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Korean Red Ginseng Improves Vascular Stiffness in Patients with Coronary Artery Disease

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Korean red ginseng (KRG) has been shown to enhance endothelium-dependent vasorelaxation in experimental animals; however, little is known about its pharmacological effects on vascular stiffness in patients with coronary artery disease (CAD). This randomized, double-blind, placebo-controlled crossover trial was carried out to determine whether KRG has beneficial effects on arterial stiffness, cardiovascular risk factors such as plasma lipid profiles and blood pressure (BP), and Rho-associated kinase (ROCK) activity. Twenty patients (mean age, 62.5 years) with stable angina pectoris were given KRG (2.7 g/day) and a placebo alternatively for 10 weeks. Blood biochemical analysis and pulse wave velocity (PWV) recording were performed on day 0 and after the completion of each treatment. ROCK activity was assessed based on the level of phospho-Thr^{853} in the myosin-binding subunit of myosin light chain phosphatase, determined by Western blot analysis of peripheral blood mononuclear cells. KRG significantly decreased the systolic BP, brachial ankle PWV, and heart femoral PWV in the patients (all $p<0.05$), but did not significantly alter the serum lipid profiles, including triglycerides and total, high-density lipoprotein, and low-density lipoprotein cholesterol levels. The ROCK activity tended to decrease ($p=0.068$) following KRG treatment. The placebo did not significantly alter any of the variables. In conclusion, KRG decreased systolic BP and arterial stiffness, probably via the inhibition of ROCK activity, in patients with CAD, but had a neutral effect on serum lipid profiles. Our data suggest that KRG has a therapeutic effect on CAD.

Keywords: Blood pressure, Coronary artery disease, Panax, Rho-associated kinases, Vascular stiffness

INTRODUCTION

Korean *Panax ginseng* (*P. ginseng*) C. A. Meyer is a medicinal herb with diverse biological effects, including immune function enhancement and anti-aging, anti-diabetic, anti-tumor, anti-apoptotic, and anti-oxidative effects [1,2]. Many of ginseng's medicinal effects are attributed to triterpene glycosides, which are known as ginsenosides; 38 ginsenosides have been identified in Korean *P. ginseng* C.A. Meyer [1]. Ginsenosides have diverse effects on the vasculature, including protection of endothelial cells against oxidative stress, prevention of apoptosis, regulation of angiogenesis, and reduction of hypertension [3-5]. Intriguingly, ginsenosides have been shown to improve endothelial function [3-5]. The ginsenosides Rg and Re cause endothelial cell-dependent relaxation by promoting the formation of nitric oxide (NO) [3]. Ginsenoside Rg3 prevents endothelial cell apoptosis via the Akt-dependent inhibition of the mitochondrial apoptotic signaling pathway [4]. Ginseng also protects endothelial cells from injury due to oxidative stress [5]. Endothelial dysfunction is regarded as not

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only the earliest manifestation of atherosclerosis [6] but also as a prognostic factor for adverse cardiovascular events and poor long-term outcomes [7]. Thus, ginseng may have beneficial effects on the prevention and treatment of atherosclerosis, although the clinical effects of ginseng on atherosclerosis are unknown.

Oxidative stress plays an important role in the pathogenesis of atherosclerosis. Rho-associated kinase (ROCK), the immediate downstream target of RhoA, is an important regulator of cellular apoptosis, cell growth, smooth muscle cell contraction, and cell migration via the control of the assembly of the actin cytoskeleton [8]. Importantly, ROCK plays a significant role in the production of reactive oxygen species (ROS) and in the regulation of endothelial nitric oxide synthase (eNOS), thereby mediating oxidative stress signaling [8,9].

Arterial stiffening increases the pulsatile component, thus exerting a detrimental load on the heart and limiting coronary perfusion. Moreover, arterial stiffness, which is measured clinically by the pulse wave velocity (PWV), is an independent predictor of cardiovascular events [10]. ROCK activity is significantly correlated with vascular stiffness [9] and endothelial function [11], suggesting that these indices are significantly affected by ROCK-mediated oxidative stress.

