



Contents lists available at ScienceDirect

## Journal of Ginseng Research

journal homepage: <https://www.sciencedirect.com/journal/journal-of-ginseng-research>

## Research Article

## Safety of red ginseng and herb extract complex (RHC) in menopausal women: A randomized, double-blind, placebo-controlled trial

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## ARTICLE INFO

## Article history:

Received 29 June 2021

Received in revised form

1 November 2021

Accepted 25 November 2021

Available online 11 December 2021

## Keywords:

Korean Red Ginseng

Herb extract

Safety

Menopause

## ABSTRACT

**Background:** Various treatments are used to relieve menopausal symptoms for women. However, herbal substances are frequently used as complementary and alternative therapies as other treatments can increase ovarian and breast cancer risk. While the herbal substances' therapeutic effect is essential, the safety of their use is considered more important. This study aims to confirm the safety of red ginseng and herb extract complex (RHC), which are used to relieve menopausal symptoms.

**Methods:** This randomized, double-blind, placebo-controlled clinical study recruited and divided 120 women experiencing menopausal symptoms into the RHC and placebo groups (60 women per group). Subjects were administered with 2 g RHC or placebo daily for 12 wk. Adverse reactions, female hormonal changes, and uterine thickness were observed and recorded on wk 0, 6, and 12. Hematologic and blood chemistry tests were also conducted.

**Results:** The reactions of the subjects who received RHC or placebo at least once were analyzed. A total of six adverse reactions occurred in the RHC group, while nine occurred in the placebo group; common reactions observed in both groups were genital, subcutaneous tissue, and vascular disorders. However, there was no statistically significant difference between the administration groups ( $p = 0.5695$ ), and no severe adverse reactions occurred in both groups.

**Conclusion:** This study confirms the safety of daily intake of 2 g of RHC for 12 wk by menopausal women.

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## 1. Introduction

Menopause is a period when symptoms like vasomotor symptoms, including hot flashes and sweating, atrophy of the genitourinary system, sleep disturbances, depression, general joint and muscle pains, and osteoporosis occur due to decreased estrogen, a female hormone produced in the ovaries [1,2]. Hormone therapy, including estrogen, is the most effective primary treatment for menopause-related symptoms, but there are concerns about its adverse effects on the breast and cardiovascular system, especially

venous thrombosis. Efforts have been made to alleviate menopause symptoms using edible crops or alternative foods like bioequivalent hormones and herbs. According to Posadzki et al. [3], it was reported that 32.9% of postmenopausal women use complementary and alternative therapies, and of these, herbal substances are the most frequently used (34.6%). On the one hand, most clinical studies on complementary and alternative therapies, including phytoestrogens, have failed to prove their effects on menopausal symptoms [4]. On the other hand, there are reports that some substances, such as isoflavone, black cohosh (*Cimicifuga heracleifolia*), or St. John's wort (*Hypericum perforatum*), are effective in alleviating menopausal symptoms [5–7]. Despite the varied results of the studies on the substances used in complementary and alternative therapies, these substances are still widely used. A 2002 Women's Health Initiative (WHI) study [8] confirmed that an increased risk of coronary artery disease, stroke, breast cancer, and venous thromboembolism of the long-term hormone therapy outweighed the benefits of reducing hot flashes, fractures, and

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colorectal cancer. In addition, long-term hormone administration increases the risks of uterine cancer and bleeding. It also causes an increased number of blood clotting factors produced by the liver, and that weight gain, edema, irregular bleeding, breast pain, and digestive disorders can also develop [9,10]. Since then, various studies on red ginseng have been carried out to develop an alternative to hormone therapy. The various effects of red ginseng can be explained by its adaptogen activity, which nonspecifically increases the body's resistance to external stress and maintains homeostasis by normalizing overall biological functions [11,12]. Red ginseng has been recognized by the Korean Ministry of Food and Drug Safety (MFDS) [13] for its functions in immunity enhancement, fatigue improvement, blood circulation improvement, memory enhancement, antioxidant activity, and beneficial effects on menopausal women's health. Among various effects, it has been reported that red ginseng is effective for treating menopausal syndromes caused by decreased estrogen based on *in vitro*, *in vivo*, and clinical tests on its function [14–16]. In particular, the efficacy of red ginseng in suppressing the decrease in bone density was confirmed through animal experiments [17], and menopausal symptom improvement and blood lipid reduction were confirmed in a clinical study conducted on postmenopausal women [18]. In addition to red ginseng, nine other functional ingredients that relieve menopausal symptoms were approved by the MFDS. However, one of these functional ingredients' safety became a critical issue in the functional food market. As a result, securing the safety of functional foods became an essential factor. Therefore, this study assessed the safety of the 12-wk administration of red ginseng complex (red ginseng and other plant extracts mixture) in menopausal women.

