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ORIGINAL RESEARCH

# Comparison of Endothelium-Dependent Vasorelaxation of Crude Ginsenosides from Mountain-Grown Ginseng and Red Ginseng

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**Abstract** Mountain-grown ginseng (*Panax ginseng* C. A. Meyer; Sansam in Korean) is believed to possess more potent biological activity than red ginseng. This study examined the endothelium-dependent vasorelaxant effects and possible mechanisms of crude ginsenosides from adventitious roots of Korean mountain-grown ginseng (GS-ARMG) and red ginseng (GS-RG) in isolated rat aorta pre-contracted with norepinephrine. GS-ARMG (0.03–3.0 mg/mL) produced transient acute relaxation in a concentration-dependent manner, with a maximum relaxation (mean± SEM) of 90±9% and a median effective concentration ($EC_{50}$) of 0.09±0.07 mg/mL. GS-ARMG displayed about 25-fold more potent activity than GS-RG (maximum relaxation 50±4%, $EC_{50}$ 2.34±1.30 mg/mL). Relaxations induced by both GS-ARMG (1.0 mg/mL) and GS-RG (1.0 mg/mL) were nearly abolished by endothelial ablation or pre-treatment with $N^G$-nitro-L-arginine, a nitric oxide synthase inhibitor, or by methylene blue, a soluble guanylate cyclase inhibitor. These inhibitory effects, however, revealed different sensitivity of GS-ARMG and GS-RG; the maximum relaxations attained were 30–38% and 13–17% that of untreated preparations, respectively, but indomethacin and cyclooxygenase inhibitors did not affect the response. None of the receptor antagonists, atropine, diphenhydramine, [D-$Pro^2$, D-$Trp^{7,9}$]-substance P, or propranolol, caused any significant inhibition to GS-ARMG-induced relaxation; however, atropine or propranolol caused a 10% reduction in the relaxation, suggesting possible involvement of a muscarinic receptor or a β-adrenoceptor in the GS-ARMG-induced relaxation. These results demonstrate that GS-ARMG produces endothelium-dependent relaxation of isolated rat aorta similar to that of GS-RG; increased nitric oxide production and increased vascular levels of cGMP in endothelial cells could contribute to the relaxation. However, GS-ARMG has more potent activity than GS-RG to relax isolated rat aorta though an active substance(s), which might be higher in mountain-grown ginseng due to the growing conditions on mountains or the processing during manufacture of GS-ARMG. These factors may contribute to understanding the biological beneficial effects of mountain-grown ginseng.

**Keywords** Vasorelaxation · Adventitious root of mountain-grown ginseng · Endothelium-dependent · Crude Ginsenosides

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## Introduction

Ginseng has been used in Asia for centuries to enhance stamina and immune function and has been suggested to have pharmacological activity in the cardiovascular, endocrine, immune, and central nervous systems (Attele et al. 1999). Its use in complementary and alternative medicine has expanded in Western countries, and it is one of the best-selling herbs in the USA (Yuan and Wu 2002). Mountain-grown ginseng (*Panax ginseng* C. A. Meyer; Sansam in Korean), which grows naturally in the mountains of Korea,

is believed to possess more potent biological activity than cultivated red ginseng. Mountain-grown ginseng is difficult to locate and excavate, and some plants have remained dormant underground for hundreds of years (Koo et al. 2007). The rarity of these mountain plants has led to several attempts to cultivate mountain-grown ginseng (In and Yang 2004; Han et al. 2003; Yoo et al. 2003), and mass-produced adventitious roots of mountain-grown ginseng (ARMG) are now available for use in complementary and alternative medicine and as a functional food in Korea.

