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Research Article

# Effect of Rg3-enriched Korean red ginseng (*Panax ginseng*) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial

Elena Jovanovski, MSc[a], Emma A. Bateman, BSc[a], Jyoti Bhardwaj, MSc[a,b], Chris Fairgrieve, MD[a], Iva Mucalo, PhD[c], Alexandra L. Jenkins, RD, PhD[a], and Vladimir Vuksan, PhD[a,b,d,e,*]

[a]*Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada;*
[b]*Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada;*
[c]*Centre for Applied Pharmacy, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia;*
[d]*Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; and*
[e]*Division of Endocrinology & Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada*

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## Abstract

Ginsenoside Rg3, present in steamed ginseng (*Panax Ginseng* C.A. Meyer), is thought to be a potent modulator of vascular function. Our objective was to clinically evaluate acute effects of ginsenoside Rg3–enriched Korean red ginseng (Rg3-KRG) on measures of arterial stiffness and peripheral and central blood pressure (BP) parameters in healthy volunteers. Using a double-blind, randomized, crossover design, 23 individuals (9 males:14 females; age, 25 ± 2 years; body mass index, 22 ± 0.6 kg/m$^2$; systolic BP/diastolic BP, 113 ± 3/70 ± 2 mm Hg) were administered 400-mg Rg3-KRG extract or 400-mg wheat bran control on two separate visits with a 7-day washout period. Aortic augmentation index and central BP were measured using applanation tonometry by radial pulse wave analysis, and peripheral BP was evaluated oscillometrically. Measurements were taken at baseline and at 1, 2, and 3 hours after intervention. Compared with control, there were significant reductions in augmentation index (−4.3 ± 8.9%, $P = .03$), central (−4.8 ± 6.8 mm Hg, $P = .01$) and brachial mean arterial pressure (−4.4 ± 6.6 mm Hg, $P = .01$), central systolic (−5.0 ± 7.9 mm Hg, $P = .01$) and diastolic BP (−3.9 ± 6.6 mm Hg, $P = .01$), and brachial systolic (−4.4 ± 10.0 mm Hg, $P = .048$) and diastolic BP (−3.6 ± 6.4 mm Hg, $P = .01$) at 3 hours after intervention compared with control. This study is the first to demonstrate Rg3-KRG extract acutely lowers central and peripheral arterial pressures in healthy adults. Further clinical evaluation is desired to quantify efficacy in higher risk individuals and in long-term settings. J Am Soc Hypertens 2014;8(8):537–541. © 2014 American Society of Hypertension. All rights reserved.

*Keywords:* Augmentation index; clinical; ginsenosides; vascular; ginseng.

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Conflict of Interest: Vladimir Vuksan is a holder of an American (No. 7,326,404 B2) and Canadian (No. 2,410,556) patent for use of viscous fiber blend in diabetes, metabolic syndrome and cholesterol lowering; currently holds grant support for ginseng research from the Canadian Diabetes Association (G-2-09-2920-VV), Canada and the National Institute of Horticultural & Herbal Science, RDA, Korea. Vladimir Vuksan received a travel grant from BTGin Co, Yuseong-gu, Daejeon, Republic of Korea. Vladimir Vuksan and Alexandra L. Jenkins are part owners of Glycemic Index Laboratories, Inc. a contract research organization. For the remaining authors, no conflicts of interest were declared.

*Corresponding author: Vladimir Vuksan, PhD, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, 30 Bond Street, 10th Floor–Donnelly Wing, Toronto, Ontario, M5B1W8, Canada. Tel.: (416) 864-5525; fax: (416) 864-5538.

E-mail: v.vuksan@utoronto.ca


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## Introduction

Less than half of individuals with hypertension reach targets for managing blood pressure (BP) using conventional medical therapies alone.[1] In addition to office BP, central BP and measures of arterial stiffness are validated independent predictors of cardiovascular disease (CVD) mortality and are among the risk factors conventional practice often fails to address.[2,3] Korean red ginseng (KRG) has been implicated in improving CVD risk factors including insulin sensitivity in type 2 diabetes mellitus and endothelial function in healthy individuals, but to date has generated neutral or moderate effects on arterial stiffness and brachial BP.[4–8] Although clinical application of KRG may show promise in the management of vascular health, the equivocal data warrant further delineation of its structure–function relationships before standardization is applied and a reliable clinical response can be established.