## 2. Materials and methods

### 2.1. Study population

The present study was conducted with the approval of the Institutional Review Board of Konkuk University (IRB# KUH 1040083). Ethical approval includes agreed processes for obtaining consent from or on behalf of all participants. Postmenopausal women with menopausal symptoms, who signed a consent form for the human study, were assessed based on test criteria through a visit evaluation. The selected subjects were randomly assigned to the RHC or placebo groups based on their registration order. The inclusion criteria were as follows: 1) menopausal women aged 45–60 yr old (amenorrhea for more than 12 mo), 2) women with a modified Kupperman Index (MKI) score of 20 or higher, and 3) women who signed the informed consent form for participating in this study. Meanwhile, the exclusion criteria were: 1) women who became menopausal from surgery or chemotherapy; 2) women who underwent hysterectomy; 3) women with a history of endometrial hyperplasia or endometrial, breast, or sex hormone-related cancers; 4) women with uncontrolled hypertension (160/100 mmHg or higher); 5) women with uncontrolled diabetes mellitus (fasting blood sugar 180 mg/dL or higher, or cases of starting or changing medication due to diabetes within 3 mo); 6) uncontrolled thyroid patients; 7) women who have had severe migraines within the last year or who have been diagnosed with thromboembolism, cerebrovascular disease, or serious cardiovascular disease; 8) women with atypical uterine bleeding after 1 yr of menopause; 9) women who have taken sleep inducers, antidepressants, selective estrogen receptor modulators, anti-hyperlipidemic drugs, antithrombotic drugs (Aspirin, Warfarin, and Clopidogrel), bisphosphonates, or calcitonin within 4 wk; 10) women who have taken plant hormones (isoflavone, flaxseed, pomegranate, horseradish, white sorghum, red shamrock, and red

ginseng products) in the form of supplements or medicines within 4 wk; 11) women who have continuously taken functional foods and herbal medicines that could affect bone health, blood lipid levels (triglyceride and cholesterol), and blood circulation within 4 wk; 12) women who were administered female hormone formulations within 6 mo; 13) women with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels exceeding 3 times the laboratory's normal upper limit; 14) women with creatinine levels exceeding 2 times the laboratory's normal upper limit; 15) women with a history of drug or alcohol abuse; 16) women who have performed intensive exercises (more than 10 h) within 3 mo; 17) women with hypersensitivity to the test drug or its ingredients; 18) women with clinically significant abnormalities based on mammographies or Pap smears (Category 0 or higher than 3 of Breast Imaging Reporting and Data System (BI-RADS)) is confirmed (in the case of BI-RADS Category 0, subject registration is possible after confirming additional test results; in the case of Pap smear, atypical squamous cell of undetermined significance can be registered); 19) women who have participated in other clinical trials within 1 mo of the start of the current study or who are planning to participate in another clinical trial during the study period; and, 20) in cases where the researchers decided that the subject is unsuitable to participate in this study.

### 2.2. Study design

This study was designed as a randomized, double-blind, placebo-controlled human study. For volunteers who signed the consent form to participate in this study, demographic, medical, and medication history surveys, physical examination, vital signs, physical measurements, laboratory tests, mammography or Pap smear, and MKI were performed. If the inclusion/exclusion criteria were met, the volunteer was registered through randomization. Subjects assigned to the RHC and placebo group received the test drug or placebo drug for 12 wk; the assignment ratio was 1 RHC group: 1 placebo group. After the baseline visit, the subjects returned after the 6th and 12th wk of test substance administration.

