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# Effect of Korean red ginseng on blood pressure and nitric oxide production

JEON Byeong Hwa[1], KIM Cuk Seong, KIM Hoe-Suk, PARK Jin-Bong, NAM Ki Yeul[2], CHANG Seok Jong[3]
(*Department of Physiology, College of Medicine, Chungnam National University, Taejon, Korea*; [2]*Korea Ginseng & Tabacco Research Institute, Taejon, Korea*; [3]*Department of Physiology, College of Medicine, Seonam University, Namwon, Korea*)

**KEY WORDS** *Korean red ginseng; saponins;* saponin-free fraction; nitric oxide; hypertension; antihypertensive

## ABSTRACT

**AIM**: To investigate the effect of crude saponin and non-saponin fraction of Korean red ginseng (KRG) on the blood pressure and nitric oxide (NO) production in the conscious rats and cultured endothelial cell line, ECV 304 cells. **METHODS**: Systolic blood pressure and heart rate were monitored in the conscious rats. Nitric oxide levels and the expression of nitric oxide synthase were measured by a spectrophotometric assay using Griess reagents and Western blotting, respectively. Nitric-oxide synthase activity was measured based on the conversion rate of [$^3$H]arginine to [$^3$H]citrulline. **RESULTS**: Systolic blood pressure was decreased by crude saponin (100 mg/kg, iv) of KRG in the conscious control and one-kidney, one-clip Goldblatt hypertensive (1K, 1C-GBH) rats. The hypotensive effect induced by crude saponin of KRG reached maximum at 2 – 4 min and slowly recovered after 20 min to the initial level in both groups. Crude saponin of KRG induced tachycardia in the conscious rats but induced bradycardia in the anesthetized rats. In contrast to crude saponin of KRG, hypotensive effect induced by saponin-free fraction was minimal. Nitric oxide concentrations were increased by the treatment of crude saponin in conscious rats as well as in the cultured ECV 304 cells. The protein expression level of endothelial constitutive nitric-oxide synthase (eNOS) in the aorta of rats was not increased by crude saponin (100 mg/kg, ip for 3 d). However, nitric-oxide synthase activity was increased by crude saponin of KRG in the aortic homogenate of rats. **CONCLUSION**: The hypotensive effect of red ginseng is mainly due to saponin fraction of KRG in the conscious rats, and this effect may be due to an increase in the nitric-oxide production by KRG.

## INTRODUCTION

Panax ginseng has been used for more than 2000 year as a general tonic in traditional oriental medicine. The pharmacological and physiological effects of red ginseng (Ginseng Radix Rubra) are being gradually disclosed. Ginseng root consists of two major ingredients; crude saponin and saponin-free fraction. Saponin shows a variety of biomedical efficacies such as anticancer, antihypertension, anti-diabetes, anti-nociception, and improving the weak body conditions as tonics[1]. Although ginseng is used for multiple purposes, it has not been proven effective for its physiological characteristics such as cardiovascular effects.

It has been well known for a long time that Korean ginseng have an anti-hypertensive effect[2-4]. Panax ginseng has a vasorelaxant effect in several vessels[5,6]. Also, ginsenosides reduced the mean blood pressure in rats[7] and the chronic treatment with Korea red ginseng reduced the blood pressure in the hypertensive patients[8]. However, several reports showed that the heart rate and mean arterial pressure were significantly reduced by the Korean ginseng when used in anesthetized animals. Because of the failure to take into account other potential regulators, such as the reflex modulation of the pressure response, The studies have been limited to the evaluation of the hemodynamic responses in anesthetized animal models. Therefore, it is important to evaluate the effect of ginseng on hemodynamics in conscious animals with intact autonomic reflex.