Evidence to date suggests that the steroidal saponin fraction of ginseng, known as ginsenosides, is a pharmacologically active component.[9] We have previously demonstrated that a ginsenoside fraction of ginseng, rather than the polysaccharide fraction, was responsible for improving augmentation index (AIx), a marker of wave reflection and arterial stiffness, in healthy individuals.[5] Within the ginsenoside fraction of KRG, particular attention was focused on ginsenoside Rg3, as it had been ascribed potent vasodilator properties in animal models and is thought to be a significant contributor to ginseng-mediated vasoactivity.[10–12] Whether these findings translate to a clinical setting and could possibly enter the therapeutic domain, is unknown. Clinical utility of a standardized ginseng extract that is enriched with ginsenoside Rg3 should therefore be considered as a novel lead for its potential application in vascular health.

The objective of the present study was, therefore, to evaluate the acute efficacy of single dose oral administration of a standardized ginsenoside Rg3-enriched KRG (Rg3-KRG) extract on measures of arterial hemodynamics including a marker of arterial stiffness, brachial BP, and central BP in healthy adult participants.

## Methods

### *Participants*

Twenty-four healthy participants were recruited using the following inclusion criteria: age 18–70 years, body mass index $<30$ kg/m$^2$, brachial BP defined as seated systolic/diastolic BP $<$ 140/90 mm Hg at screening and exclusion criteria: presence of hypertension as defined by the Joint National Committee VII criteria,[1] diabetes, kidney or liver disease, bleeding disorder, pregnancy or breastfeeding, use of prescription medication, use of herbal supplements within 3 weeks of the first study visit, self-reported presence of any major diseases, and alcohol use of $>2$ drinks per day. Participants were instructed to follow a nitrate-controlled diet for 3 days before the visits. The study was conducted in accordance with the guidelines presented in the Declaration of Helsinki. All participants gave informed written consent prior to study commencement. Regulatory approvals were obtained from St. Michael's Hospital Research Ethics Board and the Health Canada Natural Health Product Directorate (ClinicalTrial.gov Identifier: NCT01951443).

### *Study Intervention*

Within a double-blind, randomized, crossover, placebo-controlled design, study interventions included either a 400-mg dose of ginsenoside Rg3-KRG extract or 400 mg of wheat bran control. The dose of 400 mg was selected as a starting dose based on the dose previously found to affect erectile dysfunction.[13] Randomization for treatments was conducted using a random number table generated by a statistician where treatment allocation sequences occurred in approximately equal numbers (12 participants assigned to treatment then control and 12 participants assigned to the reverse sequence). The Rg3-KRG material was manufactured to contain 10% ginsenoside Rg3 and 30% total saponins, by BTGin Co Ltd (Daejeon, Republic of Korea). Briefly, KRG rootlets underwent 50% and 85% ethanol and water extraction in consecutive steps (70°C, 3 hours). The extract was treated by enzyme and acid hydrolysis to amplify ginsenoside Rg3 content, followed by substrate removal and evaporation to powder form. The final product contained the following concentrations of major ginsenosides: Rb1 (3.77 mg/g), Rg1 (0.57 mg/g), Re (1.86 mg/g), Rf (12.3 mg/g), Rb2 (1.24 mg/g), Rh1 (4.15 mg/g), Rc (0.99 mg/g), and Rg3 (100 mg/g). The extract and control interventions were administered in encapsulated form using an identical size #000 opaque capsule and were indistinguishable from each other.