Ginsenosides, the ginseng saponins, are the major pharmacologically active components of ginseng. To date, more than 30 different ginsenosides having different pharmacological effects have been isolated and identified from the root of *Panax ginseng* (Attele et al. 1999). Even within the species *Panax ginseng*, processing steps such as steaming, drying, and/or pressurizing to make a dietary supplement can affect pharmacological activity due to the different characteristics of the constituent ginsenosides (Yuan and Wu 2002). Cultivated conditions on mountains can also affect the constitution ginsenosides (Choi et al. 2007a, b). In this study, we hypothesized that the adventitious roots of mountain-grown ginseng have different biological activity than field-grown red ginseng. Ginseng extracts have cardioprotective effects that are due, at least in part, to endothelium-dependent relaxation induced by the ginsenosides. The relaxation induced by pure or mixed ginsenosides is mediated by increased release of nitric oxide (NO) from endothelial cells, which causes the accumulation of cGMP in smooth muscle (Achike and Kwan 2003; Chen 1996; Chen et al. 1997; Friedl et al. 2001; Han and Kim 1996; Jeon et al. 2000; Kang et al. 1995a, b; Kim et al. 1994; Peng et al. 1995; Scott et al. 2001). To test for differences in crude ginsenoides from the adventitious roots of mountain-grown ginseng and that from red ginseng, we compared the effects on endothelium-dependent relaxation and examined possible mechanisms of action using isolated rat aortic rings.

## Materials and Methods

*Plant Materials and Preparation of Crude Ginsenosides* Dried adventitious roots of mountain-grown ginseng and red ginseng were obtained from BioPia Co., Ltd (Yongin 449-598, Gyeonggi-Do, Korea). Crude ginsenosides were extracted by the method as described elsewhere (Ando et al. 1971). Briefly, the dried root powders were extracted with 80% methanol; the solvent was evaporated in vacuo, and then the residue was treated with diethyl ether to remove fats. The resulting extract was fractionated successively with n-butanol and water, the n-butanol phase was concentrated and lyophilized into crude ginsenosides with a yield of 4.5% for adventitious roots of mountain-grown ginseng (GS-ARMG) and 7.0% for red ginseng (GS-RG). These solids were stored at −20°C until use.

*Artery Ring Preparation* Male Sprague–Dawley rats weighing 200–250 g were stunned and bled. The descending thoracic aorta was dissected from surrounding connective tissues and cut into rings of 2–3 mm in length. Rings were subsequently transferred into 4 mL horizontal-type muscle chambers, bathed in physiological salt solution (PSS) at 37°C containing 115 mM/L NaCl, 5.0 mM/L KCl, 2.1 mM/L $CaCl_2$, 1.2 mM/L $MgCl_2$, 25.0 mM/L $NaHCO_3$, 11.0 mM/L glucose, and $KH_2PO_4$, and then gassed with 95% $O_2$ and 5% $CO_2$. Rings were mounted on stainless-steel hooks connected to a force-displacement transducer (FT03, Grass, West Warwick, RI, USA) connected to a polygraph system (RPS212, Grass) and a computer analyzer (Power Lab 400, MacLab system, Castle Hill, Australia). A basal tension of 1 g was applied. In some segments, endothelium was removed mechanically by gentle rubbing with a moistened cotton swab. Measurements assessed the functional activity of vascular endothelium in terms of whether 1 μM/L carbachol induced almost complete relaxation (>90%) in aorta stimulated with norepinephrine (NE, 300 nM/L) (Sudjarwo et al. 1992). Each experiment was performed on rings prepared from different rats. All studies were performed according to the Guiding Principles for the Care and Use of Laboratory Animals of the Ethics Committee of the Korea Food Research Institute.

*Measurement of Relaxation* To detect the relaxation effects of GS-ARMG or GS-RG, all rat aortic rings were equilibrated for 60 min under a resting tension of 1 g and then exposed repeatedly to 72 mM/L KCl PSS until the responses stabilized; then a control contraction was produced with 300 nM/L NE. After sustained tension (60% or 80% of the maximal contraction to 72 mM/L KCl PSS in endothelium-intact or denuded rings) was obtained, GS-ARMG, GS-RG, or a vehicle was added. In experiments where specific inhibitors were used, they were added 20 min prior to pre-contract with NE. The inhibitors tested were $N^G$-nitro-L-arginine (L-NNA, 10 μM/L) as an inhibitor of NO synthesis, methylene blue (1 μM/L) as a guanylate cyclase inhibitor, or indomethacin (10 μM/L) as a cyclooxygenase inhibitor. The different cellular receptor antagonists used were atropine (100 nM/L) as a selective muscarinic receptor antagonist, diphenylhydramine (10 μM/L) as a selective histamine $H_1$-receptor antagonist, [D-Pro$^2$, D-Trp$^{7,9}$]-substance P (5 μmol/L) as a substance P receptor antagonist, and propranolol (1 μM/L) as a β-adrenoceptor antagonist (Kim et al. 1999; Vanhoutte 2004; Fukuda et al. 2005).