[1] Correspondence to Byeong Hwa Jeon, MD, PhD, *Department of Physiology, College of Medicine, Chungnam National University*, 6 *Munhwa-dong, Tung-gu, Taejon 301 – 131, Korea*. Phn 82-42-580-8214. Fax 82-42-585-8440. E-mail bhjeon@cnu.ac.kr
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Endothelium is the major source of the endothelium-derived relaxing factor, nitric oxide (NO), which plays an important role in the control of vascular tone[9,10]. Ginsenosides induced endothelium-dependent relaxation and increased the tissue content of cGMP in isolated rat thoracic aorta[7]. Also, ginsenosides enhanced the release of NO from endothelial cells[8,11]. Recently, Ginsenoside Rg3 mediates endothelium-dependent relaxation in rat aorta[12]. However, the effect of Korean red ginseng on the nitric oxide production *in vivo* remains unknown.

In the present study, to evaluate the hemodynamic changes and NO production by red ginseng, we have studied the effect of crude saponin and saponin-free fraction on the blood pressure and NO production in the conscious rats and cultured endothelial cells.

## MATERIALS AND METHODS

**Materials** Crude saponin (CS) and saponin-free fraction (SFF) purified from Korean red ginseng (KRG, Ginseng Radix Rubra) were kindly provided from the Korea Ginseng and Tobacco Research Institute (Taejon, Korea). KRG was produced and processed by the Korea Ginseng and Tobacco Research Institute from the roots of 6-year-old fresh KRG using extraction and partitioning procedure for crude saponin[13]. The yields for ginseng saponin from KRG was 4.37 %, Main composition of crude saponin was ginsenosides—Rb1: 12.59 %, Rb2: 6.18 %, Rc: 6.86 %, Rd: 3.43 %, Re: 6.64 %, Rf: 2.06 %, Rg1: 15.79 %, and Rg3: 1.37 %. Amount of saponin fraction in crude saponin was 56.29 %.

**Induction of one-kidney, one-clip Goldblatt hypertesive (1K, 1C-GBH) rats** 1K, 1C-GBH rats were made by the partial ligation of left renal artery combined with contralateral nephrectomy as previously described[14].

**Blood pressure monitoring in conscious rats** Male Sprague-Dawley rats, weighing between 250 – 350 g, were used for blood pressure monitoring in conscious rats. Rats were anesthetized with ketamine (100 mg/kg) for implantation of intravascular catheters into the right jugular vein and right carotid artery. The catheters were constructed of polyurethane tubing and filled with heparinized saline ($1 \times 10^6$ U/L). The catheters were secured in position, tunneled to the nape of the neck, exteriorized, and sealed with a stainless steel pin. All rats were housed individually in plastic cages after surgery and given food and water *ad lib*. After an overnight recovery from surgery, the rats were weighed and their catheters connected to tygon extension lines filled with heparinized saline ($1 \times 10^6$ U/L). Arterial blood pressure was monitored in conscious rats by connecting arterial line and heart rate was taken from arterial blood pressure pulses. The animals were placed in circular opaque testing chambers (diameter = 25 cm) containing wood chip bedding and rested for at least 3 to 4 h prior to recording pulsatile blood pressure and heart rate.

**Cell Culture** Transformed human umblical cord endothelial cell, ECV304 cell line, was purchased from ATCC. ECV304 cells were grown in M199 media supplemented with 20 % heat-inactivated fetal calf serum at 37 ℃ in 5 % $CO_2$/95 % air. Medium was changed every 48 to 72 h before the experiment was begun.

**Nitric oxide measurements** Plasma (150 μL) or cell-free supernatant of culture media were ultra-filtered by centrifugation at 14 000 × *g* for 30 min, using 10 kd molecular weight filters (Ultrafree-MC, Millipore). NO assay was performed in a standard flat-bottomed 96-well polystyrene microtitre plate containing 50 μL/well of standard or sample. The assay was blanked against phosphate-buffered saline. Fifty microlitres of nitrate reductase and β-NADPH were added to each well giving final concentration of 300 U/L and 25 μmol/L, respectively. The plate was incubated at room temperature for 3 h. Excess β-NADPH was consumed by addition of 10 μL of phosphate buffer solution containing *L*-glutamic dehydrogenase, α-ketoglutaric acid, and $NH_4Cl$ (final concentrations 500 U/L, 4 mmol/L, 100 mmol/L) followed by a 5-min incubation at 37 ℃. The nitrite concentration was then measured by the addition of 50 μL each of Griess reagents 1 and 2, and the absorbance read at 540 nm using a plate reader after a 10-min incubation at room temperature.