## Protocol

Screened and eligible participants attended the Risk Factor Modification Centre, St. Michael's Hospital in a fasted state on two separate mornings, separated by a minimum of 1 week washout period. Individuals first underwent anthropometric measures and completed a questionnaire. Baseline measures of aortic AIx, a marker of arterial stiffness, and aortic BP were performed noninvasively in triplicate via applanation tonometry of the radial artery using the SphygmoCor Vx Pulse Wave Analysis system (AtCor Medical, Sydney, Australia) by two trained investigators. Brachial BP was also evaluated in triplicate oscillometrically 1 minute apart (HEM907-XL; Omron Healthcare, Kyoto, Japan). Following baseline measures, treatment was administered orally with 200 mL of water. Additional measures were obtained at 1-hour intervals for a study

session duration of 3 hours after intervention. Symptom adverse events were evaluated subjectively through a symptoms questionnaire at 1-hour intervals during study session and within 24 hours following acute dosing.

### *Statistical Analysis*

The primary outcome measure was aortic AIx, where all values are adjusted for a heart rate of 75 beats per minute. Secondary outcome measures included brachial and central BP and mean arterial pressure. Changes in each outcome measure relative to baseline were computed and plotted. Repeated measures analysis of variance assessed independent and interactive effects of intervention relative to control on incremental hemodynamic indices. Statistical analyses were performed using the NCSS statistical software (Kaysville, Utah). All results are expressed as mean ± standard deviation (SD). To detect differences in AIx adjusted for heart rate of 75 beats per minute of 4% at a SD of 4.5% unit change with 80% power at a level of $P < .05$ ($\alpha = 0.05$ and $1-\beta = 0.8$) and accounting for a 10% attrition rate, a total of 24 participants were to be recruited.

## Results

Twenty three individuals with the following baseline characteristics completed the study: 9 males:14 females; age, 25 ± 2 years; body mass index, 22 ± 0.6 kg/m$^2$; systolic BP, 113 ± 3 mm Hg, diastolic BP, 70 ± 2 mm Hg; and AIx: 9.5 ± 11.6%. One participant withdrew from the study because of time commitments unrelated to the study. The design was uniform within sequences and periods. There was no significant carryover effect of study interventions. Repeated measures analysis of variance demonstrated a significant effect of Rg3-KRG on reduction of aortic AIx posttreatment relative to control (−4.3 ± 8.9%, $P = .03$; Figure 1). Additionally, measured hemodynamic indices including central systolic (−5.0 ± 7.9 mm Hg, $P = .01$; Figure 1) and diastolic BP (−3.9 ± 6.6 mm Hg, $P = .01$; Figure 1), brachial systolic (−4.4 ± 10.0 mm Hg, $P = .048$; Figure 1) and diastolic BP (−3.6 ± 6.4 mm Hg, $P = .01$), central mean arterial pressure (−4.8 ± 6.8 mm Hg, $P = .01$), and brachial mean arterial pressure (−4.4 ± 6.6 mm Hg, $P = .01$) were significantly reduced at the end of posttreatment period relative to control (Table 1). There were no differences between treatments for self-reported adverse effects. One participant experienced mild headaches posttreatment in both interventions and another participant experienced transient anxiety posttreatment in the control group. Data in the text are presented as mean ± SD.

## Discussion

This study is the first to demonstrate that ginseng enriched with ginsenoside Rg3 acutely improved indices of vascular function in healthy young adults with BP in the low–normal range. The magnitude of pulse wave reflection observed at the end of study session is in line with angiotensin converting enzyme inhibitor, an antihypertensive agent, reported in a recent meta-analysis.[14] These results are noteworthy in the context of mounting evidence relating increased arterial stiffness to adverse effects on ventricular afterload and the strong independent association between indices of wave reflection, including aortic AIx, and CVD risk.[15] The observations here corroborate cumulating evidence on vasoactive agents, which lower brachial BP yet may have an additional favorable impact on aortic AIx.[12,16,17]

While this study cannot attribute the significant shift in hemodynamics to a specific bioactive compound, our study