*Materials and Reagents* Carbachol, indomethacin, L-NNA, methylene blue, NE, atropine, [D-Pro$^2$, D-Trp$^{7,9}$]-substance

P, propranolol, and diphenylhydramine were purchased from Sigma (St. Louis, MO, USA). All drugs were dissolved in PSS.

*Data Analysis* Relaxation was expressed in terms of a percentage decrease in the maximal contraction caused by NE (300 nM/L). The $EC_{50}$ value (the concentration to produce 50% maximal contraction in response to NE in endothelium-intact rings) was determined from the concentration–response curve by linear interpolation. All results are expressed as mean±SEM. The number of rings obtained from different rats is represented by *n*. Student's *t* test and one-way ANOVA with Student–Newman–Keul's test were used to evaluate between-group differences, with *P* values of less than 0.05 regarded as significant.

## Results

*Effects of GS-ARMG or GS-RG on the NE Contraction of Rat Aortas* Figure 1 shows the experimental protocols to investigate the effect of GS-ARMG (0.3 mg/mL) and GS-RG (0.3 mg/mL) to the endothelium-intact or endothelium-denuded aorta pre-contracted with NE (300 nM/L). GS-ARMG caused both transient acute relaxation and gradual relaxation. In the denudation of endothelium, GS-ARMG practically did not induce acute relaxation while the gradual vascular relaxation was not influenced (Fig. 1a). The pattern of relaxation of GS-RG to both endothelium-intact and endothelium-denuded aorta was quite similar to that of GS-ARMG (Fig. 1b); however, the sensitivity of endothelium-dependent relaxation differed between GS-ARMG and GS-RG. Thus, the endothelium-dependent relaxation was preferentially compared between GS-ARMG and GS-RG. The transient acute relaxation induced by both GS-ARMG and GS-RG (0.03–3.0 mg/mL) was concentration-dependent on NE-induced tone in endothelium-intact arteries (Fig. 2), with an $EC_{50}$ of 0.09±0.07 mg/mL ($n$=26) in GS-RG, which was more than 25 times lower than that of GS-RG ($EC_{50}$=2.34±1.30 mg/mL, $n$=16).

*Effects of NO and Endothelium-Dependent Relaxation* We first investigated the effects of endothelium-derived factors on GS-ARMG-induced relaxation because the endothelium-dependent relaxation induced by crude or pure ginsenosides is mediated by increased release of NO from endothelial cells, which causes accumulation of cGMP in smooth muscle (*8–18*). The relaxation induced by GS-ARMG (1.0 mg/mL) was significantly inhibited by $N^G$-nitro-L-arginine (L-NNA, 10 μM/L) and methylene blue (1 μM/L; $n$=3–6); however, the sensitivity differed between GS-ARMG (1.0 mg/mL) and GS-RG (1.0 mg/mL), and maximum relaxations attained were 30–38% and 13–17%, respectively, that of the untreated preparations (Fig. 3). In contrast, indomethacin (10 μM/L) had no effect on the relaxation induced by either GS-ARMG or GS-RG ($n$=4–5; Fig. 3).