**Nitric-oxide synthase activity** Isolated aorta was homogenized and solubilized in a buffer containing 50 mmol/L Tris, 0.1 % mercaptoethanol, 0.1 mmol/L edetic acid, 0.1 mmol/L egtazic acid, 1 mg/L leupeptin, 1 mmol/L PMSF, 1 μmol/L pepstatin A, adjust to pH 7.4. The homogenates were centrifuged at 14 000 × *g* at 4 ℃ for 30 min. NOS activity was determined in the supernatant by the conversion of *L*-[$^3$H]arginine to *L*-[$^3$H]citrulline. Aortic extracts were incubated in a buffer containing 50 mmol/L HEPES, 1 mmol/L $MgCl_2$, 1 mmol/L $CaCl_2$, 1 mmol/L DTT, 2 mmol/L NADPH, 3 μmol/L $THB_4$, 3 μmol/L FAD, 3 μmol/L

FMN, 10 mg/L calmodulin, 74 MBq/L [$^3$H]arginine. Incubations were performed for 20 min at 37 ℃ in the presence or in the absence of 0.1 mmol/L of *L*-nitroarginine methylester (*L*-NAME) to determine the non-specific conversion of *L*-[$^3$H]arginine. *L*-[$^3$H]arginine was separated from *L*-[$^3$H]citrulline by a Dowex AG 50WX8 (sodium form) column.

**Western blot analysis** Briefly, thoracic aortas were obtained from the control and the KRG-treated rats and homogenized on ice with a polytron homogenizer in the buffer composed of 50 mmol/L Tris-HCl (pH 7.4), 2 % SDS, 1 mmol/L dithiothreitol, 1 mg/L leupeptin, and 1 mmol/L phenylmethylsulphonyl fluoride. The homogenized tissues were centrifuged at 10 000 × *g* for 30 min and the supernatant was stored at −70 ℃ until further analysis. Aliquots of tissue homogenates were used for protein assay (Protein assay reagent, Bio-Rad, USA). Western blot analysis was carried out to determine the endothelial NOS (eNOS) protein mass by use of an anti-eNOS monoclonal antibody (Transduction Laboratories) as previously described[15].

**Statistical analysis** Data were expressed as $\bar{x} \pm s_x$ and analyzed by unpaired *t*-test. $P < 0.05$ was considered significant.

## RESULTS

**Effect of crude saponin and saponin-free fraction of KRG on the blood pressure in conscious rats** After intravenous injection of crude saponin (100 mg/kg), systolic blood pressure (SAP) gradually decreased and reached a minimum level after 2−4 min in conscious control rats [(112.1 ± 7.2) mmHg for control *vs* (80.3 ± 7.3) mmHg for crude saponin, $P < 0.01$] and 1K, 1C-GBH rats [(189.0 ± 9.1) mmHg for control *vs* (160.0 ± 6.5) mmHg for crude saponin, $P < 0.01$]. And then, blood pressure slowly recovered to the initial level for 20 min. However, saponin-free fraction (100 mg/kg, iv) showed little effect on the blood pressure in the conscious control rats [(123.0 ± 1.5) mmHg for control *vs* (119.3 ± 5.7) mmHg for saponin-free fraction] and 1K, 1C-GBH rats [(178.3 ± 4.4) mmHg for control *vs* (167.0 ± 7.0) mmHg for saponin-free fraction at 2 min]. (Fig 1)

**Effect of crude saponin and saponin-free fraction of KRG on the heart rate in conscious rats** After crude saponin (100 mg/kg) was iv injected, heart rate increased significantly and reached maximum at 2−4 min in control rats [(322.0 ± 25.6) bpm for control *vs* (382.0 ± 30.9) bpm for crude saponin, $P < 0.01$] and 1K, 1C-GBH rats [(376.0 ± 13.6) bpm for control *vs* (430.0 ± 28.5) bpm for crude saponin, $P < 0.01$]. And heart rate slowly recovered to initial heart rate after 20 min. However, saponin-free fraction had no effect on the heart rate in either groups. (Fig 2)

