Effects of Korean Red Ginseng (*Panax ginseng* C.A. Mayer) and Its Isolated Ginsenosides and Polysaccharides on Arterial Stiffness in Healthy Individuals

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BACKGROUND

Preclinical studies indicate a role of Korean red ginseng (KRG) in the modulation of vascular function; however, clinical evidence is scarce. Therefore, the objective of this study was to investigate the effect of KRG root on peripheral blood pressure (BP) and augmentation index (AI), an emerging method to assess cardiovascular risk beyond conventional BP measurements. Furthermore, in an attempt to elucidate which of the major components of KRG is responsible for these effects, the ginsenoside and polysaccharide fractions isolated from the same KRG root were also investigated.

METHODS

The study was designed as an acute randomized, controlled, double-blind, crossover trial. A total of 17 healthy fasted individuals (gender: 9 males:8 females, age: 30 ± 9 years, body mass index: 25 ± 3 kg/m^2, systolic BP (SBP): 110 ± 10.1, diastolic BP (DBP): 65 ± 7 mm Hg) received, on separate occasions, four treatments consisting of: 3 g of either placebo, KRG root, or a KRG root bioequivalent dose of ginsenoside or polysaccharide fractions. BP and AI were measured by applanation tonometry at baseline, 1, 2, and 3 h post-treatment.

RESULTS

Compared to placebo, 3 g of KRG significantly lowered radial AI by 4.6% ($P = 0.045$), whereas the ginsenoside fraction comparably decreased AI by 4.8% ($P = 0.057$), and no effect was observed with the polysaccharides. There were no differences in BP between treatments.

CONCLUSION

Although preliminary, this study is the first to demonstrate that KRG may improve arterial stiffness as measured by AI. In addition, it appears that ginsenosides may be the principal pharmacologically active component of the root, rather than the polysaccharide fraction. This study supports the results seen with KRG in the preclinical studies and warrants further investigation on acute and long-term endothelial parameters.

Keywords: *arterial stiffness; augmentation index; blood pressure; ginseng; hypertension; vascular*

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The use of herbal medicine is markedly increasing, with the ginseng root ranking among the top selling products worldwide.[1] The steamed variety of *Panax ginseng*, Korean red ginseng (KRG), one of the most popular and studied species of ginseng, has repeatedly demonstrated preclinical potential as a vasodilatory agent. However, to date, clinical evidence from the limited number of randomized–controlled trials on hemodynamic properties of ginseng shows either neutral or moderate blood pressure (BP)–lowering effects.[2–4] Considering that vasodilatory agents may have little direct effect on reduction in initial stroke pressure (systolic BP), but may markedly lower the reflected pulse wave and therefore left ventricular workload,[5] these beneficial effects on arterial pressure waves can occur with or without a reduction in conventional BP.[3–5] Augmentation index (AI), an independent marker of increased total and cardiovascular disease mortality,[6] is a noninvasive measure of arterial wave reflection that may provide additional hemodynamic information on potentially vasoactive compounds such as KRG.

Nearly all preclinically observed vascular effects of KRG, including vasodilatation, platelet's adhesion inhibition, and nitric oxide release stimulation,[7] have been attributed to ginsenosides, the dammarane triterpene saponin components of ginseng.[8] The corresponding evaluation of ginseng

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polysaccharides, another potentially major pharmacologically active fraction, is generally lacking.[9] Thus far, neither ginseng component has undergone comparative clinical scrutiny for their purported vascular effects.

This study therefore examines the effect of KRG root, and its ginsenoside and polysaccharide fractions, extracted from the same root and delivered at doses bioequivalent to that of the original KRG root. This is the first acute, randomized, crossover trial to evaluate the effect of KRG root on arterial stiffness *via* pulse wave analysis. Second, the study design would allow us for the first time to directly compare the effects of unprocessed KRG root to its major fractions—ginsenosides and polysaccharides—for potential hemodynamic stimulation in humans.

