm, eight subjects from the 400 mg treatment arm and nine subjects from the placebo arm (a total of 23 subjects). The effect of treatment on FMD reached a level of significance ($p = 0.046$). A *post-hoc* analysis revealed that the final FMD values after 12 weeks of treatment increased in both the 200 mg RGC and 400 mg RGC arm compared to baseline values, but this increase reached a level of significance only in the 400 mg RGC group (2.14 ± 1.82%, $p = 0.013$). When the rate of improvement as expressed in the number of subjects who demonstrated positive change (>70% increase) in FMD was analyzed, a statistically significant effect was shown ($p = 0.002$ by Fisher's Exact test). All eight subjects (100%) from the 400 mg treatment arm underwent a positive relative change compared with 2/6 subjects (33.3%) from the 200 mg treatment arm and 2/9 subjects (22.2%) in the placebo arm (Figure 1). The change in the 400 mg treatment was significant compared to both the 200 mg arm and the placebo arm ($p = 0.015$ and $p = 0.0023$, respectively).

Changes in lipid peroxidation, as expressed in TBARS values, between baseline and study closure reached borderline significance ($p = 0.056$) only in the 400 mg treatment arm. There were no significant differences in lipid peroxide assay results over time in any of the groups. The values from the two RGC treatment groups were combined in order to study the effect of the study product. A significant difference was detected within the combined RGC groups, mean LDL oxidation-TBARS value decreased from 586.9 ± 48.8 nmol/ml at baseline to 556 ± 34.9 nmol/ml after 12 weeks ($p = 0.013$) (Figure 2).

Safety

All subjects who were enrolled into the study and received at least one dose were included in the safety analysis. Treatment with RGC was safe and well tolerated by the 50 participants.

One serious adverse event was heartburn that had evolved into chest pain and resolved spontaneously on the following day: it was considered moderate in degree and unlikely to be related to the study product. All other adverse events were mild or moderate and none were considered as being related to the study product. There were no clinically significant changes in vital signs or laboratory values throughout the study period.

Discussion

Abnormal vascular function, hypertension and lipid oxidation increase the risk of atherosclerosis and heart disease. Employing healthy lifestyle strategies to complement treatments in primary prevention of cardiovascular disease may be proved useful in targeting these risk factors. Controlled nutrition rich with types of foods containing bioactive nutrients is one of the most important lifestyle factors in the management of risk factors. The results of this randomized, double-blind, placebo-controlled study indicated that a daily consumption of RGC powder may improve FMD, decrease DBP and improve oxidative stress in subjects with prehypertension and mild hypertension who are not medically treated. These results are in accordance with previous published studies, and additionally show that such effects were achievable with nutritionally adequate amounts and not with potentially harmful super doses (Detampel et al., 2012; Tome-Carneiro et al., 2012b).

FMD had been studied in healthy and at-risk populations following both acute and chronic administration of grape products. Chronic consumption of grape powder (the equivalent of 2.5 cups of fresh grapes) by healthy volunteers for 3 weeks as well as acutely as a single dose with or without a high-fat meal resulted in a significant improvement in FMD (Chaves et al., 2009). This improvement was not, however, achieved following 2 weeks' consumption of wine grape solids (800 mg of polyphenols) after a low-fat breakfast or a high-fat lunch (van Mierlo et al., 2010). Interestingly, more consistent results were obtained with non-healthy populations: grape powder administered for 30 days to individuals with metabolic syndrome resulted in a significant increase in FMD compared to placebo (Barona et al., 2012). Moreover, a single dose of grape extract given to subjects with coronary heart disease significantly improved their FMD as well (Lekakis et al., 2005), and similar results were obtained with a single dose of either red or white wine given to the same population (Whelan et al., 2004). The results of the latter study revealed no differences between the effect of red and white wine, raising some doubt about the role of alcohol on these results. On the other hand, a study on the effect of polyphenols, ethanol and urates in normalizing FMD levels concluded that red wine and dealcoholized red wine induce similar vasodilatation in isolated vessels, whereas polyphenols-stripped red wine and ethanol did not (Boban et al., 2006). Furthermore, a recent review of human clinical studies on the effect of moderate alcohol consumption on cardiovascular disease confirmed that wine and

Table 3. Hematology and chemistry parameters.