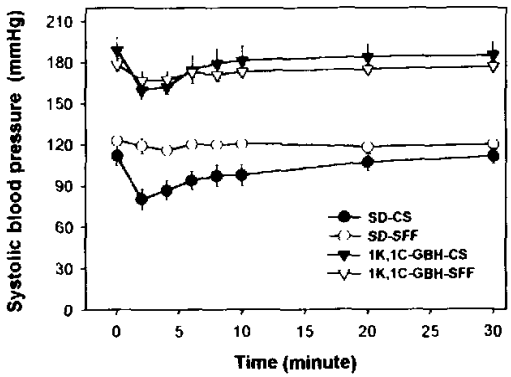


**Fig 1. Time-dependent changes in systolic blood pressure after intravenous injection of crude saponin (CS, 100 mg/kg) and saponin-free fraction (SFF, 100 mg/kg) of Korean red genseng (KRG) in the conscious normotensive Sprague Dawley (SD) rats and one-kidney one clip Goldblatt hypertensive (1K, 1C-GBH) rats. $n = 6$ different rats for each group. $\bar{x} \pm s_x$.**

**Effect of anesthetic on the change of heart rate induced by crude saponin of KRG** After

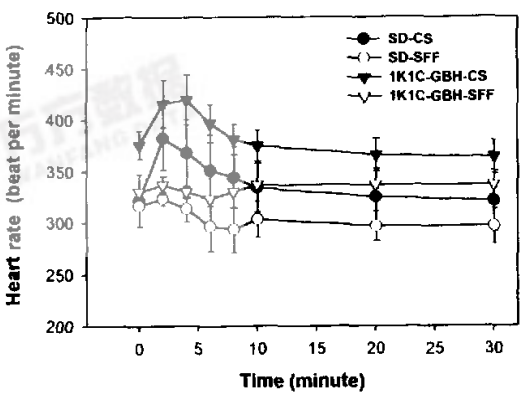


**Fig 2. Time-dependent changes in heart rate after intravenous injectionof crude saponin (CS, 100 mg/kg) and saponin-free fraction (SFF, 100 mg/kg) of KRG in the conscious normotensive SD rats and one-kidney one clip Goldblatt hypertensive (1K, 1C-GBH) rats. $n = 6$ different rats for each groups. $\bar{x} \pm s_x$.**

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crude saponin (100 mg/kg) was iv injected to anesthetized rats, heart rate decreased and reached minimum at 1 min, and slowly recovered to initial level after 30 min. Therefore, even though the crude saponin of KRG induced reflex tachycardia in the conscious rats, heart rate was significantly reduced by crude saponin in the anesthetized rats (Fig 3).

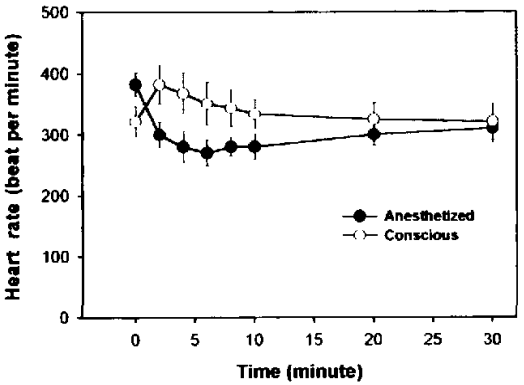


**Fig 3. Effect of anesthetic on the change of heart rate after intravenous injection of crude saponin (CS, 100 mg/kg) in the urethane (1 g/kg)-induced anesthetized rats and conscious rats. $n$ = 6 different rats for each group. $\bar{x} \pm s_{\bar{x}}$.**

**Effect of KRG on the NO production** Treatment with crude saponin (100 mg/kg) of KRG for 72 h resulted in slight elevation of plasma NOx production in control rats [(3.38 ± 0.39) μmol/L for control *vs* (4.59 ± 0.68) μmol/L for crude saponin, $P = 0.23$] and 1K, 1C-GBH rats [(3.45 ± 0.27) μmol/L for control *vs* (4.54 ± 0.51) μmol/L for crude saponin, $P < 0.05$]. Similarly, NO production was significantly elevated by crude saponin of KRG (0.1 g/L) in ECV304 cells [(2.92 ± 0.24) μmol/L for control *vs* (6.27 ± 0.86) μmol/L for crude saponin, $P < 0.01$], also, it was significantly increased by the pretreatment of saponin-free fraction of KRG [(2.93 ± 0.24) μmol/L for control *vs* (3.80 ± 0.13) μmol/L for saponin-free fraction, $P < 0.05$] (Tab 1).