METHODS

Subjects. A total of 17 healthy subjects were recruited based on following inclusion criteria: age: 18–65 years, normal BP (seated SBP <140 mm Hg and diastolic BP (DBP) <90 mm Hg), and exclusion criteria: hypertension, diabetes, kidney or liver disease, pregnancy, use of herbal supplements within 3 weeks of the first study visit, use of prescription medication, presence of any major diseases, gastrointestinal disorders, heavy alcohol (>3 drinks/day) or cigarette use (>10 cigarettes/day). Subjects were instructed to follow a nitrate-controlled diet for 3 days before the visits. Also, subjects whose body weight changed >5% from the commencement of the study were excluded in order to eliminate confounding weight variations. The study was approved by the Research Ethics Board at St Michael's Hospital and the Natural Health Product Directorate, Health Canada, and was conducted at the Clinical Nutrition and Risk Factor Modification Centre, St Michael's Hospital (Toronto, Canada). Written consent was obtained from all subjects.

Treatments. Four treatments were randomly administered: (i) 3 g of dried, ground KRG rootlet part of root, (ii) 1.22 g of ginsenoside extract delivering 105 mg total saponin-equivalent to the total ginsenosides from 3 g of KRG rootlets, (iii) 0.21 g of polysaccharide extract delivering 172 mg of polysaccharide-equivalent to the polysaccharide content of 3 g of KRG rootlets, and (iv) 3 g of cornstarch control. A dose of 3 g was chosen in consideration of the 1–3 g dose recommended by the Commission E monograph and WHO ginseng monograph.[10,11] Further, an unpublished dose finding study showed 3 g to be most effective in reducing brachial BP, though findings did not reach significance. The KRG was selected by the Korea Ginseng Research Institute (Korean Ginseng Manufacturing Plant, National Agricultural Cooperative Federation, Chungbuk, South Korea), to be representative of the KRG that is cultivated, produced, and exported for market, obtained from the same source that we previously found to be effective in maintaining diabetes control.[12] The same root batch was used to extract the ginsenoside and the polysaccharide fractions. The ginsenoside extract was produced at the University of Ottawa by repeated extraction using 80% food-grade ethanol. Total content of ginsenoside Rb1, Rb2, Rc, Rd, Rg_3, Rg1, Re, and Rf were determined in triplicate by high-performance liquid chromatogrpahy/mass spectrometry. Total ginsenoside concentration of KRG root and ginsenoside extract was 3.5 and 8.6% of dry weight, respectively. To extract the polysaccharide fraction, the remaining residue underwent repeated hot-water extraction at 90 °C for 1 h, was filtered out from the aqueous supernatant by 99% ethanol precipitation, and dried by lyophilization. The resulting extract contained ~85% of polysaccharides, as determined by gas chromatography analysis, with ginsenosides removed.

The weighing, encapsulation, and blinding of all treatments were performed by an individual otherwise not involved in the study. All treatments were individually encapsulated and coded in six identical size 500 mg opaque capsules.

Protocol. The study was conducted in a randomized, double-blind, crossover manner. Subjects underwent four separate morning visits, following 10–12 h overnight fast. Visits were separated by at least 3 days to minimize carry-over effects. Participants were advised to maintain consistent dietary and physical activity patterns throughout the study. At each visit, anthropometric measurements, dietary and compliance questionnaires preceded a baseline measurement of AI and BP followed by administration of study capsules with 200 ml of water. Ingestion time was kept standard between visits. AI and BP were measured at fasting, 1, 2, and 3 h after administration of experimental treatment. Subjects remained seated and did not consume any food or beverages over the test period.

AI and BP measurements were conducted in a quiet, temperature-controlled room according to the following procedure. Adhering to American Heart Association criteria, brachial BP was recorded following a 10-min seated resting period, on the dominant arm using an automatic cuff oscillometric device (HEM-9000AI; Omron Healthcare, Kyoto, Japan). Three readings were averaged to determine SBP and DBP. Subsequently, the radial artery waveform was obtained noninvasively by applanation tonometry (HEM-9000AI; Omron Healthcare). The same position was used for each AI measurement, obtaining continuous steady-state recordings over a period of 30 s; three measurements were taken at each time point, and the mean AI was used for subsequent analysis. Radial AI was calculated as follows: reflected wave peak pressure (SBP^2) – DBP/(first peak SBP – DBP) × 100 (%) (refs. 5,6).