### 2.3. Randomization

Subjects are assigned to Groups A and B based on the pre-made allocation code of the block randomization method in the order of their participation in the clinical trial. The size of each block is either 6 or 12, and the ratio of each group is 1:1. The randomization table is a permutation of random numbers (random number of A or B) generated through SAS system's randomization program sequentially applied from subject number 1 created.

### 2.4. Preparation of Korean Red Ginseng herb extract complex

The subjects were instructed to take 2 tablets of the test substance (test drug or placebo drug) with water twice a day for 12 wk (2 tablets of 500 mg taken twice daily, 30 min before breakfast and dinner to reduce the interaction with food and increase the bioavailability). A 500 mg tablet of the test drug contained 375 mg red ginseng extract, 102.6 mg plant extract (peony, baekchuk, bokryeong, bamboo leaf, angelica), 22.4 mg other excipients (hydroxypropylmethylcellulose (C<sub>56</sub>H<sub>108</sub>O<sub>30</sub>), sucrose fatty acid ester, stearic acid (C<sub>18</sub>H<sub>36</sub>O<sub>2</sub>), and silicon dioxide (SiO<sub>2</sub>)). Meanwhile, a 500 mg tablet of the placebo contained 372.1 mg crystalline cellulose, 100 mg maltodextrin, 2.5 mg magnesium stearate, 10 mg silicon dioxide, 4.5 mg hydroxypropylmethylcellulose, 10 mg red ginseng flavor, and 0.9 mg food coloring.

### 2.5. Safety assessments

After randomization, 60 subjects in the RHC group and 60 subjects in the placebo group who took the test substance at least once were analyzed. Information on adverse reactions was evaluated by non-directive questioning on each visit during the study period. In addition, the subjects reported voluntarily during or between visits, and physical examination, laboratory tests, or other evaluations were carried out. During the investigation of adverse reactions, the date of onset and disappearance, the degree and result of the adverse reaction, the measures are taken in relation to the test substance and the causal relationship with the test substance, the name of the drug other than the test substance, and treatment of adverse reactions were included. At each visit, adverse reactions were checked, and all adverse reactions detected were monitored continuously until the relevant adverse reactions disappeared, stabilized, or the situation became explanatory. All observed adverse reactions were coded according to the medical dictionary for regulatory activities (MedDRA), and all adverse reactions during the study period were calculated and compared using the number of subjects and the number of occurrences. Moreover, the relevance to the test substance (test drug and control drug) and the severity of the adverse reactions were analyzed and presented. The relationship between the test substance and the adverse reaction was assessed by each subject as “Possibly related,” “Probably related,” “Definitely related,” or “Unknown.” Meanwhile, the adverse reactions reported as “Unknown” were treated as relevant to the test substance, and detailed information was presented separately. For clinical pathology tests (hematologic and blood chemistry tests), the subjects’ general health status was evaluated by conducting clinical pathology tests during the baseline and 12th wk after administering the test substance (or during the dropout visit). Subjects were instructed to come to the hospital after 8 h of fasting on the day of the examination. Vital signs (blood pressure and pulse) were measured during the baseline visit and on the 6th and 12th wk after taking the test substance. Changes in

blood estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and endometrial thickness were measured during the baseline and the 12th wk after taking the test substance.

### 2.6. Statistical analysis

Statistical analysis was performed using SAS (version 9.4, SAS Institute, Cary, North Caroline, USA). For demographic evaluation and safety evaluation analysis, a two-sided test was performed with a significance level of 0.05. For the *p*-values of all analyses, a *p*-value of <0.05 was considered significant. The proportion of subjects with an adverse reaction between groups was calculated and analyzed using the Chi-square test or Fisher’s exact test. For hematologic and blood chemistry test results, vital signs (blood pressure and pulse), bodyweight test results, blood E2, FSH, LH, and endometrial thickness, the intragroup comparison of the differences before and after intake was performed by paired *t*-test or Wilcoxon signed-rank test. In addition, the comparison between the RHC and the placebo groups was evaluated to determine if there is a statistically significant difference by performing a two-sample *t*-test or Wilcoxon rank-sum test depending on the satisfaction of normality.

