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Effects of red ginseng supplementation on menopausal symptoms and cardiovascular risk factors in postmenopausal women: a double-blind randomized controlled trial

Sun Young Kim, MD,[1] Seok Kyo Seo, MD,[2] Young Mi Choi, MD,[2] Young Eun Jeon, MD,[1] Kyung Jin Lim, MD,[2] SiHyun Cho, MD,[1] Young Sik Choi, MD,[2] and Byung Seok Lee, MD, PhD[1]

Abstract

Objective: The aim of this study was to evaluate the effects of red ginseng (RG) on menopausal symptoms and cardiovascular risk factors in postmenopausal women.

Methods: A randomized, placebo-controlled, double-blind clinical trial was conducted with postmenopausal women between the ages of 45 and 60 years. A total of 72 women were randomly assigned to either an RG group (supplemented with 3 g of RG, including 60 mg of ginsenosides, per day) or a placebo group for 12 weeks. We analyzed changes in menopausal symptoms (the Kupperman index and the menopause rating scale), cardiovascular risk factors (lipid profiles, high-sensitivity C-reactive protein, and carotid intima-media thickness), and serum estradiol levels from baseline to 12 weeks.

Results: Significant improvements in the Kupperman index (P = 0.032) and in the menopause rating scale (P = 0.035) scores were observed in the RG group compared with the placebo group. Total cholesterol (P = 0.009) and low-density lipoprotein cholesterol (P = 0.015) significantly decreased in the group receiving RG. The RG group also showed a significant decrease in carotid intima-media thickness (P = 0.049). Serum estradiol levels were not influenced by RG supplementation.

Conclusions: RG could be an attractive herbal dietary supplement for relieving menopausal symptoms and conferring favorable effects on markers of cardiovascular disease in postmenopausal women.

Key Words: Red ginseng – Menopausal symptoms – Cardiovascular risk factors – Postmenopausal women.

For many years, women have used herbal extracts to relieve menopausal symptoms.[1,2] Recent research results have been mixed regarding the efficacy of these approaches.[3-6] In addition, the actions of herbal preparations have not been sufficiently investigated, and there are limited data regarding the safety of these preparations.

Ginseng is a kind of herbal medicine that has tonic effects and strengthens immune function, as it is thought to have pharmacological activities in the endocrine, immune, cardiovascular, and central nervous systems. Its use has spread even to Western countries, and it is regarded as an alternative medicine.[7,8] Red ginseng (RG; *Panax ginseng* C.A. Meyer), one of the most popular forms of ginseng, is obtained by steaming and drying naturally dried and unpeeled 6-year-old raw white ginseng.

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From the [1]Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Gangnam-gu, Seoul, Korea; and [2]Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea.

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Address correspondence to: Byung Seok Lee, MD, PhD, Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, 146-92 Dogok-dong Gangnam-gu, Seoul, 135-720, Republic of Korea. E-mail: dr222@yuhs.ac

RG has been widely used to treat diseases such as cancer and cardiovascular disease (CVD) in East Asian countries, especially Korea, China, and Japan, for the past 2,000 years.[9] RG has physiologically active components that are absent in raw white ginseng. RG, with its specific medical components, is superior to traditional ginseng, which lacks these components.[10] RG is known to contain phytoestrogens, which are plant-like estrogens with chemical structures and functions similar to those of human estrogen.[11,12] Previous studies have shown that RG is effective against the psychological and emotional symptoms that are common in postmenopausal women.[13,14] However, no clinical study has investigated the efficacy of RG as an alternative therapy for postmenopausal women. Therefore, we investigated the effects of RG on menopausal symptoms in this study. In addition, we evaluated the effect of RG on cardiovascular risk factors in postmenopausal women.

METHODS

Participants

This study was conducted from August 2009 to May 2010 in the Department of Obstetrics and Gynecology at Gangnam Severance Hospital at the Yonsei University College of Medicine. Study volunteers were recruited from the general population through advertisement. All participants were postmenopausal women aged between 45 and 60 years. Women were eligible if