**Effects of crude saponin of KRG on NOS activity and eNOS proteins** NOS activities were significantly greater in the crude saponin of KRG-treated aortic homogenates than those in the control rats ($P < 0.01$) and 1K – 1C GBH rats ($P < 0.05$) (Tab 2).

The degree of eNOS protein expression in aortas of 1K, 1C-GBH rats was much greater than that in the control rats. However, eNOS protein expression in the aorta of rats treated with crude saponin of KRG was not increased compared with control levels (Fig 4).

**Tab 1. Effects of crude saponin and saponin-free fraction of Korean red ginseng on the nitric oxide production in the rats and cultured endothelial cells. $\bar{x} \pm s_{\bar{x}}$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* basal level.**

| | | NOx (μmol/L) |
|---|---|---|
| SD rats | Basal ($n = 6$) | 3.38 ± 0.39 |
| | Crude saponin ($n = 6$) | 4.59 ± 0.68[a] |
| 1K,1C-GBH rats | Basal ($n = 6$) | 3.45 ± 0.27 |
| | Crude saponin ($n = 6$) | 4.54 ± 0.51[b] |
| Endothelial cells | Basal ($n = 5$) | 2.93 ± 0.24 |
| | Crude saponin ($n = 5$) | 6.27 ± 0.86[c] |
| | Saponin-free fraction ($n = 5$) | 3.80 ± 0.13[b] |

Nitrite and nitrate (NOx) production was measured as indirect measurement of NO production with modified Griess reaction. Crude saponin (100 mg/kg) was ip injected for 72 h in the SD rats and 1K, 1C-GBH rats. Cultured endothelial cells were treated with crude saponin (0.1 g/L) and saponin-free fraction (0.1 g/L) for 72 h

**Tab 2. Effects of crude saponin of Korea red ginseng on the nitric oxide synthase activity in the homogenate of rat aortas. $\bar{x} \pm s_{\bar{x}}$. $P$ values *vs* basal level.**

| | $n$ | NOS activity (fmol/mg·min) | Significance |
|---|---|---|---|
| SD rats | | | |
| Basal | 3 | 25.9 ± 4.4 | |
| Crude Saponin | 3 | 56.1 ± 5.5 | $P < 0.01$ |
| 1K,1C-GBH rats | | | |
| Basal | 3 | 35.4 ± 3.1 | |
| Crude Saponin | 3 | 48.5 ± 3.3 | $P < 0.05$ |

Crude saponin (100 mg/kg, ip) was treated for 72 h in SD rats and 1K,1C-GBH rats.

## DISCUSSION

We demonstrated in the present study that crude saponin of KRG significantly decreased blood pressure, but saponin-free fraction very slightly decreased blood pressure in the control rats and 1K,1C-GBH rats. Crude saponin of KRG used in this experiment contained 56.3 % of ginsenosides, which is a mixture of saponins of KRG. Therefore, hypotensive effect of KRG was mainly due to the saponin fraction of KRG. Our results are supported by other *in vitro* reports. Purified ginsenoside Rg1 and Re caused endothelium-dependent