	RGC 200 mg Mean ± SD		RGC 400 mg Mean ± SD		Placebo Mean ± SD	
	Baseline	Visit 9	Baseline	Visit 9	Baseline	Visit 9
Hematology						
RBC (10^6/uL)	4.9 ± 0.6	5.0 ± 0.6	5.0 ± 0.5	5.1 ± 0.4	4.8 ± 0.4	4.9 ± 0.4
Hemoglobin (g/dL)	14.6 ± 1.4	14.7 ± 1.4	15.1 ± 1.0	15.1 ± 1.1	14.6 ± 1.1	14.7 ± 0.9
Hematocrit (%)	43.1 ± 4.4	43.8 ± 4.5	44.3 ± 3.1	44.5 ± 3.0	43.1 ± 3.3	43.1 ± 2.7
MCV (fL)	88.5 ± 4.5	88.0 ± 3.7	88.1 ± 4.2	87.9 ± 4.8	88.9 ± 3.8	88.4 ± 4.0
MCH (pg)	30.2 ± 1.6	29.7 ± 1.7	30.1 ± 2.0	29.9 ± 2.0	30.3 ± 1.6	30.1 ± 1.7
MCHC (%)	34.1 ± 1.0	33.7 ± 1.0	34.1 ± 1.0	34.0 ± 1.2	34.1 ± 0.6	34.1 ± 0.8
RDW (%)	13.5 ± 0.9	13.5 ± 0.8	13.5 ± 0.9	13.3 ± 0.9	13.1 ± 0.4	13.0 ± 0.5
Leukocytes (10^6 uL)	6.8 ± 1.2	6.9 ± 1.4	6.9 ± 2.2	7.0 ± 1.7	6.4 ± 1.0	6.3 ± 1.1
Neutrophils absolute (10^3 uL)	3.9 ± 0.9	3.9 ± 0.8	4.0 ± 1.5	4.2 ± 1.3	3.9 ± 0.8	3.9 ± 0.7
Neutrophils (%)	56.8 ± 7.8	57.0 ± 6.3	57.4 ± 5.8	59.5 ± 6.8	61.1 ± 8.4	61.2 ± 7.8
Lymphocytes (%)	31.7 ± 8.2	31.5 ± 7.6	31.3 ± 4.5	29.4 ± 5.2	28.4 ± 8.1	28.4 ± 6.6
Lymphocytes absolute (10^3 uL)	2.1 ± 0.8	2.2 ± 0.8	2.2 ± 0.8	2.0 ± 0.6	1.8 ± 0.6	1.8 ± 0.6
Monocytes (%)	8.1 ± 2.1	7.9 ± 2.0	7.9 ± 1.7	7.8 ± 1.6	7.5 ± 2.0	7.4 ± 1.8
Monocytes absolute (10^3 uL)	0.53 ± 0.15	0.54 ± 0.16	0.54 ± 0.16	0.53 ± 0.13	0.48 ± 0.14	0.47 ± 0.14
Eosonophils (%)	2.7 ± 2.1	3.1 ± 1.8	2.6 ± 1.8	2.7 ± 1.4	2.6 ± 2.5	2.5 ± 2.5
Eosinophils absolute (10^3 uL)	0.47 ± 0.95	0.21 ± 0.12	0.36 ± 0.21	0.17 ± 0.11	0.18 ± 0.21	0.16 ± 0.20
Basophils (%)	0.5 ± 0.3	0.6 ± 0.3	0.6 ± 0.4	0.7 ± 0.4	0.5 ± 0.2	0.5 ± 0.2
Basophils absolute (10^3 uL)	0.05 ± 0.13	0.02 ± 0.04	0.02 ± 0.04	0.04 ± 0.05	0.00 ± 0.00	0.01 ± 0.02
Platelets (10^3 uL)	236.5 ± 56.0	224.7 ± 49.6	233.1 ± 40.0	230.4 ± 45.2	228.7 ± 50.1	232.8 ± 49.8
MPV (fL)	8.7 ± 0.8	8.9 ± 1.1	8.8 ± 1.0	8.7 ± 0.9	8.6 ± 0.9	8.6 ± 0.9
Chemistry						
Glucose (mg/dL)	87.0 ± 12.8	82.5 ± 10.7	89.3 ± 8.6	86.7 ± 14.4	89.7 ± 13.1	84.7 ±12.2
BUN (mg/dL)	15.3 ± 4.0	13.8 ± 2.0	16.3 ± 3.9	16.6 ± 3.6	15.4 ± 3.6	16.1 ± 4.0
Sodium (mmol/L)	142.0 ± 2.4	140.4 ± 1.7	142.0 ± 2.5	141.3 ± 2.1	140.9 ± 2.5	141.6 ± 2.2
Potassium (mmol/L)	4.5 ± 0.3	4.2 ± 0.3	4.4 ± 0.2	4.5 ± 0.8	4.3 ± 0.4	4.3 ± 0.4