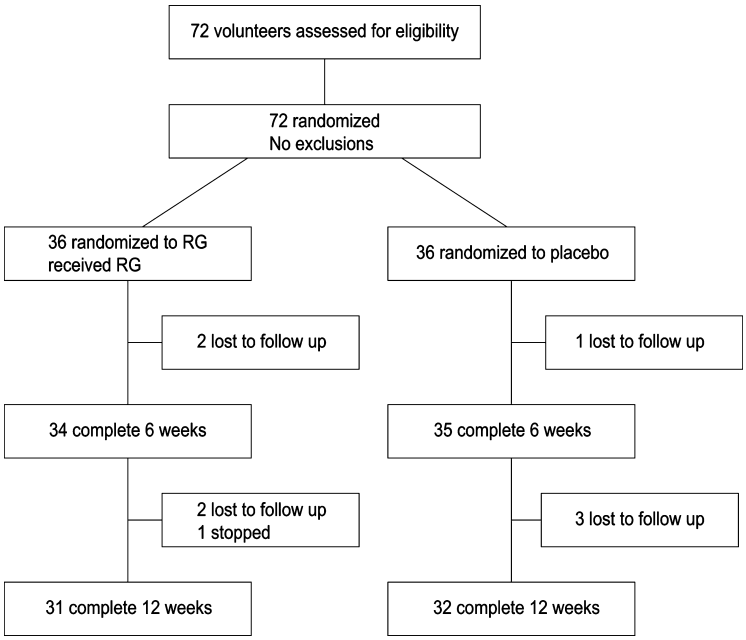

FIG. 1. Trial flow diagram. RG, red ginseng.

they had menopausal symptoms, had been experiencing amenorrhea for at least 12 months, and had not used hormone therapy (HT) for the past 6 months. Women with uncontrolled hypertension, diabetes, hypercholesterolemia, a history of cancer, and CVD were excluded from this trial. A total of 72 postmenopausal women agreed to participate in this study, and written consent was obtained from all participants. The institutional review board of Yonsei University approved this study.

Study design

This study was conducted as a double-blind randomized controlled trial. We used computer randomization and an allocation ratio of 1:1. Thirty-six participants were randomly assigned to the placebo group, and another 36 were placed in the RG group. At each clinic visit, height, weight, and body mass index were measured for each participant. After allowing participants to rest for a minimum of 10 minutes, systolic and diastolic blood pressures were measured twice by an automatic blood pressure manometer, and the averages were obtained.

The Korea Ginseng Corporation (Daejeon, Korea), a producer and exporter of commercially available standardized ginseng extracts, provided the RG and placebo supplements. RG was provided as soft capsules. Each capsule contained 500 mg of RG, including 10 mg of ginsenosides. The RG group took two capsules three times a day (RG 1 g × 3) for 12 weeks. The placebo group was provided with identically shaped capsules containing 95.25% cornstarch, 4% ginseng aromatic powder, 0.15% natural dye, and 0.6% caramel dye. The placebo was also taken three times a day for 12 weeks.

Data collection

We obtained and compared participants' physical measurements (height, weight, blood pressure, and body mass index), menopausal symptoms, blood samples, and carotid intima-media thickness (CIMT) at baseline and at 12 weeks to evaluate the effects of RG.

Evaluation of menopausal symptoms and hot flashes

Menopausal symptoms and hot flashes were evaluated using the Kupperman index[15,16] and the Menopause Rating Scale (MRS) questionnaire.[17,18]

Blood samples

Blood was taken from the antecubital vein after a fast of at least 8 hours. Serum total cholesterol (TC) and triglyceride (TG) levels were measured using enzymatic assays. High-density (HDL-C) and low-density (LDL-C) lipoprotein cholesterol were measured through selective inhibition methods. Serum high-sensitivity C-reactive protein (hs-CRP) was measured using the turbidity test by applying latex aggregation methods. For all

TABLE 1. *Baseline characteristics of the study participants*

	RG group (n = 36)	Placebo group (n = 36)	*P*
Age, y	52.98 ± 3.04	55.01 ± 3.67	0.101
Age at menopause, y	50.37 ± 3.73	51.32 ± 2.47	0.412
BMI, kg/m^2	22.35 ± 2.36	22.03 ± 2.42	0.731
Systolic BP, mm Hg	118.53 ± 14.59	121.29 ± 12.56	0.785
Diastolic BP, mm Hg	74.86 ± 9.25	72.89 ± 10.75	0.610
TC, mg/mL	138.11 ± 43.78	128.52 ± 39.24	0.082
LDL-C, mg/mL	78.12 ± 27.53	73.09 ± 27.85	0.472
HDL-C, mg/mL	38.02 ± 12.37	36.64 ± 12.32	0.783
TG, mg/mL	104.75 ± 46.77	102.90 ± 50.34	0.764
hs-CRP, mg/L	0.39 ± 0.48	0.29 ± 0.31	0.335

Data are presented as mean ± SD.
RG, red ginseng; BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; hs-CRP, high-sensitivity C-reactive protein.

