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Antioxidative effects of Korean red ginseng in postmenopausal women: A double-blind randomized controlled trial

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ABSTRACT

Ethnopharmacological relevance: Red ginseng (RG) has been widely used to treat various diseases in East Asian countries. Previous studies have shown the anti-oxidative and anti-diabetic effects of RG. This study aimed to investigate the effects of RG on oxidative stress and insulin resistance in postmenopausal women.

Materials and methods: We performed a randomized, double-blind, placebo-controlled trial in 82 postmenopausal women aged 45–60 years. Participants were randomized to receive 3 g red ginseng daily or placebo for 12 weeks. Antioxidant enzymes activity (superoxide dismutase, glutathione peroxidase) and oxidative stress markers (malondialdehyde, 8-hydroxydeoxyguanosine) were assessed, and the homeostatic model assessment of insulin resistance index was calculated at the baseline and at the end of the trial.

Results: A total of 71 postmenopausal women completed the study. Serum superoxide dismutase activity was significantly increased after the 12-week RG supplementation ($P<0.001$), and these changes were statistically significant compared with the placebo group ($P=0.004$). Serum malondialdehyde levels showed a tendency to decrease after the 12-week RG supplementation ($P=0.001$), but these changes were not statistically significant compared with the placebo group ($P=0.064$). No statistically significant changes in serum glutathione peroxidase and 8-hydroxydeoxyguanosine were noted. Further, RG supplementation showed no effects on fasting glucose, fasting insulin, and insulin resistance.

Conclusions: The results suggest that RG may reduce oxidative stress by increasing antioxidant enzyme activity in postmenopausal women.

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1. Introduction

Many women experience symptoms of hot flushes, night sweats, and sleep disturbances during menopause. Additionally, postmenopausal women are at an increased risk for cardiovascular disease (CVD) and osteoporosis. Although hormone therapy primarily has been used to improve symptoms and prevent diseases, increasing numbers of women are using herbal products, because of concerns related to the possible health risks of long-term hormone therapy. However, very little scientific information is available to determine the efficacy and safety of such herbal products. Clinical results regarding the efficacy of herbal remedies have been inconsistent, and the mechanisms of action of these herbs have not been adequately investigated (Eden, 2012; Taku et al., 2012). Some herbal therapies have been shown to cause serious adverse effects (Cheema et al., 2007).

Ginseng (*Panax ginseng* C.A. Meyer) roots have been widely used as herbal medicine to improve general health and to treat various diseases, including cancer and cardiovascular diseases, in East Asian countries. Considering these effects, ginseng may hold value in treating postmenopausal women. The major active components of ginseng are ginsenosides, which possess various biological and pharmacological activities. Red ginseng (RG) is obtained by steaming and drying 6-year-old white ginseng, and as a result of this processing, the composition of the ginsenosides changes significantly (Kim et al., 2000). RG thus contains newly identified ginsenosides, which are absent in white ginseng, and it is believed to be more pharmacologically active than white ginseng. A previous randomized controlled trial (RCT) reported

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that ginseng extract alleviated some menopausal symptoms, such as depression, and also improved general health and well-being (Wiklund et al., 1999). Our previous study also showed that RG reduced the Kupperman index and Menopause Rating Scale scores (J.Y. Kim et al., 2012; S.Y. Kim et al., 2012). Further, studies have found that RG has beneficial effects on cardiovascular risk factors.

CVD is a major cause of death in postmenopausal women, and insulin resistance is an independent risk factor of CVD. Oxidative stress is believed to be the pathogenic mechanism connecting insulin resistance to β-cell and endothelial cell dysfunction, eventually leading to overt diabetes and CVD (Evans et al., 2005). Oxidative stress reflects an imbalance between reactive oxygen species (ROS) production and antioxidant defenses. Mostly, previous studies have shown the antioxidative effects of ginseng, which increases superoxide dismutase (SOD) and catalase activities while decreasing the malondialdehyde (MDA) level in humans as well as in rats (J.Y. Kim et al., 2012; S.Y. Kim et al., 2012; Ramesh et al., 2012a,b; Wei et al., 2012). Additionally, ginseng has been reported to have an insulin-sensitizing effect (Cheng, 2010).

Thus, it remains unclear whether consumption of RG reduces oxidative stress or increases antioxidant capacity in postmenopausal women. In fact, a recent RCT reported that long-term supplementation with American ginseng (AG; *Panax quinquefolius* L.) may even cause oxidative stress in postmenopausal women (Dickman et al., 2009). In addition, there are no clinical studies on the effects of RG on insulin resistance in postmenopausal women. Therefore, the present study was conducted to investigate the effects of RG on oxidative stress and insulin resistance in postmenopausal women.