Chloride (mmol/L)	105.1 ± 2.2	104.8 ± 1.5	104.3 ± 3.2	103.5 ± 2.2	104.9 ± 2.8	104.4 ± 1.7
Creatinine (mg/dL)	1.07 ± 0.13	1.05 ± 0.15	1.11 ± 0.11	1.12 ± 0.11	1.10 ± 0.14	1.10 ±0.17
Magnesium (mg/dL)	2.2 ± 0.2	2.0 ± 0.3	2.2 ± 0.1	2.5 ± 1.4	2.1 ± 0.2	2.0 ± 0.2
Uric acid (mg/dL)	6.1 ± 1.4	6.3 ± 1.3	5.5 ± 1.0	5.5 ± 1.1	6.0 ± 1.2	5.6 ± 1.3
Phosphorous (U/L)	3.4 ± 0.5	3.1 ± 0.5	3.2 ± 0.4	3.3 ± 0.4	3.3 ± 0.4	3.3 ± 0.4
AST (U/L)	26.5 ± 7.7	22.5 ± 4.3	28.2 ± 7.3	25.6 ± 8.9	24.9 ± 8.2	23.8 ± 5.8
Alkaline phosphatase (U/L)	67.5 ± 15.6	68.6 ± 16.4	71.6 ± 20.3	73.5 ± 20.0	64.8 ± 14.8	65.2 ± 15.7
Albumin (g/L)	44.5 ± 2.3	44.2 ± 2.0	44.1 ± 2.0	44.8 ± 2.8	44.3 ± 2.3	44.3 ± 1.8
ALT (U/L)	32.0 ± 19.7	23.9 ± 9.9	32.5 ± 13.4	26.7 ± 12.8	26.7 ± 15.3	25.6 ± 9.4
Total bilirubin (mg/dL)	0.69 ± 0.33	0.66 ± 0.32	0.77 ± 0.38	0.69 ± 0.37	0.82 ± 0.38	0.77 ± 0.38
GGT (U/L)	25.9 ± 13.7	24.2 ± 10.5	23.9 ± 12.9	25.3 ± 10.1	22.4 ± 8.5	22.8 ± 8.8
CRP (mg/L)	2.6 ± 3.5	3.6 ± 4.7	1.6 ± 1.8	1.8 ± 2.0	2.2 ± 2.0	1.9 ± 1.7
Iron (mcg/dL)	93.2 ± 31.1	81.8 ± 24.0	101.0 ± 31.4	94.7 ± 35.6	94.9 ± 25.0	89.6 ± 24.5
Transferrin (mg/dL)	259.2 ± 35.1	260.4 ± 34.3	266.7 ± 30.2	262.5 ± 32.9	257.6 ± 33.6	260.4 ± 43.9
Transferrin saturation (%)	24.8 ± 7.3	17.3 ± 5.9	27.5 ± 9.9	29.0 ± 12.6	26.3 ± 7.4	24.6 ± 8.5
Cholesterol (mg/dL)	188.6 ± 27.1	184.2 ± 27.3	180.5 ± 27.7	184.0 ± 29.9	200.3 ± 32.6	208.8 ± 31.3
Triglycerides (mg/dL)	124.9 ± 54.1	131.3 ± 42.7	111.6 ± 70.3	118.9 ± 71.3	120.1 ± 57.5	133.6 ± 67.4
HDL (mg/dL)	55.3 ± 19.4	46.4 ± 11.5	55.6 ± 11.7	56.9 ± 10.6	55.7 ± 16.3	56.1 ± 13.9
LDL (mg/dL)	108.3 ± 22.6	111.5 ± 23.3	102.6 ± 22.5	103.3 ± 27.0	120.4 ± 30.1	126.2 ± 27.7
Risk factor for myocardial infarct	3.7 ± 0.7	4.1 ± 0.9	3.3 ± 0.7	3.1 ± 0.6	3.9 ± 1.0	3.9 ± 1.0
Zinc (mcg/dL)	88.1 ± 23.3	91.1 ± 16.7	83.7 ± 23.9	98.3 ± 25.2	88.1 ± 14.7	91.1 ± 18.8
Ferritin (ng/mL)	94.4 ± 61.1	84.9 ± 51.5	85.9 ± 52.5	73.7 ± 47.9	97.0 ± 86.8	87.0 ± 77.8
TSH (mu/L)	2.3 ± 1.1	2.4 ± 1.5	2.0 ± 1.1	2.1 ± 1.1	1.6 ± 0.7	1.8 ± 1.0
Insulin	16.6 ± 3.9	18.1 ± 6.5	17.1 ± 9.8	18.0 ± 10.1	22.0 ± 8.6	18.1 ± 7.4
HbA1c (%)	5.7 ± 0.5	5.7 ± 0.4	5.7 ± 0.4	5.8 ± 0.4	5.5 ± 0.5	5.5 ± 0.4