Peripheral blood monocytes can penetrate the vascular wall to become tissue macrophages, which play a significant role in inflammation and oxidative stress during atherogenesis [12]. In this regard, arterial pathogenesis may be identified indirectly by analyzing peripheral blood monocytes [11]. The aim of this study was to determine whether Korean red ginseng (KRG) has an effect on arterial stiffness and cardiovascular risk factors such as blood pressure (BP) and lipid profiles in patients with coronary artery disease (CAD). We also measured ROCK activity in peripheral blood mononuclear cells (PBMCs) to indirectly assess the effect of KRG on vascular oxidative stress.

MATERIALS AND METHODS

Subjects

This study was performed as a prospective, randomized, double-blind, placebo-controlled crossover trial. We analyzed 20 male subjects (age, 62.4±3.1 years) with stable angina and ≥50% stenosis in at least one coronary artery as revealed by coronary angiography. The exclusion criteria for the study included acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass surgery within the previous 3 months, severe heart failure (left ventricular ejection fraction, <30%), a liver transaminase level >2 times the upper limit of normal, creatinine >2.0 mg/dL, malignancy, inflammatory disease, and other severe medical diseases. After an initial screening visit, the subjects were randomized to receive KRG (900 mg orally three times daily) or a placebo for 10 weeks. After a subsequent 6-week washout period, the subjects received the alternate treatment regimen for another 10 weeks (Fig. 1). The ginsenoside components of KRG include 17 protopanaxadiol ginsenosides, 13 protopanaxatriol (PPT) ginsenosides, and one oleanane ginsenoside [1]. The subjects were instructed to adopt therapeutic lifestyle changes based on National Cholesterol Education Program Adult Treatment Panel III recommendations [13]. The subjects provided informed consent before enrollment, and the study protocol was approved by the Ethical Committee.

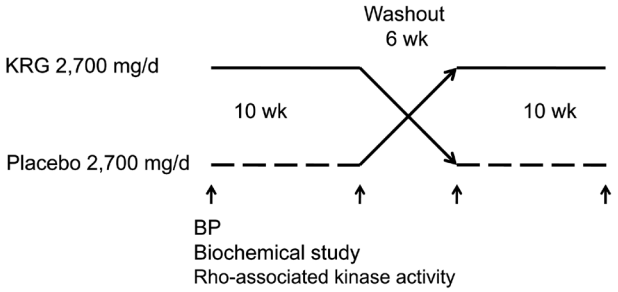

Fig. 1. Schematic of the experimental design. Patients with coronary artery disease received Korean red ginseng (KRG) at 2.7 g/day or a placebo alternatively, for a 10-week period each. Biochemical studies of peripheral blood and measurements of blood pressure (BP) were performed at baseline and at the endpoint for each treatment.

Measurement of serum lipoproteins

The fasting serum levels of lipids, including triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol, were measured by enzymatic colorimetric assay (total cholesterol and triglycerides) and selective inhibition enzymatic assay (HDL and LDL cholesterol), using a Hitachi 7600 Analyzer (Hitachi, Tokyo, Japan).

Measurement of arterial stiffness

Heart femoral (hf) PWV and brachial ankle (ba) PWV were measured using a VP2000 vascular device composed of a TU-100 tonometry sensor and a BP-203 RPEII automatic pulse wave analysis device (Colin Corp., Komaki, Japan). PWV was calculated by dividing the distance that the pulse wave traveled by the elapsed time. The measurements were made at 22°C in a silent room after a 12 hour fast. Conditions that could have influenced

endothelial function, such as caffeine, alcohol, a high-fat diet, vitamin C, smoking, and exercise, were avoided for 12 hours before the measurement. Drugs that could have affected endothelial function, including angiotensin converting enzyme inhibitors, angiotensin II type I receptor blockers, statins, and NO donors, were withheld for at least four times the half-life of the drug. A fixed dose of amlodipine (5 mg) was used to control the BP in patients during this period.