2. Materials and methods

2.1. Participants

This study was performed between December 2010 and July 2011 at the Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul. Participants were recruited from the general population by advertisement. All participants were postmenopausal women aged between 45 and 60 years. Menopause was defined as the cessation of menstrual periods for 12 months and was confirmed by a serum follicle stimulating hormone (FSH) concentration greater than 40 mIU/mL. None of the participants were current smokers. Participants with uncontrolled hypertension, diabetes mellitus (DM), hypercholesterolemia, and CVD were excluded. Those using medications affecting oxidative stress or insulin resistance were also excluded.

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, and written informed consent was obtained from all participants.

2.2. Study design

This study was designed as a single-center, double-blind RCT. After the initial screening visit and examination, 82 participants were evenly allocated to the RG and placebo groups using a computer-generated random number sequence. RG and placebo capsules were provided by the Korea Ginseng Corporation (Daejeon, Korea). The RG group received 1 g of RG while the placebo group received identically shaped capsules composed of 95.25% cornstarch, 4% ginseng aromatic powder, 0.15% natural dye, and 0.6% caramel dye, to be taken 3 times a day for 12 weeks. Each RG capsule contained 500 mg of RG. The ginsenoside composition in the RG was analyzed by high-performance liquid chromatography. It was found to contain Rg1 (2.61 mg/g), Rb1 (4.26 mg/g), Rb2 (1.65 mg/g), Rg2s (0.20 mg/g), Rg3s (0.13 mg/g), Rc (1.80 mg/g), Rd (0.29 mg/g), Re (1.71 mg/g), Rf (0.67 mg/g), and Rh1 (0.11 mg/g).

2.3. Measurements

Anthropometric measurements were obtained and blood was drawn for laboratory testing at the initial (week 0) and final (week 12) visits. Body weight and height were measured with the subjects in light indoor clothing, and body mass index (BMI) was calculated as the weight divided by the height squared (kg/m^2). Blood pressure was measured with the participant in the sitting position, after 5 min of rest, using an automated device (TM-2665P; A&D Co., Ltd., Tokyo, Japan). Blood samples were collected in sterile tubes from an antecubital vein, and they were centrifuged at $300 \times g$ for 10 min. The serum samples were stored at $-80\ ^{\circ}C$ until analysis.

Enzyme-linked immunosorbent assays (ELISAs) using commercial kits were used to measure serum SOD (Cayman Chemical Company, Ann Arbor, MI, USA) and glutathione peroxidase (GPx) (BioVision Inc., Milpitas, CA, USA) activities for antioxidative enzyme activities. MDA and 8-hydroxydeoxyguanosine (8-OHdG) were measured as oxidative stress markers similarly (Cell Biolabs Inc., San Diego, CA, USA). Plasma fasting glucose levels were measured using a Chemistry Autoanalyzer (Hitachi model 7600-110, Tokyo, Japan), and serum fasting insulin levels were measured by commercial ELISA (USCN Life Sciences Inc., Wuhan, China). Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR) with the following equation: HOMA-IR=(fasting insulin [μIU/mL] × fasting plasma glucose [mg/dL]/405).

2.4. Statistical analysis

Data were analyzed by intention-to-treat analysis and expressed as mean ± SD. Independent *t* test was used to identify between-group differences. A paired *t* test was used to compare the mean changes from baseline to 12 weeks within each group. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, IL, USA). *P*-values of < 0.05 were considered to be statistically significant.

3. Results

Seventy-one participants completed the 12-week study (Fig. 1). Eleven women dropped out of the study because of failure to follow the regimen or failure to attend the follow-up session.

Table 1 shows the baseline characteristics of the participants. No significant between-group differences were found in age, age at menopause, body mass index, blood pressure, fasting glucose levels, estradiol (E_2) levels, FSH levels, and liver enzyme levels at baseline.

Table 2 shows the antioxidant enzyme activities and oxidative stress marker levels before and after treatment. The activity of serum SOD, an antioxidant enzyme, was significantly increased after the 12-week RG supplementation ($P < 0.001$), and these changes were statistically significant compared with the placebo group ($P=0.004$). No statistically significant change in serum GPx activities was observed after the 12-week RG supplementation. Serum levels of the oxidative stress marker MDA were significantly decreased after the 12-week RG supplementation ($P=0.001$), but these changes were not statistically significant compared with the placebo group ($P=0.064$). Further, no statistically significant change in serum 8-OHdG levels was observed after the 12-week RG supplementation (Table 2).