beer seem to have greater cardiovascular protection than spirits due to their polyphenolic content (Chiva-Blanch et al., 2013), lending further support to the ''French paradox'' paradigm (Catalgol et al., 2012). Finally, the results of a recent meta-analysis showed that the acute effect of grape polyphenols on FMD was more significant in subjects with a smoking history or coronary heart disease compared to healthy subjects (Li et al., 2013). Recent studies in which the effect of chronic consumption of polyphenols berries (e.g. cranberry, blueberry) on vascular function and oxidation stress was evaluated in subjects with cardiovascular risk factors, revealed reduction of both parameters, accordingly (Dohadwala et al., 2011; Riso et al., 2012).

Few studies focused on the effect of resveratrol on FMD. In a recent double blind 6-week crossover study, chronic administration of 75 mg of *trans*-resveratrol to healthy obese individuals increased their FMD by 23% and correlated negatively with their baseline FMD (Wong et al., 2013). Resveratrol at a dose of 100 mg per day that was consumed for 3 months by individuals with metabolic syndrome reportedly increased their FMD by more than 150% (Fujitaka et al., 2011), and daily supplementation of lower doses of resveratrol for 3 months improved the FMD of patients after myocardial infarction (Magyar et al., 2012). Acute administration of 270 mg resveratrol to overweight/obese individuals with mildly elevated BP increased their FMD and was linearly related to plasma concentrations of FMD