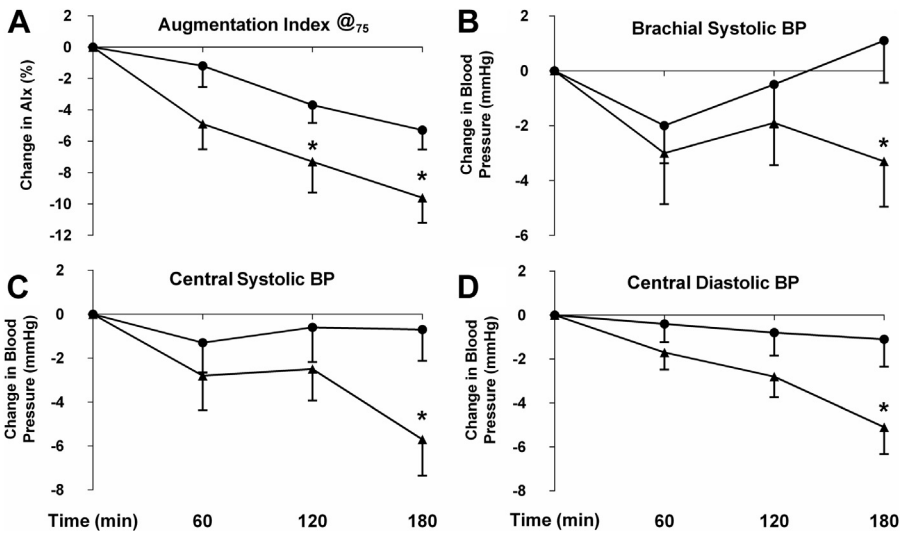


**Figure 1.** Acute effects of administration of 400-mg Rg3-enriched Korean red ginseng (–▲–) vs. control (-●-) on (A) augmentation index (AIx) adjusted for 75 beats per minute, (B) brachial systolic BP, (C) central systolic BP, and (D) central diastolic BP in 23 young, healthy individuals. Values are presented as mean change from baseline over 3 h postingestion. BP, Blood pressure; @$_{75}$, adjusted for 75 beats per minute. Data are presented as mean ± standard error of the mean; *, Significant effect of intervention, $P < .05$ (repeated measures analysis of variance).

**Table 1**
Mean hemodynamic values (±SD) at baseline and change from baseline in 23 healthy participants administered in a random sequence, 400 mg of Rg3-enriched Korean red ginseng or 400 mg wheat bran control, in a crossover design

| Time | 0 min | | 60 min | | 120 min | | 180 min | | *P* Value* |
|---|---|---|---|---|---|---|---|---|---|
| Treatment | Control | Ginseng | Control | Ginseng | Control | Ginseng | Control | Ginseng | |
| Outcome Measure | | | | | | | | | |
| Brachial SBP (mm Hg) | 113.30 ± 15.0 | 112.59 ± 16.6 | −2.04 ± 6.6 | −3.04 ± 8.9 | −0.52 ± 7.5 | −1.87 ± 7.4 | 1.09 ± 7.4 | −3.28 ± 7.9† | .14 |
| Brachial DBP (mm Hg) | 68.96 ± 9.2 | 69.67 ± 10.3 | −0.78 ± 3.7 | −0.93 ± 3.6 | −0.26 ± 5.5 | −1.74 ± 3.6 | −1.48 ± 5.6 | −5.04 ± 5.5† | .02 |
| Brachial MAP (mm Hg) | 83.54 ± 10.2 | 84.12 ± 11.6 | −0.86 ± 4.1 | −1.87 ± 4.6 | 0.07 ± 5.7 | −2.16 ± 4.0† | −0.42 ± 5.4 | −4.84 ± 6.9† | .01 |
| Central SBP (mm Hg) | 99.9 ± 11.7 | 100.2 ± 14.5 | −1.34 ± 6.5 | −2.78 ± 7.5 | −0.64 ± 7.6 | −2.45 ± 6.9 | −0.75 ± 6.9 | −5.71 ± 7.9† | .04 |
| Central DBP (mm Hg) | 70.6 ± 10.1 | 71.1 ± 10.5 | −0.41 ± 4.0 | −1.74 ± 3.7 | −0.75 ± 5.1 | −2.83 ± 4.5 | −1.13 ± 6.0 | −5.06 ± 5.9† | .04 |
| Central MAP (mm Hg) | 79.8 ± 9.8 | 80.8 ± 11.5 | 0.82 ± 6.6 | −2.10 ± 4.6† | −0.98 ± 5.4 | −2.77 ± 4.4 | −0.74 ± 6.4 | −5.53 ± 6.2† | .01 |
| Central PP (mm Hg) | 29.90 ± 6.3 | 28.86 ± 7.6 | −0.37 ± 4.9 | −1.16 ± 5.9 | 0.50 ± 5.5 | 1.71 ± 7.8 | 0.72 ± 5.8 | −1.13 ± 7.7 | .44 |
| Heart Rate (BPM) | 66.47 ± 11.7 | 65.06 ± 13.4 | −6.21 ± 3.5 | −6.20 ± 6.4 | −7.70 ± 5.0 | −7.47 ± 6.4 | −4.49 ± 7.0 | −1.50 ± 8.7 | .05 |