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Insulin resistance and inflammatory marker were examined before and after treatment. Fasting levels of plasma glucose, serum insulin, and insulin resistance (HOMA-IR) were not significantly altered after the 12-week RG supplementation (data not shown). No statistically significant changes in inflammatory marker and liver enzyme levels were noted after the 12-week RG supplementation (Table 3).

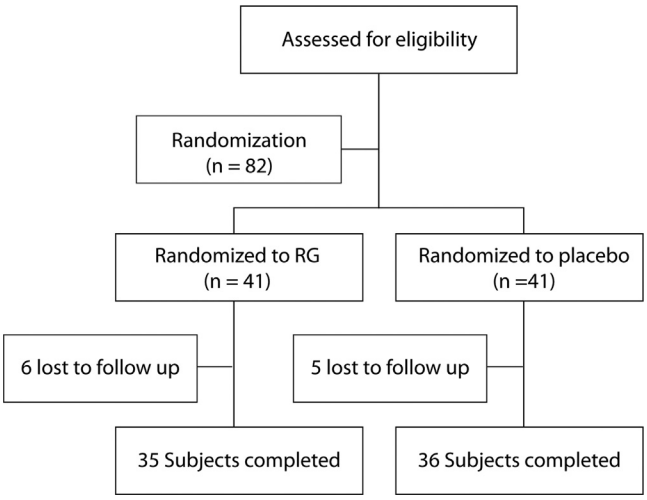

Fig. 1. Trial flow diagram. RG, red ginseng.

Table 1
Baseline demographic and clinical characteristics of participating postmenopausal women.

	RG group (n=35)	Placebo group (n=36)	P
Age, y, mean ± SD	53.86 ± 3.21	54.33 ± 2.52	0.488
Age at menopause, y, mean ± SD	49.69 ± 2.68	50.39 ± 1.73	0.210
BMI, kg/m^2, mean ± SD	22.99 ± 2.34	22.46 ± 2.08	0.335
Systolic BP, mm Hg, mean ± SD	116.19 ± 9.78	118.06 ± 10.10	0.451
Diastolic BP, mm Hg, mean ± SD	72.50 ± 8.62	74.64 ± 8.52	0.319
Fasting glucose, mg/dL, mean ± SD	97.09 ± 8.11	95.22 ± 8.37	0.344
Fasting insulin, μU/mL, mean ± SD	6.24 ± 1.34	6.17 ± 1.32	0.824
AST, IU/L, mean ± SD	23.17 ± 4.33	23.86 ± 5.74	0.570
ALT, IU/L, mean ± SD	17.54 ± 8.20	19.72 ± 10.64	0.338
γ-GT, IU/L, mean ± SD	20.00 ± 9.04	20.08 ± 9.00	0.969
FSH, mIU/mL, mean ± SD	80.29 ± 26.70	77.33 ± 24.76	0.629
E2, pg/mL, mean ± SD	10.39 ± 11.92	8.23 ± 5.52	0.335

RG, red ginseng; BMI, body mass index; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyltransferase; FSH, follicle-stimulating hormone; E2, estradiol.

4. Discussion

In the present study, RG supplementation at the given dose showed antioxidative effects in postmenopausal women, as indicated by several serum antioxidant enzymes activity and oxidative stress markers. RG increased the serum levels of the antioxidant enzyme SOD. However, it did not improve insulin resistance in the postmenopausal women.

It has long been recognized that the risk of CVD increases after menopause. This may occur because of estrogen deprivation directly or because of the greater prevalence of CVD risk factors including hypertension, diabetes, and hypercholesterolemia at the time of menopause (Pai and Manson, 2013). The precise underlying mechanism remains unclear. The link between oxidative stress and estrogen deficiency has been demonstrated in numerous studies. Estrogen seems to attenuate oxidative stress by preventing local ROS generation and scavenging ROS. Therefore, oxidative stress caused by estrogen depletion is considered to play an important role in the pathogenesis of CVD in postmenopausal women (Arias-Loza et al., 2013; E.H. Kim et al., 2013; G.H. Kim et al., 2013; White et al., 2010). Our previous study demonstrated that RG consumption had favorable effects on some cardiovascular risk factors in postmenopausal women (J.Y. Kim et al., 2012; S.Y. Kim et al., 2012), and in the present study, we evaluated the effect of RG on oxidative stress. Antioxidant enzymes, such as SOD, GPx, and catalase (CAT), protect against cellular damage by reactive oxygen species (ROS). SOD converts superoxide into hydrogen peroxide. Thereafter, GPx and CAT convert hydrogen peroxide to water. Excess ROS generation causes oxidative damage to lipids, proteins, and DNA: MDA is a marker of lipid peroxidation and 8-OHdG is a maker of oxidative damage to DNA.