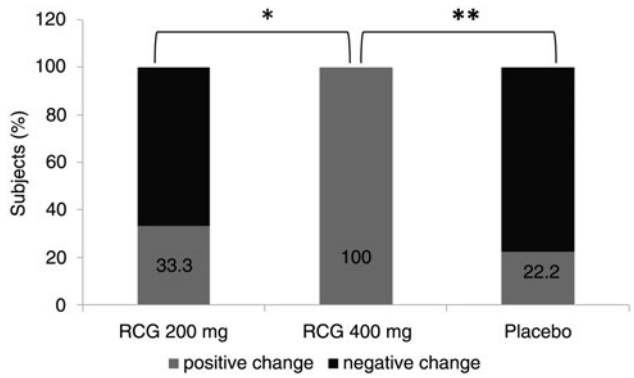

Figure 1. The percentage of subjects with relative positive change in flow-mediated dilation values >70% after 12 weeks of treatment with red grape cell (RGC) powder or placebo. *$p < 0.05$, **$p < 0.005$.

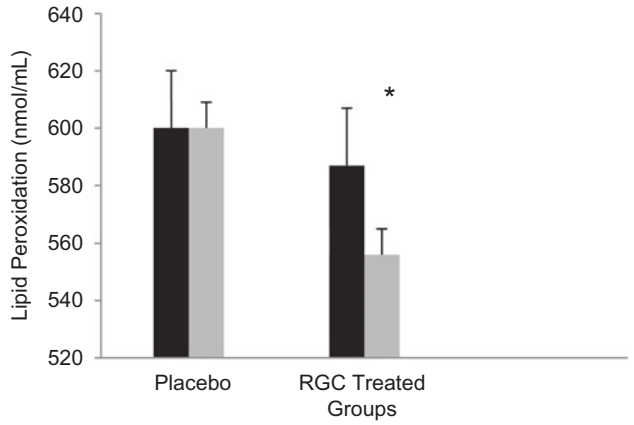

Figure 2. Lipid peroxidation (TBARS assay). Combined red grape cell (RGC) treatment groups versus placebo (black bar represents baseline; and grey bar represents post treatment). Values are presented as mean ± SD; *$p < 0.05$.

(Wong et al., 2011). It would appear that grape-derived polyphenols and resveratrol specifically exert their beneficial effect on FMD in at-risk populations (e.g. overweight individuals with prehypertension and mild hypertension).

Red grape-derived polyphenols sources show mixed effects on BP (Hooper et al., 2008). Animal studies conducted on a rat model of hypertension using grape powder, unripe red grape juice or resveratrol (Dolinsky et al., 2013; Nematbakhsh et al., 2013; Thandapilly et al., 2012) showed a decrease in both DBP and SBP. In contrast, red wine with and without alcohol decreased both DBP and SBP in clinical studies conducted on a population at high cardiovascular risk (Chiva-Blanch et al., 2012), while consumption of grape polyphenol powder significantly reduced only SBP (Barona et al., 2012). Resveratrol (10 mg) consumed by subjects with a history of cardiovascular disease significantly improved left ventricular diastolic pressure (Magyar et al., 2012), but recent studies that included subjects with prehypertension and mild hypertension showed that the consumption of red wine polyphenols, grape juice or grape seed extract had no effect on BP (Botden et al., 2012; Dohadwala et al., 2010; Ras et al., 2013).