Measurement of ROCK activity

ROCK activity in PBMCs was measured as the amount of phospho-Thr^{853} in the myosin-binding subunit (MBS) of myosin light chain phosphatase [11]. Blood was collected at room temperature into heparinized tubes, an equal volume of phosphate-buffered saline was added, and the samples were mixed with Ficoll-Paque^{TM} solution (GE Healthcare, Waukesha, WI, USA). After centrifugation at 400 g for 30 minutes at room temperature, the plasma layer was removed by pipetting, and the PBMCs were isolated after washing, as recommended by the manufacturer's guidelines. The cells were fixed in 10% trichloroacetic acid (in acetone) and 10 mmol/L dichlorodiphenyltrichloroethane, collected by centrifugation, and stored at -70°C until analyzed. For Western blot analysis, the cells were dissolved in 10 μL of 1 mol/L Tris base and then mixed with 100 μL of extraction buffer (8 mol/L urea, 2% SDS, 5% sucrose, and 5% 2-mercaptoethanol). Equal amounts of cell extracts were separated by 7% SDS-PAGE and transferred to nitrocellulose membranes. The membranes were incubated with rabbit anti-phospho-Thr^{853}-MBS or rabbit anti-MBS polyclonal antibodies (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA) at 4°C for 12 hours, followed by incubation with secondary antibody at room temperature for 2 hours. Immunoreactive bands were visualized by enhanced chemiluminescence (ECL detection kit; Amersham Pharmacia Biotech, Piscataway, NJ, USA). ROCK activity is expressed as the ratio of phospho-Thr^{853}-MBS to MBS in each sample [11].

Statistical analysis

All data are expressed as means±SEM. Statistical analyses were performed using SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA). The Wilcoxon signed ranks test was used to compare continuous variables between the baseline and endpoint and to compare endpoint values of continuous variables between the two treatment arms in the same subjects. Values of $p<0.05$ were considered to indicate statistical significance.

RESULTS

Effect of KRG on systolic BP

Twenty of the 21 enrolled subjects completed the study; one patient was excluded for surgery to treat an abdominal aortic aneurysm. Table 1 lists the baseline clinical characteristics of the patients. Four patients had type II diabetes, and 14 patients had hypertension. Ten patients had single-vessel disease, and the remainder had multi-vessel disease. The drugs used by the patients for the treatment of CAD were as follows: angiotensin converting enzyme inhibitor ($n=10$), AT_1 receptor inhibitor ($n=8$), NO donor ($n=7$), calcium channel blocker ($n=12$), β blocker ($n=1$), aspirin ($n=11$), clopidogrel ($n=9$), and statins ($n=11$). The administration of these drugs had begun at least 1 month prior to the study enrollment and continued throughout the experimental period without a change in dose. The 10-week treatment with KRG significantly decreased the systolic BP (141±7 vs. 129±7 mmHg, $p<0.05$), but not diastolic BP (84±4 vs. 81±5 mmHg, $p>0.05$) (Fig. 2), in the patients. The placebo had no significant effect on either systolic or diastolic BP.

Effect of KRG on vascular stiffness

Both ba-PWV and hf-PWV were assessed in non-smoking subjects before and after treatment with KRG ($n=8$) and with placebo ($n=9$), as a case-control study. KRG significantly decreased both hf-PWV (1136±145 vs. 1006±107 cm/s, $p<0.05$) (Fig. 3A) and ba-PWV

Table 1. Baseline clinical characteristics of subjects with coronary artery disease

Clinical indices	Baseline value
Age (yr)	62.4±3.1
Male/female	12/8
BMI (kg/M^2)	25.5±0.8
Waist/hip	0.9±0
LVEF (%)	58.4±2.5
Hypertension	14
Smoker/ex-smoker	3/8
Previous MI	6
Diabetes	4
CAD extent (1/2/3 VD)	10/8/2
T Chol (mg/dL)	178.3±10.4
Triglyceride (mg/dL)	155.8±27.7
HDL Chol (mg/dL)	49.6±2.6

BMI, body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; CAD, coronary artery disease; VD, vessel disease; T Chol, total cholesterol; HDL Chol, high density lipoprotein cholesterol.

