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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.

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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