*Effect of Receptor Antagonists on Endothelium-Dependent Relaxation* Since the above data suggested that relaxation induced with GS-ARMG was less sensitive to pre-treatment with L-NNA or methylene blue than that induced with GS-RG, we investigated the underlying pathway by using different endothelial cell receptor antagonists. None of the receptor antagonists, atropine (100 nM/L), diphenhydramine (10 μM/L), [D-$Pro^2$, D-$Trp^{7,9}$]-substance P (5 μM/L),

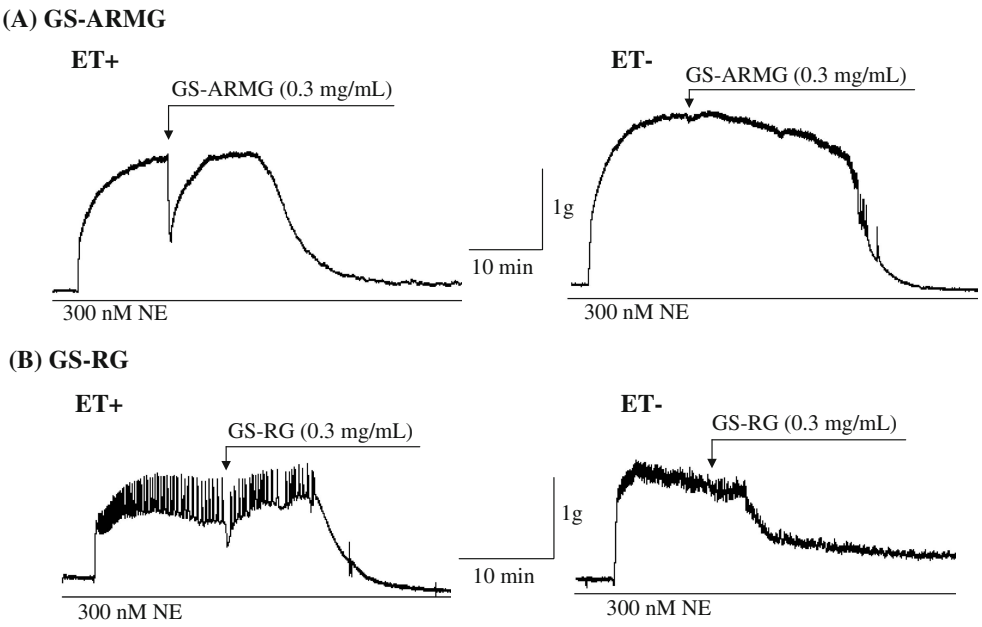


**Fig. 1** Representative traces of contractive responses to norepinephrine (NE, 300 nM/L) in rat aortic rings and the responses to GS-ARMG (**a**) and GS-RG (**b**) on contractive responses on endothelium-intact (ET+) and endothelium-denuded (ET−) rat aortas ($n$=4, respectively)

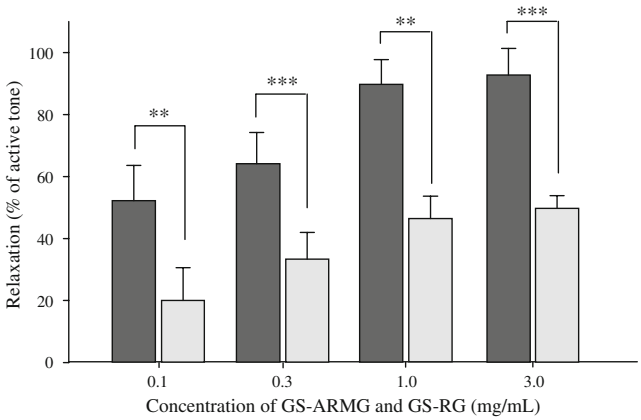


**Fig. 2** The concentration-dependency of GS-ARMG (*black bars*, 0.1–3.0 mg/mL) or GS-RG (*gray bars*, 0.1–3.0 mg/mL)-induced vascular relaxation in the endothelium-intact rat aortas. The relaxation response was presented as the percentage relaxation of the norepinephrine-induced contraction (100%=complete relaxation, $n$=3–7, respectively). $^{**}P<0.01$, $^{***}P<0.001$, compared with the corresponding controls ($n$=3–8, respectively). Values are mean±SEM