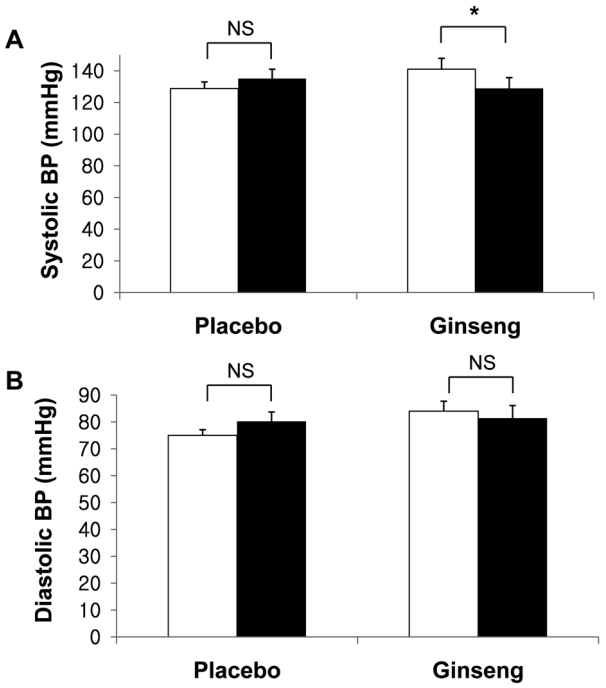

Fig. 2. Changes in systolic (A) and diastolic (B) blood pressure (BP) following a 10-week treatment with Korean red ginseng or placebo. Data are expressed as means±SEM. NS, not significant; □ baseline; ■ endpoint; $^{*}p<0.05$.

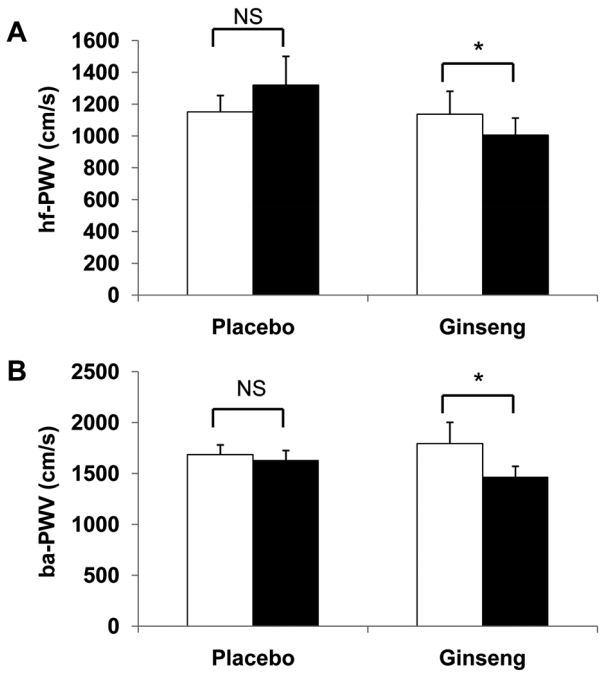

Fig. 3. Changes in heart femoral (hf)- pulse wave velocity (PWV) (A) and brachial ankle (ba)-PWV (B) in patients with coronary artery disease following a 10-week treatment with Korean red ginseng or placebo. Data are expressed as means±SEM. NS, not significant; □ baseline; ■ endpoint; $^{*}p<0.05$.

(1794±208 vs. 1468±102 cm/s, $p<0.05$) (Fig. 3B). In contrast, the placebo did not significantly change either PWV (Fig. 3).

Effect of KRG on plasma lipid profiles

KRG showed a trend toward beneficial effects on the lipid profiles, but the effects on serum total cholesterol (186±8 mg/dL vs. 168±6 mg/dL), LDL cholesterol (119±10 mg/dL vs. 101±7 mg/dL), and HDL cholesterol (46±2 mg/dL vs. 48±2 mg/dL) were not significant (baseline vs. endpoint, all $p>0.05$). There was no change in the triglyceride level with KRG treatment (161±16 mg/dL vs. 161±20 mg/dL, $p>0.05$). The placebo did not significantly change the serum level of triglycerides, HDL cholesterol, or LDL cholesterol (data not shown), but the plasma total cholesterol level was modestly increased with placebo treatment (173±6 mg/dL vs. 194±10 mg/dL, $p<0.05$).