TABLE 2. *Changes in menopausal symptoms by group*

	RG group (n = 36), mean ± SD	P^a	Placebo group (n = 36) mean ± SD	P^a	P^b
KI	baseline: 18.93 ± 11.28 week 12: 13.32 ± 10.15	0.021	baseline: 15.21 ± 12.08 week 12: 15.10 ± 11.73	0.898	0.032
MRS	baseline: 12.45 ± 8.79 week 12: 8.32 ± 6.75	0.027	baseline: 10.23 ± 7.30 week 12: 9.26 ± 7.51	0.512	0.035
Hot flash of KI	baseline: 5.25 ± 3.59 week 12: 3.51 ± 2.36	0.032	baseline: 5.37 ± 3.79 week 12: 4.87 ± 2.94	0.651	0.046
Hot flash of MRS	baseline: 1.85 ± 1.15 week 12: 1.10 ± 0.79	0.096	baseline: 1.86 ± 1.22 week 12: 1.63 ± 0.86	0.715	0.121

RG, red ginseng; KI, Kupperman index; MRS, Menopause Rating Scale.
[a]Paired *t* test comparing mean at baseline with mean at week 12 by group.
[b]Independent *t* test comparing supplementation effects between two groups.

tests, an ADVIA 2400 (Siemens, Washington, DC) was used. The serum estradiol (E_2) level was measured through radioimmunoassay using a Coat-A-Count Estradiol kit (Diagnostic Products Corporation, Los Angeles, CA) with a detection limit of 10.0 pg/mL. The intra-assay coefficient of variation for the measurements of serum E_2 concentrations using this method was less than 10%.

Analysis of CIMT

High resolution B-mode ultrasonography (Philips iU22 xMATRIX ultrasound system) was used, and CIMT was measured using 12.5-MHz transducers. Participants were positioned in a supine position with the head rotated to the left by 45°, and the right common carotid artery was assessed. After the bifurcation site of the two parallel lines of the near wall and far wall of the right common carotid artery was confirmed, the intima-media thickness of the far wall was measured. To minimize any potential bias, a single examiner blinded to clinical information measured the CIMT. The intraexaminer coefficient of variation for repeated measures of CIMT was less than 5%.

Statistical methods

Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL). All data are presented as mean ± SD. In all group comparisons, efficacy analysis was based on the intention-to-treat principle. The last observation carried forward approach was used for missing data.

The independent *t* test was used to compare changes from baseline to 12 weeks between the two groups. In addition, a paired *t* test was used to compare baseline data with changes at 12 weeks for each group. $P < 0.05$ was considered significant for all data analyses.

RESULTS

Sixty-three participants completed the 12-week protocol (Fig. 1). Nine women dropped out of the study because of failure to follow the regimen or failure to follow up. Baseline demographic characteristics, lipid profiles, and hs-CRP were not significantly different between the two groups (Table 1).

There were significant differences in menopausal symptoms between the two groups. After 12 weeks, the Kupperman index for the RG group was significantly reduced from 18.93 ± 11.28 to 13.32 ± 10.15 compared with the placebo group (from 15.21 ± 12.08 to 15.10 ± 11.73; $P = 0.032$), and the MRS score significantly dropped from 12.45 ± 8.79 to 8.32 ± 6.75 compared with the placebo group (10.23 ± 7.30 to 9.26 ± 7.51; $P = 0.035$). Similarly, the hot flash score on the Kupperman index significantly decreased from 5.25 ± 3.59 to 3.51 ± 2.36 in the RG group ($P = 0.046$). Although not significant, the hot flash score on the MRS decreased in the RG group compared with the placebo group (Table 2).

In the RG group, TC significantly decreased from 138.11 ± 43.78 to 108.82 ± 46.79 mg/dL compared with the placebo group (from 128.52 ± 39.24 to 128.03 ± 40.19 mg/dL; $P = 0.009$). LDL-C significantly declined from 78.12 ± 27.53 to 60.02 ± 25.56 mg/dL after 12 weeks compared with the placebo group (from 73.09 ± 27.85 to 71.24 ± 30.41 mg/dL; $P = 0.015$). There were no significant differences between the two groups regarding HDL-C and TG (Table 3).