Study outcomes and statistical analyses. Change in radial AI, the primary outcome, normalized for a heart rate of 75 beats/min relative to baseline, was calculated at 60, 120, and 180 min for each treatment. Independent and interactive effects of treatment and protocol-time (post-treatment: 0–180 min inclusive) on change in AI was assessed by repeated-measures two-way analysis of variance and considered significant at $P < 0.05$. Repeated-measures one-way analysis of variance with the Tukey test determined differences between treatment-associated means at each time point. Effect of treatment on

SBP and DBP, secondary outcome measures, was assessed in the same manner using NCSS2000 Statistical Software (NCSS, Kaysville, UT). Linear regression analysis to determine a time trend response was conducted using SPSS release 16.0 (SPSS, Chicago, IL). All data are expressed as mean ± s.e.m. A sample size of 15 subjects (+15% attrition rate) was calculated as efficient (80% power) to demonstrate a change by 4% (s.d. = 5%) in AI ($\alpha = 0.05$).

RESULTS

A total of 17 individuals, 10 males and 7 females, age range: 19–50 years: mean ± s.d.: age: 30 ± 9 years, body mass index: 25 ± 3 kg/m^2, resting SBP/DBP: 110 ± 10.59/65.10 ± 7.3 mm Hg, were included in the study. Subjects randomly consumed each of the four treatments at separate visits. Symptoms reported during and after tests did not differ significantly between any of the treatments, except for headaches, which occurred in a significantly higher number of subjects taking the ginsenoside extract alone ($n = 2$), compared to control ($n = 0$). There was a significant dependent and independent effect of treatment and time on AI changes, such that the effect of treatment was dependent on protocol-time ($P = 0.034$). The Tukey–Kramer test revealed a significant reduction in AI with KRG root treatment at 180 min compared to control ($P = 0.045$) (**Table 1**). The maximum decrease occurred at 180 min, by 6.06 ± 2.21% and a 6.32 ± 2.34 % (absolute value) decrease in AI with ginsenoside extract ($P = 0.057$) and KRG ($P = 0.045$), respectively. Ginsenoside-containing treatments did not significantly differ from each other ($P = 0.17$). Polysaccharide extract did not significantly affect AI. A time trend response analysis using linear regression showed incremental AI to be significantly and negatively associated with time of measurement for the ginsenoside extract ($P < 0.001$; $r^2 = 0.23$; $r = 0.48$) and the KRG root ($P < 0.001$; $r^2 = 0.18$; $r = 0.43$).

There was no effect of treatment or time–treatment interaction on change in mean SBP and DBP. The mean absolute AI and BP values did not differ significantly between any of the treatments at baseline. There was no effect of study period on AI, SBP, or DBP.

DISCUSSION

We report here, for the first time, that acute consumption of KRG resulted in a significant amelioration of pulse wave reflection, as measured by AI, compared to a control in healthy individuals. Furthermore, a decrease in AI was observed following consumption of ginsenoside, but not polysaccharide fraction, and results suggest that the effect may extend beyond the 3 h measured in this study. These findings are of interest because of the strong association between indices of wave reflection and cardiovascular disease risk.[13] It has been suggested that increases in AI indicate amplified or early-return wave reflections from the periphery that unfavorably affect ventricular after-load and compromise coronary perfusion, predisposing one to ischemia.[13] This is relevant, as with similar effects on conventional BP, some antihypertensive treatments have an additional favorable impact on central AI.[14]

Given the acute nature of the therapy, it is postulated that decreased AI mirrors changes in wave reflection from peripheral sites and increased tone of muscular vessels. Support for this hypothesis originates from abundant preclinical evidence. Mechanistically, the hemodynamic activity of KRG may be underpinned by its ability to cause vasodilatation *via* enhancement of the nitric oxide/cyclic guanosine monophosphate pathway.[15,16] A recent clinical study described an acute increase in exhaled nitric oxide following KRG administration supporting the proposed mechanism.[15] As nitric oxide has been directly related to wave reflections and arterial stiffness,[17] in addition to vasodilatation, it represents one of the potential mechanisms liable for the observed AI modifications by KRG therapy.