Effect of KRG on ROCK activity

ROCK activity was measured in PBMCs by Western blot analysis before and after treatment with KRG or placebo in four subjects. KRG treatment markedly decreased ROCK activity to 22% of the baseline activity (Fig. 4). However, this decrease did not reach statistical significance ($p=0.068$) owing to the small sample size. Placebo treatment did not significantly change the ROCK activity (Fig. 4).

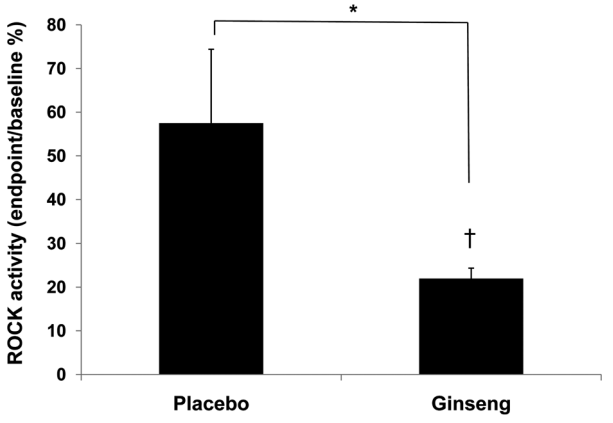

Fig. 4. Changes in Rho-associated kinase (ROCK) activity in peripheral blood mononuclear cells (PBMCs) following a 10-week treatment with Korean red ginseng or placebo in four patients with coronary artery disease. ROCK activity of PBMCs was assessed by Western blot analysis of phospho-Thr^{853} in the myosin-binding subunit (MBS) of myosin light chain phosphatase. Results are expressed as the percentage ratio (endpoint/baseline) of phospho-Thr^{853}-MBS/total MBS. Data are expressed as means±SEM. $^{*}p=0.068$; $^{\dagger}p=0.068$ for endpoint vs. baseline.

DISCUSSION

In the present study, KRG significantly decreased systolic BP and vascular stiffness, as indicated by a drop in ba-PWV and hf-PWV, in patients with stable CAD. A KRG-induced decrease in systolic BP has been reported

in previous studies [14,15]. Han *et al.* [14] reported that treatment with KRG at 4.5 g/day for 8 weeks decreased the 24-hour mean systolic BP, but not diastolic BP, in 24 patients with essential hypertension; however, it did not change the BP in patients with white-coat hypertension. In a separate study [15], one-time treatment with KRG (50 mg/kg) decreased the mean BP and heart rate in 12 healthy, non-smoking male volunteers [15]. In contrast, other studies have shown no effect of ginseng on BP [16-18], as neither long-term (12 weeks) [16] nor one-time treatment [17] with North American ginseng significantly changed the BP in patients with hypertension. These discrepant reports may be attributable to the heterogeneity of ginsenoside preparations or differences among the study subjects. Korean *P. ginseng* C. A. Meyer contains a variety of ingredients, including carbohydrates, polyacetylene, alkaloids, and lipophilic compounds; however, the key active ingredient in ginseng is a carbohydrate called a saponin or ginsenoside [1,19]. The pharmacological effects of ginseng are substantially influenced by the intestinal bacteria that transform the herbal components into bioactive compounds, and variations in the metabolic activities of these microbes have been reported [20].

In the present study, KRG treatment for 10 weeks significantly reduced both ba-PWV, which is used as an index of vascular stiffness in the central aorta and peripheral muscular arteries, and hf-PWV, which reflects vascular stiffness in the central aorta. An increase in ba-PWV (>14 m/s) is an independent variable for risk stratification based on the Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease [21]. Furthermore, vascular stiffness in the central aorta has emerged as an important predictor of cardiovascular events [22] and mortality [23]. Therefore, our data suggest that KRG may reduce the risk for major cardiovascular events by reducing vascular stiffness in the central aorta and peripheral muscular arteries in patients with stable CAD. In a separate study, one-time treatment with KRG or a ginsenoside extract, but not a polysaccharide extract, decreased the augmentation index, but not BP, in healthy subjects [18]. The augmentation index is a commonly used measure of arterial stiffness and an independent marker of increased total and cardiovascular mortality [22].