BPM, beats per minute; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.
All values expressed as mean ± SD. Measured values at 60 min, 120 min, and 180 min are expressed as change from baseline (0 min).
*Effect of treatment × time interaction of interventions, two-way repeated measures analysis of variance.
†Different from control, repeated measures analysis of variance ($P < .05$).

supports preclinical literature that orally ingested Rg3 ginsenosides may, in part, be the vasoactive components responsible for acute benefits. Among the major ginsenosides, ginsenoside Rg3 demonstrated the greatest potency in inducing an endothelium dependent relaxation in the rat aorta.[11,12] Pharmacokinetic study of 20 (R) ginsenoside Rg3 time–concentration curves in a two-compartment open model suggested a half-life $\alpha$ of 0.46 hours and half-life $\beta$ of 4.9 hours, therefore a rapid absorption and elimination of Rg3.[18] This is the first trial in humans to study hemodynamics of the concentrations of ginsenoside Rg3 at ~30 times those present in the natural root. In our preceding trial with unenriched KRG, a similar effect on AIx was observed although the magnitude of hemodynamic effect was to a lesser extent.[5] Such acute improvements in vascular indices have not been observed to date in clinical trials examining unenriched *Panax ginseng* roots, which demonstrated variable vascular effects.[4,5,19]

The effects on pulse wave morphology, and AIx in particular, observed after Rg3-KRG administration may be attributed not only to modification of viscoelastic properties of the aorta and large arteries, but also to improvement in reflective properties of the peripheral arteries. Given the acute nature of this trial, it is plausible to infer that the effect of our interventions was related to the alteration of vascular resistance features rather than changes in aortic wall properties.

The efficacy of the Rg3-KRG contributes to a growing field of clinical evidence targeted toward stepwise screening and fractionation of potentially bioactive components in ginseng. This is contrary to the uncontrolled, observational study of high public impact, conducted by Siegel[20] in 1979 that contraindicated ginseng in hypertension. The study by Siegel[20] and other studies in which the ginseng species and product composition are not reported highlight the need for adequate characterization of study material and methods, so that findings may be reproduced and corroborated or challenged. The use of efficacy-based standardized preparations in ginseng research, exemplified here, is a prerequisite step in the formulation of guidelines controlling its consumption and component-based recommendations for its use.

The strength of this study includes a crossover design and the stringent inclusion criteria of healthy individuals with no concomitant medications, both of which reduced potential variability in treatment effect. We opted to use an acute phase I-like type, rather than chronic trial design given the uncertainty of the effect of Rg3-KRG on hemodynamics in humans and in the duration that allowed us to abstain from potential confounding effects of meal administration. However, this clinical trial of acute design should be used to provide experimental basis for further investigations. A dose–response relationship, corroborated by functional arterial markers including circulating biomarkers of the nitric oxide synthesis pathway, should be established in the background of a longer scale trial using Rg3-KRG.

## Conclusion

This study contributes to the growing body of evidence from clinical trials on the hemodynamic effects of ginseng and its isolates. Although other studies are required to see if this effect can be reliably repeated, in addition to longer term trials, this study provides evidence that in healthy individuals, an Rg3-KRG supplement may be considered a viable possibility in the armamentarium of proactive CVD risk management strategies.

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