At 12 weeks, the serum hs-CRP level in the RG group decreased from 0.39 ± 0.48 to 0.29 ± 0.36 mg/L, whereas it

TABLE 3. *Changes in lipid profiles from baseline to week 12 by group*

	RG group (n = 36), mean ± SD	P^a	Placebo group (n = 36), mean ± SD	P^a	P^b
TC, mg/dL	baseline: 138.11 ± 43.78 week 12: 108.82 ± 46.79	0.001	baseline: 128.52 ± 39.24 week 12: 128.03 ± 40.19	0.962	0.009
LDL-C, mg/dL	baseline: 78.12 ± 27.53 week 12: 60.02 ± 25.56	0.001	baseline: 73.09 ± 27.85 week 12: 71.24 ± 30.41	0.555	0.015
HDL-C, mg/dL	baseline: 38.02 ± 12.37 week 12: 34.23 ± 13.42	0.061	baseline: 36.64 ±12.32 week 12: 35.20 ± 14.01	0.299	0.312
TG, mg/dL	baseline: 104.75 ± 46.77 week 12: 95.28 ± 41.51	0.052	baseline: 102.90 ± 50.34 week 12:103.98 ± 46.82	0.228	0.063

RG, red ginseng; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
[a]Paired *t* test comparing mean at baseline with mean at week 12 by group.
[b]Independent *t* test comparing supplementation effects between two groups.

TABLE 4. *Change in mean serum levels of hs-CRP and E_2 from baseline to week 12 by group*

	RG group (n = 36), mean ± SD	P^a	Placebo group (n = 36), mean ± SD	P^a	P^b
hs-CRP, mg/L	baseline: 0.39 ± 0.48 week 12: 0.29 ± 0.36	0.030	baseline: 0.29 ± 0.31 week 12: 0.28 ± 0.29	0.393	0.298
E_2, pg/mL	baseline: 38.52 ± 23.37 week 12: 36.72 ± 20.19	0.513	baseline: 39.09 ± 29.52 week 12: 37.81 ± 26.44	0.728	0.631

E_2, estradiol; RG, red ginseng; hs-CRP, high-sensitivity C-reactive protein.
[a]Paired *t* test comparing mean at baseline with at week 12 by group.
[b]Independent *t* test comparing supplementation effects between two groups.

only changed from 0.29 ± 0.31 to 0.28 ± 0.29 mg/L in the placebo group. There was no significant difference between the two groups with respect to the change in serum hs-CRP. In both groups, serum E_2 levels dropped after the 12-week regimen, but the decrease was not significant (Table 4). In contrast, CIMT was significantly reduced from 0.735 ± 0.069 to 0.705 ± 0.066 mm ($P = 0.049$) in the RG group compared with the placebo group (from 0.734 ± 0.070 to 0.733 ± 0.062 mm; Table 5).

DISCUSSION

In the current study, we examined the effects of RG on menopausal symptoms in healthy postmenopausal women using the Kupperman index and the MRS and its effects on cardiovascular risk factors through measuring lipid profiles, an inflammatory marker, and CIMT.

Most clinical trials using common herbs including phytoestrogens have demonstrated no significant effects on menopausal symptoms.[5,19] Nevertheless, several studies have suggested that phytoestrogens may alleviate menopausal symptoms. Some herbal preparations such as black cohosh and St. John's wort have also been reported to be effective in relieving menopausal symptoms.[20-22] Despite conflicting results regarding the efficacy of these substances, many women take herbal products including phytoestrogens for the relief of menopausal symptoms.

According to a previous randomized controlled trial,[23] ginseng did not show clear effects on vasomotor symptoms but did show signs that indicated improvement in the health-related quality of life. However, the results of our study show that RG reduced the Kupperman index and the MRS score, suggesting that RG improved menopausal symptoms, including hot flashes. This discrepancy between the results of our study and those of the previous study may be attributed to differences in regimen (species of ginseng), dose, and methodology for the assessment of menopausal symptoms. We used RG instead of plain *Panax ginseng*, and our participants took 3 g of RG per day, whereas the daily dose was 200 mg of ginseng in the previous study. In addition, we used the Kupperman index and the MRS to assess menopausal symptoms, whereas the authors of the previous study used a Women's Health Questionnaire and an assessment of "general psychological well-being."