Previous in vitro and animal studies have shown the antioxidative effects of RG (Cho et al., 2013; E.H. Kim et al., 2013; G.H. Kim et al., 2013; Park et al., 2012; Ramesh et al., 2012a,b). RG extract has exhibited protective effects against oxidative damage in various cell lines (Cho et al., 2013; E.H. Kim et al., 2013; G.H. Kim et al., 2013; Park et al., 2012). Further, RG supplementation was found to increase SOD, GPx, and catalase levels and decrease MDA levels in various tissues such as the liver, kidney, heart, and lungs in animal models (Ramesh et al., 2012a,b). However, few human studies have demonstrated the effects of RG on oxidative stress. Only one RCT evaluated the effects of RG supplementation on biomarkers of oxidative stress in healthy subjects (J.Y. Kim et al., 2012; S.Y. Kim et al., 2012). Both low- (3 g/d) and high-dose (6 g/d) RG supplementation significantly reduced oxidative DNA damage and plasma oxidized low-density lipoprotein cholesterol levels and enhanced plasma SOD activity. In contrast, plasma GPx and catalase activities were increased only after the high-dose supplementation. These results are consistent with the findings of the present study, i.e. that serum SOD activities were significantly

Table 2
Changes in antioxidant enzymes activity and oxidative stress markers from baseline to week 12.

	RG group (n=35)	P^a	Placebo group (n=36)	P^a	P^b
SOD, U/mL, mean ± SD	Baseline: 287.10 ± 51.56 Endpoint: 343.89 ± 62.60	< 0.001	Baseline: 291.54 ± 48.41 Endpoint: 303.37 ± 43.94	0.306	0.004
GPx, mU/mL, mean ± SD	Baseline: 0.51 ± 0.14 Endpoint: 0.49 ± 0.10	0.470	Baseline: 0.51 ± 0.05 Endpoint: 0.50 ± 0.12	0.922	0.629
MDA, nmol/mg, mean ± SD	Baseline: 222.03 ± 59.72 Endpoint: 182.05 ± 53.31	0.001	Baseline: 219.17 ± 62.00 Endpoint: 205.51 ± 56.81	0.149	0.064
8-OHdG, ng/mL, mean ± SD	Baseline: 14.02 ± 3.44 Endpoint: 13.89 ± 2.51	0.855	Baseline: 14.57 ± 2.95 Endpoint: 15.53 ± 2.66	0.261	0.323

RG, red ginseng; SOD, superoxide dismutase; GPx, glutathione peroxidase; MDA, malondialdehyde; 8-OHdG, 8-hydroxydeoxyguanosine.

[a] Comparison by paired t test between means at baseline and at week 12 by group.

[b] Comparison of supplementation effects between two groups by independent t test.

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Table 3
Changes in inflammatory marker and liver enzymes from baseline to week 12.

	RG group ($n=35$)	P^a	Placebo group ($n=36$)	P^a	P^b
IL-6, pg/mL, mean ± SD	Baseline: 1.64 ± 0.44 Endpoint: 1.68 ± 0.45	0.604	Baseline: 1.55 ± 0.51 Endpoint: 1.68 ± 0.45	0.144	0.496
AST, IU/L, mean ± SD	Baseline: 23.17 ± 4.33 Endpoint: 24.03 ± 3.61	0.242	Baseline: 23.86 ± 5.74 Endpoint: 24.83 ± 4.75	0.162	0.908
ALT, IU/L, mean ± SD	Baseline: 17.54 ± 8.20 Endpoint: 19.03 ± 10.76	0.371	Baseline: 19.72 ± 10.64 Endpoint: 20.67 ± 12.25	0.419	0.787
γ-GT, IU/L, mean ± SD	Baseline: 20.00 ± 9.04 Endpoint: 21.11 ± 14.51	0.420	Baseline: 20.08 ± 9.00 Endpoint: 19.08 ± 8.69	0.168	0.176

IL-6, interleukin-6; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyltransferase.

[a] Comparison by paired *t* test between means at baseline and at week 12 by group.

[b] Comparison of supplementation effects between two groups by independent *t* test.

increased but serum GPx activities remained unchanged after RG (3 g/d) consumption. Thus, RG seems to exhibit its antioxidative effects in a dose-dependent manner.