From a component-based perspective of KRG evaluation, our study suggests that ginsenosides are accountable for KRG vasoactive effects, demonstrating responses comparable to KRG root. Lack of significant contribution to pulse pressure components produced by polysaccharide fraction could possibly suggest administration of submaximal dosage to produce a clinically manifested effect or a true lack of activity. Given the insufficiently described photochemistry of ginseng polysaccharides,[18] it is unknown whether oral administration preserves the structures needed to trigger vascular reactivity.[19]

Table 1 | Mean acute changes in AI and BP following treatment consumption

	Time (min)	Control	KRG rootlets	GE	PE	*P* value[c]
Baseline AI (%)[a]	0	67.43 ± 3.61	66.90 ± 3.37	67.09 ± 3.54	66.74 ± 3.88	0.56
Change in AI from baseline[a]						
%	60	−1.66 ± 1.76	−2.94 ± 1.52	−2.95 ± 2.02	−2.88 ± 2.16	0.23
%	120	−0.97 ± 1.76	−4.98 ± 2.02	−3.66 ± 2.98	−4.05 ± 2.31	0.08
%	180	−1.47 ± 1.77	−6.06 ± 2.21[d]	−6.32 ± 2.34[d]	−3.24 ± 2.13	0.03
Difference from control (% at 3 h)			−4.59 ± 1.75	−4.85 ± 2.02	−2.13 ± 1.94	
Mean change in SBP[b]	—	1.87 ± 1.42	1.50 ± 1.32	−0.41 ± 1.41	2.75 ± 1.46	0.76
Mean change in DBP[b]	—	1.23 ± 1.22	1.05 ± 1.11	0.65 ± 0.95	0.82 ± 1.35	0.27

All data are mean ± s.e.m., 95%. Difference from control = treatment group change in AI from baseline at time 180 – control group change in AI from baseline at time 120 min.
AI, radial augmentation index; DBP, diastolic blood pressure; GE, ginsenoside extract; KRG, Korean red ginseng; PE, polysaccharide extract; SBP, systolic blood pressure.
[a]Mean of three consecutive AI measurements. [b]Mean overall change of BP from baseline. [c]One-way repeated-measures analysis of variance. [d]Significant change in AI relative to control.

An intriguing observation is the lack of a significant alteration in peripheral SBP by any of the treatments. This is, to an extent, in agreement with our previous studies that showed neutral or moderate effects of KRG on BP.[3,4] Findings of this study imply that the observed changes in AI, by both ginsenoside-containing treatments, may occur independent of their effects on SBP. The KRG treatment and its ginsenoside fraction generated a decrease in reflected peak pressure, without significant alterations in the ejected systolic wave. Due to an expected time lag between ejected and reflected waves in the radial artery of young healthy individuals, a decrease in wave reflection amplitude may not manifest as a decrease in SBP measured with a brachial cuff.[20] Conversely, due to possible discrepancies between response of peripheral BP and central BP to vasoactive substances[21] due to differential increases in pulse amplitude as it travels distally,[21] the sole measurement of peripheral BP may introduce a possible underestimation of KRGs impact on central BP.[22] Therefore, the possibility of such an effect should not be overlooked.

Limitations of the study include the relatively small number of subjects and dosing protocol. The study was not powered to detect significant differences in brachial BP precluding any conclusions on BP effects. Further research will need to be undertaken to further investigate this phenomenon. As discussed, it is unknown whether oral administration is the appropriate method of administration for polysaccharides making it premature to discount the potential activity of this ginseng fraction.

In conclusion, this study provides preliminary clinical evidence regarding the possible hemodynamic mechanisms of KRG action, addressing the issue from a component- and efficacy-based perspective. We have shown for the first time that KRG can generate favorable acute effects on wave reflections, an independent predictor of cardiovascular disease, with a negligible impact on brachial BP. Systematic fractionation of the root identified the ginsenoside fraction as the active component and further fractionation may clarify individual ginsenosides involved in attenuation of wave reflections. Increased reactivity of vasomotor function and/or endothelium-mediated vascular response could possibly underlie the present observations and merit further extensive investigation by a more direct approach. Additionally, future studies will monitor the observed effect over a longer time period and examine a range of doses in order to identify the length of KRG effects and optimal dose.

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