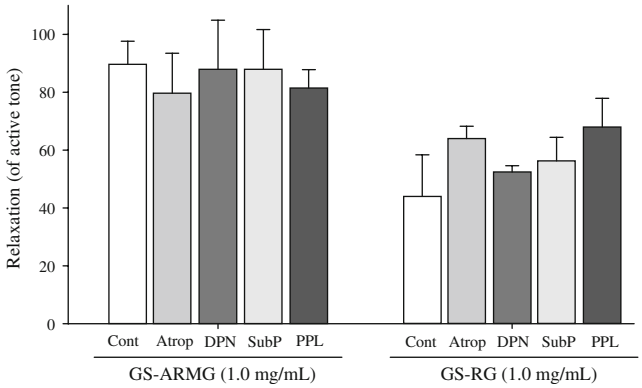


**Fig. 4** Comparison of the response to GS-ARMG or GS-RG of endothelium-intact and receptor antagonists pretreated rat aortas. The endothelium-intact rings pre-contracted with norepinephrine, after which GS-ARMG or GS-RG added to the muscle (Cont, 1.0 mg/mL). The quiescent preparations were pretreated with atropine (Atrop, 100 nM/L), diphenylhydramine (DPN, 10 μM/L), [D-Pro$^2$, D-Trp$^{7,9}$] substance P (SubP, 5 μM/L), and propranolol (PPL, 1 μM/L) for 20 min ($n$=3–4, respectively). Values are mean±SE

or propranolol (1 μM/L), caused any significant inhibition to the relaxation induced by GS-ARMG ($n$=3–4), but pre-treatment with atropine or propranolol caused an approximately 10% reduction in the relaxation (Fig. 4).

## Discussion

Ginseng is used to alleviate vasomotor symptoms such as menopausal hot flashes, as are black cohosh, dong quai, evening primrose oil, licorice, and soy (Cheema et al. 2007). However, the pharmacological efficacy of ginseng varies depending on the age of the roots, where it was cultivated, and how it was processed (Kiefer and Pantuso 2003). In this study, we characterized the vasomotor activity of crude ginsenosides from adventitious roots of mountain-grown ginseng and red ginseng to provide a scientific foundation for potential clinical development. Our results demonstrate for the first time that the relaxation of rat aorta caused by GS-ARMG is mediated by an endothelium-dependent mechanism and that the potency was about 25-fold that of GS-RG, implying that GS-ARMG is approximately 25-fold more potent than GS-RG in inducing endothelium-dependent relaxation. The endothelium-dependent relaxation induced by GS-ARMG was abolished by removal of the endothelium and was significantly suppressed by pre-treatment with the NO synthase inhibitor L-NNA. After NO is released from the endothelial cells, it diffuses into arterial smooth muscle, activating guanylate cyclase (Moncada and Higgs 2002), thereby increasing cGMP formation, which leads to vaso-relaxation. To verify the contribution of cGMP to the relaxant effect of GS-ARMG, we tested the influence of a soluble guanylate cyclase inhibitor, methylene blue (Ragazzi et al. 1995). This compound markedly antagonized the GS-ARMG-induced relaxation. These results clearly show that aortic relaxation caused by GS-ARMG in both endothelium and vascular smooth muscle is mediated by NO production/release and a cGMP-dependent mechanism (Furchgott 1983). Similar results have been observed with ginsenosides extracted from *P. ginseng* (Kim et al. 1999) and the purified ginsenosides $Rg_1$, $Rg_3$, and Re (Kang et al. 1995b) as well as from aqueous extract of Siberian ginseng (Kwan et al. 2004).