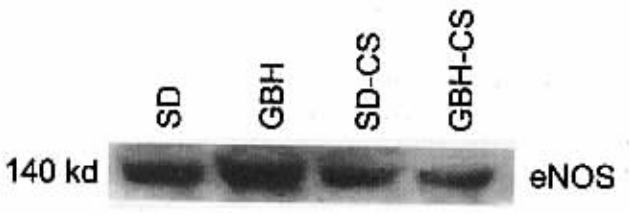


**Fig 4. Western blot analysis of endothelial nitric oxide synthase in the aortic homogenate of control rats (SD) and one-kidney, one-clip Goldblatt hypertensive (GBH) rats. Crude saponin (CS, 100 mg/kg) was ip injected for 3 d in the both groups. Protein extracts (100 μg) obtained from the rat aortas were separated by 7.5 % SDS-PAGE and electrophoretically transferred to nitrocellulose membrane. The membrane blots were incubated with a mouse monoclonal antibody diluted 1:1500 (Transduction Laboratory, USA). The membranes were then incubated with a 1:1000 dilution of the rabbit anti-mouse immunoglobulin G conjugated to horseradish peroxidase (Amersham, USA). The signal strengths were analyzed using an ECL detection system (Amersham, USA) after autoradiography.**

relaxation with the formation of cyclic GMP which reduces vascular tone[11]. Rg3 was also reported as one of the most potent vasodilator[12]. However, the hypotensive effect of KRG was transient and anti-hypertensive effect of KRG was not specific in the hypertensive rats (Fig 1). The transient effect of KRG on the blood pressure needs further evaluations.

Anesthesia is known to influence cardiovascular function. Therefore, the evaluation of changes of blood pressure and heart rate in the anesthetized rats was limited due to the blocking of the autonomic nervous system. In the present study, crude saponin of KRG induced tachycardia in conscious rats. On the other hand, heart rate was significantly decreased by the crude saponin in anesthetized rats. It is suggested that the tachycardia induced by crude saponin in conscious rats may be due to compensation against hypotension that resulted from the lowering of peripheral resistance. The bradycardia induced by crude saponin of KRG may be due to direct inhibition of heart in the anesthetized state, in which nervous reflex control and synaptic transmission in autonomic nervous system is reduced. Therefore, crude saponin of KRG has dual properties, that is, lowering effect of peripheral resistance and negative chronotropic effect on the heart itself.

Nitric oxide (NO) is a novel physiological messenger which is a small molecule that diffuses freely through the cell membrane[16]. In the vascular system, NO is produced in the endothelium, from which it diffuses both into the lumen and out into the wall of the vessel. In the lumen, it stimulates cGMP production, reducing platelet adhesion; in the wall the cGMP relaxes vascular smooth muscle. So, NO plays an important role in the control of vascular tone[9,10].

In the present study, crude saponin of KRG might stimulate NO production in the conscious rats as well as cultured endothelial cells. Also it stimulated NOS activities but did not affect the eNOS protein expression in the aorta of rats. These findings suggested that crude saponin of KRG did not affect the translational levels of NO synthase but affect the activity of NO synthase in the rat aorta. Ginsenoside Rg3 is a major mediator of the endothelium-dependent NO-mediated relaxation in response to ginsenosides in isolated rat aorta, possibly via activation of tetraethylammonium-sensitive $K^+$ channels[12]. Therefore, increased NOS activity by crude saponin of KRG may be due to membrane hyperpolarization via $K^+$ channel opening in endothelial cells. The anti-hypertensive effect of saponin fraction may be partly mediated by the enhanced NO release from the endothelial cells.

Endothelium-dependent responses were impaired in the hypertensive rats such as 1K, 1C-GBH rats[14]. In the present study, the crude saponin of KRG reduced blood pressure, even though the anti-hypertensive effect was short and transient, as well as stimulated the NO production in the 1K, 1C- GBH rats. So crude saponin of KRG has a beneficial effect on the control of hypertension. It was also known that dietary ginsenosides of KRG improved endothelium-dependent relaxation in the thoracic aorta of hypercholesterolemic rabbit[17]. However the toxicity and other systemic effects of KRG need further evaluation.

In summary, KRG has a transient anti-hypertensive effect, mainly due to its saponin fraction. Crude saponin of KRG stimulated NO production in *in vivo* and *in vitro* conditions. Enhanced NO production by KRG might be due to the increase of $Ca^{2+}$-dependent NOS activities in the rat aorta. We suggested that anti-hypertensive effect of KRG saponin fraction might be partly mediated by the enhanced NO release from endothelial cells.

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