PWV is defined by the Moens-Korteweg equation: $PWV^2=E\cdot h/2r\cdot\rho$, where E is the Young's modulus; h, the wall thickness; r, the internal radius at the end of diastole; and ρ, the blood density [22]. PWV is affected by age, BP, heart rate, vascular smooth muscle tone, vascular hypertrophy, vascular remodeling, and components of the vascular wall such as collagen and elastin [22]. Importantly, atherosclerosis decreases vascular elasticity and increases vascular stiffness, thereby increasing PWV [24]. PWV is also affected by endothelial function and is regulated by endothelium-derived NO and hyperpolarizing factor [25,26]. KRG has probable anti-oxidative properties; it is known to promote NO production and to protect endothelial cells from oxidative stress [2,15,27,28]. The ginsenoside PPT protects endothelial cells from hydrogen peroxide-induced cell injury and death by ameliorating oxidative stress [27]. In addition, ginsenoside Rg1 functions as an agonist at the glucocorticoid receptor, leading to the production of NO by eNOS via the non-transcriptional PI3K/Akt pathway [28]. KRG also inhibits hydrogen peroxide-induced cell death by decreasing the expression of the pro-apoptotic protein caspase-3 and the pro-inflammatory protein cyclooxygenase 2, and increasing the expression of the anti-apoptotic protein Bcl-2 [2]. Consistent with this, KRG increased the NO concentration in the exhaled breath of healthy human subjects [15].

Oxidative stress is important in the development of atherosclerosis and endothelial dysfunction. The activation of ROCK can aggravate oxidative stress through the inhibition of NO production and enhanced ROS production [8,29]. The activation of G protein-coupled receptors by angiotensin II can stimulate ROS production via the AT_1 receptor/Rho/ROCKs/Rac1/NAD(P)H oxidase pathway [29]. In addition, Rho/ROCK inversely regulates eNOS expression by alteration of eNOS mRNA stability, thus inhibiting NO production [8]. The inhibition of RhoA or ROCK leads to PI3K/Akt activation and eNOS phosphorylation, suggesting a role for ROCK in eNOS activation [30]. ROCK activity is an independent predictor of carotid femoral-PWV [9]. It also plays a significant role in vascular contraction via Ca^{2+} sensitization by phosphorylating the regulatory subunit of smooth muscle myosin phosphatase, thereby inhibiting myosin phosphatase activity and increasing myosin regulatory light chain phosphorylation [31]. Two ROCK isoforms, ROCK1 and ROCK2, have been identified. Although isoform-specific roles for ROCK are unknown, ROCK1 in bone marrow-derived cells contributes significantly to neointima formation following vascular injury, by affecting vascular smooth muscle cell proliferation, proinflammatory adhesion molecule production, and leukocyte infiltration [32]. In this regard, the KRG-induced decrease in ROCK activity in the present study may ameliorate oxidative stress, thereby

reducing vascular stiffness, in patients with stable CAD.

We did not observe any significant difference in the serum level of triglycerides or total, HDL, or LDL cholesterol in this study. Consistent with this, ginseng did not significantly change the plasma total cholesterol or triglyceride level in patients with diabetes [33] or CAD [34] in earlier studies. However, Kim and Park [35] reported that oral administration of *P. ginseng* (6 g/day) for 8 weeks reduced the total and LDL cholesterol levels and increased the HDL cholesterol level in healthy young subjects.

In conclusion, KRG reduced the systolic BP and the vascular stiffness in the central aorta and peripheral muscular arteries, probably via the inhibition of ROCK activity, in patients with CAD. Given the importance of PWV as a predictor of future cardiovascular events, our data suggest a therapeutic effect of KRG on CAD. Further study is needed to understand the pharmacological effects of KRG on the progression of atherosclerotic plaque formation and the prevention of acute coronary syndrome in patients with CAD.

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