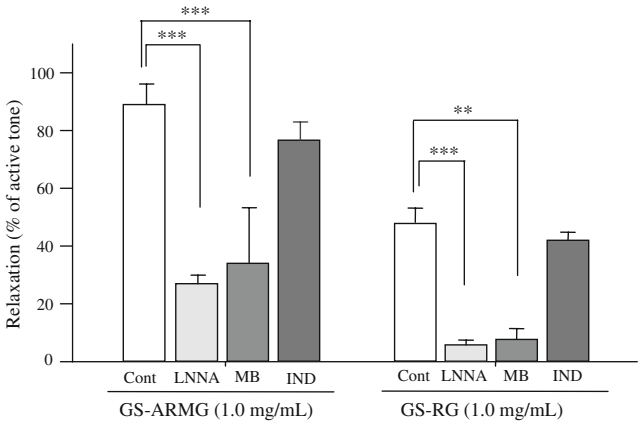


**Fig. 3** Comparison of the responses to GS-ARMG or GS-RG of endothelium-intact and inhibitors pretreated rat aortas. The endothelium-intact rings pre-contracted with norepinephrine, after which GS-ARMG or GS-RG added to the muscle (Cont, 1.0 mg/mL). The quiescent preparations were pretreated with L-NNA (LNNA, 10 μM/L), methylene blue (MB, 1.0 μM/L), and indomethacin (IND, 10 μM/L) for 20 min. $^{**}P<0.01$, $^{***}P<0.001$, compared with the corresponding controls ($n$=3–8, respectively). Values are mean±SEM

Indomethacin, a cyclooxygenase inhibitor, did not affect the action of GS-ARMG, indicating that vasoactive prostanoids might not contribute to the relaxation. It is well known that various agonists stimulate NO release via endothelial receptors, including acetylcholine, histamine, substance P, and isoproterenol (Furchgott 1983; Hirano et al. 1991; Gray and Marshall 1992; Szarek et al. 1992). We examined the effects of atropine, a muscarinic receptor antagonist; diphenylhydramine, a selective histamine $H_1$-receptor antagonist; [D-Pro$^2$, D-Trp$^{7,9}$]-substance P, a substance P receptor antagonist; and propranolol, a β-adrenoceptor antagonist on the endothelium-dependent relaxation induced by GS-ARMG. None of the receptor antagonists caused significant inhibition of the relaxation, suggesting that GS-ARMG may not interact with these receptors to induce endothelium-dependent relaxation. However, the possible involvement of a muscarinic receptor or a β-adrenoceptor in the relaxation induced by GS-ARMG cannot be excluded because atopine or propranolol pretreatment caused an approximately 10% reduction in the relaxation in this study. In addition, partial inhibition after pretreatment with atropine or propranolol on the endothelium-dependent relaxation was also observed even with high concentrations of aqueous extracts of Siberian ginseng (2 mg/mL) (Kwan et al. 2004) or the ginsenoside $Rg_3$ ($10^{-5}$ M; Rapoport and Murad 1983). Mountain-cultivated *Panax ginseng* was recently compared with field-cultivated ginseng in terms of the composition and content of ginsenosides, and higher amounts of ginsenosides, particularly Rh2 produced by steam-processing or acid hydrolysis (Shibata 2001), were detected in mountain-cultivated *Panax ginseng* (Choi et al. 2007a, b). There is no scientific evidence that Rh2 contributes to endothelium-dependent relaxation via NO production from endothelial cells rather than inhibiting NO production in lipopolysaccharide-stimulated cells (Park et al. 2003). Therefore, we believe that a substance other than Rh2 might contribute to the relaxation and might accumulate more in mountain-grown ginseng due to the growing conditions on mountains or the processing of adventitious root of mountain-grown ginseng.

In conclusion, GS-ARMG induces endothelium-dependent and endothelium-independent relaxation in isolated rat aortas similarly to GS-RG, while the sensitivity of endothelium-dependent relaxation of GS-ARMG has 25-fold more potent activity in relaxing isolated endothelium-intact rat aortas. Increased NO production and increased vascular levels of cGMP in the endothelial cells could contribute to this relaxation. This study helps explain the beneficial biological effects of adventitious root of mountain-grown ginseng on the cardiovascular system. The possible active components in adventitious root of mountain-grown ginseng and the accumulation pathway should be further investigated to better understand potential links between the ginsenoside compounds and their beneficial effects on vascular health.

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