Further investigation is clearly needed to better understand the mechanism by which polyphenols affect BP and endothelial function. Some plausible explanations could be the ability of polyphenols to act as free radical scavengers, metal chelators and enzyme modulators (Rodrigo et al., 2012). Polyphenols are also excellent inhibitors of lipid peroxidation (Lapointe et al., 2006) as shown recently, specifically for RGC *in vitro* (Azachi et al., 2014). Of special interest is the ability of grape-derived polyphenols to enhance nitric oxide (NO) levels. NO is a well-established mediator of both FMD and BP (Green, 2005; Green et al., 2014; Zhu et al., 2005) and it is significantly affected by RGC. NO production is induced by the activity of eNOS, which was found to be increased by grape polyphenols (Räthel et al., 2007). This notion finds support in a recent study, in rat model of metabolic syndrome in which RGC supplementation attenuated the increase in BP, plasma triglycerides and insulin. In addition, incubation of human umbilical vein endothelial cells (HUVECs) with RGC demonstrated a concentration-dependent inhibition of ET-1 secretion and increase in the level of eNOS (Leibowitz et al., 2013). Thus, it is likely that BP reduction observed by RGC is mediated mainly by direct vasorelaxation and decreased peripheral resistance.

Cumulative evidence suggests that moderate red wine consumption exerts a cardioprotective effect, however, the alcohol and sugar content of red wine have curtailed its medical use. In contrast, RGC is devoid of alcohol and has very low levels of carbohydrates published previously in Azachi et al. (2014). It is believed that the beneficial effects of red wine are due to polyphenols such as flavonoids and stilbenes (mainly resveratrol).The amount of *trans*-resveratrol in the skins of fresh grapes is 50–100 mg/kg (Guerrero et al., 2009). The *trans*-resveratrol content in red wine has been reported by various sources as being between 0.1 and 15 μg/ml (Frémont, 2000), depending upon the resveratrol content in the grapes and the length of time the grape skin remains in contact with the fermenting liquid. This is the reason why most of the investigations on the effects of products contain extracts of red grape polyphenol and resveratrol in animal models as well as in humans have used pharmacological doses of resveratrol or other grape products unrealistically high to be considered for use in an ordinary diet (Tome-Carneiro et al., 2012a). Moreover, recent reviews have raised concerns regarding the chronic consumption of high resveratrol doses and its interaction with other medications and interference in cell metabolism (Detampel et al., 2012). This may be attributed to its effects on various cytochrome P450 (CYP) isoenzymes. It was also suggested that high doses may interfere with absorption and affect the first-pass metabolism, resulting in higher systemic exposure to co-administrated CYP substrates (Tome-Carneiro et al., 2013). Both these concerns were minimized in our study since our subjects consumed small daily doses of RGC, i.e. in an amount equivalent to only 3.5–7 mg of resveratrol. In a recent bioavailability study of RGC, resveratrol has shown high rate of absorption and considerable presence time in the circulation. One of the factors that may improve RGC-resveratrol solubility and hence its bioavailability is glycosylation of the resveratrol parent compound, which is the predominant form of resveratrol in RGC (Azachi et al., 2014). Indeed, here we identified that the glycoside form of *trans*-resveratrol is piceid. These findings may help to explain the effectiveness of these low doses of RGC. Moreover, these significantly smaller doses suggest the presence of synergism between resveratrol and other polyphenols in RGC, a notion that was supported in recent studies that showed a synergistic effect of grape polyphenols, including resveratrol, in vascular smooth muscle proliferation and in lipid peroxidation (Kurin et al., 2012; Mikstacka et al., 2010).

Our results indicate that different concentrations may be needed for producing different effects. For example, improvement in FMD was reached by the higher dose of RGC. DBP seemed to respond better to the lower dose, but the level of significance for lipid per-oxidation improved after combining the two groups, which may indicate that a larger study group would have been needed to achieve significance with either of the two studied doses.

In summary, our results indicated a significant effect of RGC powder on endothelial function and a positive effect on oxidative stress and DBP while using a nutritional range of consumption within a normal range and not at high concentrations like those used in most of the other studies. Consuming very low amounts of RGC comparable to drinking two glasses of wine a day carried a significant advantage and facilitated daily long-term use of RGC. Further research is needed to confirm the effect of RGC on blood pressure and vascular function.

Declaration of interest

Bioharvest Ltd. supplied the study material and financial support.

NV and EN declares they have no conflict of interest in relation to this work.

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