There was no difference in serum E_2 between the RG and placebo groups. Although precisely how RG improves menopausal symptoms is not known, it may be that RG has estrogenic activity and thus plays a role similar to selective estrogen receptor modulators. Previous studies have suggested that ginseng may have both direct and indirect estrogenic activity.[12,24,25] Ginsenosides Rb1 and Rh1, which are crucial components of ginseng, have estrogenic activity.[11,25] Another study[12] confirmed that ginsenoside Rb1 activates both estrogen receptor–α and estrogen receptor–β, which may provide possible scientific evidence for the use of ginseng in the alleviation of estrogen-related symptoms. In addition, although it could not be confirmed in the current study, one possible explanation for our result is that regardless of E_2 level, RG may help relieve menopausal symptoms by elevating the testosterone level, a finding that was reported in an animal study.[26]

Decreased levels of estrogen elevate TC and LDL-C, and lower HDL-C, which are known as risk factors for CVD. Women who receive HT show positive effects on their lipid profiles,[27-29] and some herbal preparations such as soy isoflavones and black cohosh have been shown to improve plasma lipid levels in postmenopausal women.[30-32] RG reduces platelet aggregation and carotid artery thrombosis in normocholesterolemic rats.[33] Furthermore, RG improves blood lipid profiles in hyperlipidemic rabbits.[34] These results are assumed to be associated with ginsenosides because ginsenosides have effects on vasodilation via nitric oxide release and reduce TC and TG levels via cyclic adenosine monophosphate production.[35,36] The RG group in our study showed significant reductions in TC and LDL-C but not in HDL-C or TG. Both TC and LDL-C decreased by approximately 20%, and the major effect of RG is thought to be the reduction of LDL-C rather than an increase in HDL-C. The results of our study are similar to those of previous studies including animal data.[30-34]

hs-CRP and CIMT are known as surrogate markers in the development of CVD.[37-43] It is generally accepted that hs-CRP levels have a tendency to increase in persons receiving HT.

TABLE 5. *Changes in CIMT from baseline to week 12 by group*

	RG group (n = 36), mean ± SD	P^a	Placebo group (n = 36), mean ± SD	P^a	P^b
CIMT, mm	baseline: 0.735 ± 0.069 week 12: 0.705 ± 0.066	0.001	baseline: 0.734 ± 0.070 week 12: 0.733 ± 0.062	0.178	0.049

RG, red ginseng; CIMT, carotid intima-media thickness.
[a]Paired *t* test comparing mean at baseline with at week 12 by group.
[b]Independent *t* test comparing supplementation effects between two groups.

However, available data have shown that hs-CRP level changes are affected not only by HT but also by other factors including obesity, age, smoking, and ethics.[44-49] Therefore, HT's direct influence on level of hs-CRP is uncertain. Although not significant, the level of hs-CRP was lower in the RG group than in the placebo group in this study. Based on the result, we could suggest that RG is rather safe because of the lower hs-CRP level.

Several studies have indicated that RG plays a role in the modulation of vascular function. One recent study showed that RG may improve arterial stiffness in healthy individuals.[50] Joo et al[10] reported a decrease in the thickness of the aortic vascular wall in normal white rats fed with RG for 3 months. Similarly, in the current study, CIMT was significantly decreased in the RG group compared with the placebo group after 12 weeks of supplementation. Therefore, RG supplementation could be an effective method for the prevention of CVD. Further studies are needed to assess changes in CIMT in women with initially abnormal levels of CIMT after long-term supplementation with RG.

To our knowledge, the current study is the first double-blind randomized controlled trial to investigate the effect of 12 weeks of RG supplementation on menopausal symptoms in healthy menopausal women using the Kupperman index and the MRS. In addition, the effect of RG on cardiovascular risk factors was examined through assessing lipid profiles, hs-CRP, and CIMT. In addition, this is the first clinical study to suggest that RG may contain potent phytoestrogens, which implies the need for further studies that test this potential class of phytoestrogens.

The limitations of this study are the small sample size and the fact that a direct mechanism for menopausal symptom improvement was not characterized. In addition, because no assessments were made regarding the potential dangers or adverse effects of RG, further studies are needed to examine both the safety and efficacy of long-term RG intake.

CONCLUSIONS

This study demonstrates that RG has beneficial effects on menopausal symptoms in postmenopausal women. In addition, RG decreased TC, LDL-C, and CIMT. Therefore, RG could be an attractive herbal dietary supplement for the relief of menopausal symptoms and the prevention of CVD especially for women who are unable to receive HT or for whom HT is not recommended. Further clinical studies are needed to investigate the therapeutic effects of RG on postmenopausal women who have moderate to severe menopausal symptoms and abnormal lipid profiles.

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