A previous double-blind placebo controlled study showed that AG supplementation may cause oxidative stress in postmenopausal women (Dickman et al., 2009). Consumption of AG (1 g/d for 4 months) increased the levels of oxidative stress markers, including plasma MDA and urinary 8-OHdG. These findings contradict the current results, that RG supplementation reduces oxidative stress by increasing the levels of antioxidant enzymes in postmenopausal women. In our study, serum MDA levels tended to decrease after RG consumption. In the previous study mentioned above, the participants were older than those in our study, and the dose of ginseng was only one-third that used in our study. Thus, insufficient supplementation with ginseng seems to have an insubstantial effect on the greater ROS production related to age. In addition, there is a marked difference in ginsenoside composition between AG and RG, most probably because of the different manufacturing processes used to produce these herbal therapeutics (Kim et al., 2000). Ginsenosides can be classified into diol and triol types, depending on the position of the sugar moieties, which are bound to β-OH at C-3 and/or C-20 in the diol type or to the α-OH at C-6 and/or β-OH at C-20 in the triol type. Differences in sugar type, number, and position seem to be associated with variances in the effects of ginsenosides. In fact, some ginsenosides show pro-oxidative effects, instead of anti-oxidative effects, when sugar moieties are not bound to C-20 (Helms, 2004). As well, structural changes in diol type ginsenosides caused by heat processing are closely connected with elevated free radical-scavenging activities (Kang et al., 2007). These factors could explain the difference in results between these studies.

Accumulating evidence indicates that oxidative stress leads to result in insulin resistance and chronic inflammation by inducing abnormal changes in intracellular signaling related to the regulation of cellular function (Evans et al., 2005). Considering the antioxidant properties of RG, it is assumed that RG intake improves insulin resistance. Some previous animal studies have shown that RG increases insulin sensitivity by enhancing the insulin-signaling pathway that regulates GLUT4 and adiponectin production by adipocytes, which seems to be associated with its anti-obesity and anti-diabetic effects (Lee et al., 2009, 2012). Among the various ginsenosides, Rh2 and Re have been found to improve insulin resistance in animal models (Attele et al., 2002; Lee et al., 2007). However, we found no evidence that RG affects fasting blood glucose and insulin resistance (HOMA-IR) in postmenopausal women. These results are consistent with those of previous human studies that investigated the effects of RG on β-cell function and insulin sensitivity (Reeds et al., 2011). Consumption of RG (3 g/d for 2 weeks followed by 8 g/d for 2 weeks) or ginsenoside Re (250 mg/d for 2 weeks followed by 500 mg/d for 2 weeks) in insulin-resistant subjects was not found to improve β-cell function or increase insulin sensitivity. The discrepancy in results between human and animal studies can be explained by the difference in bioavailability of RG after oral ingestion. Ginsenoside Re is insoluble in water and is rapidly hydrolyzed by mild acidic conditions like gastric fluid. Therefore, it is thought to be poorly absorbed after oral ingestion by humans, which may be why it does not exhibit anti-diabetic effects.

To our knowledge, this is the first RCT to investigate the antioxidative effects of RG in postmenopausal women. Moreover, we attempted to investigate whether oxidative stress is associated with insulin resistance or inflammatory reaction. Given that our previous study showed the favorable effects of RG on cardiovascular risk factors (J.Y. Kim et al., 2012; S.Y. Kim et al., 2012), the effect of RG in reducing oxidative stress is likely to contribute to decreased CVD risk. However, ginsenoside constitution differs among commercially available products, so it is possible that other ginseng products do not possess antioxidative properties.

The present study has some limitations: our sample size was small, and only Korean individuals were included. Therefore, the results may not be applicable to the general population or individuals of other ethnicities, and a precise conclusion about the RG effects on oxidative stress cannot be established on the basis of this study alone. In addition, the potential dangers or adverse effects of RG were not assessed, except its effects on liver enzyme levels, although no participants dropped out because of side effects. Side effects of RG have been reported, including nervousness, sleeplessness, and dizziness; uterine bleeding is also a major concern with RG use. Therefore, further investigations are needed to ascertain the safety and efficacy of RG for long-term use.

5. Conclusions

This double-blind RCT showed that RG supplementation significantly increased serum SOD activity compared with the placebo. In addition, it decreased serum MDA levels compared with the placebo, although with only slight statistical significance. Our results suggest that RG may reduce oxidative stress by increasing antioxidant enzyme activity in postmenopausal women.

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