## 3. Results

### 3.1. Characteristics of the study population

Between December 2018 and October 2019, a total of 120 participants were screened. The number of retaining participants and justification for dropping out in each phase were shown in the CONSORT flow diagram (Fig. 1). The study evaluation included all subjects who consumed the test substance at least once after randomization, and Table 1 compares the subjects’ demographic information and characteristics before administration. The examination of demographic information and characteristics before

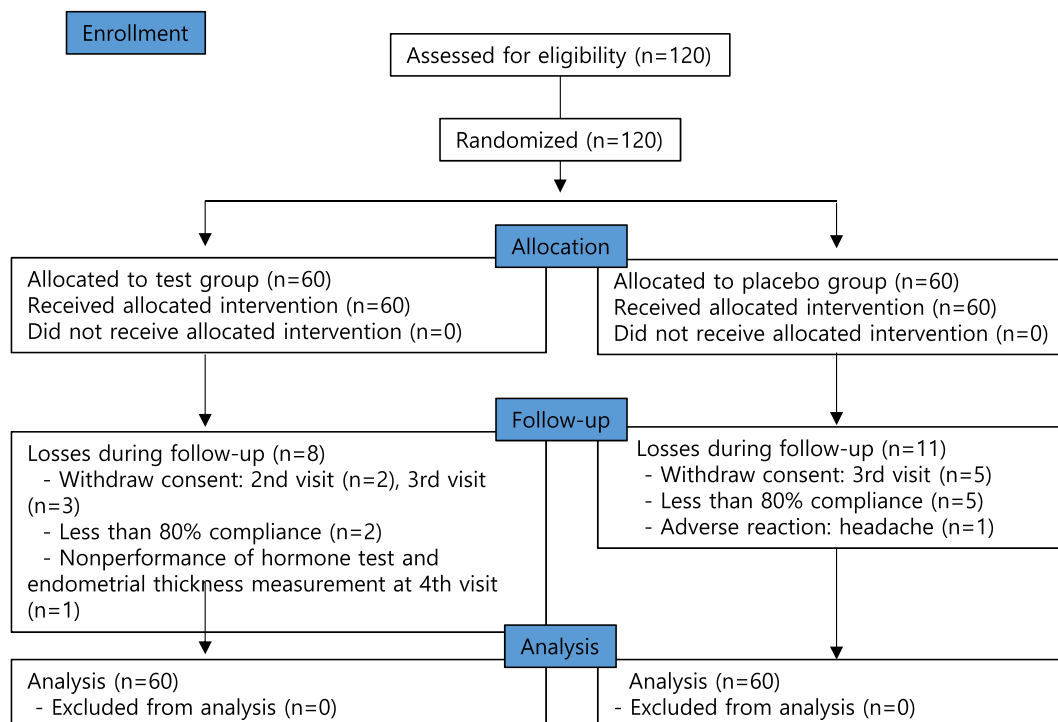


Fig. 1. CONSORT flow diagram of subjects selection and allocation.

**Table 1**  
Demographic information and pre-administration characteristics of human subjects.

		RHC Group (N = 60)	Placebo Group (N = 60)	Total (N = 120)	p-value
Gender n (%)	Female	60 (100.00)	60 (100.00)	120 (100.00)	–
Age (yr old)	Mean ± SD	54.40 ± 2.98	53.03 ± 3.53	53.72 ± 3.32	0.1036 <sup>a</sup>
	Min, Max	47.00, 59.00	46.00, 59.00	46.00, 59.00	
Last menstrual period (mo ago)	Mean ± SD	45.07 ± 36.10	41.13 ± 31.24	43.10 ± 33.68	0.6154 <sup>a</sup>
	Min, Max	12.00, 180.00	12.00, 120.00	12.00, 18.00	
Exercise n (%)	None	24 (40.00)	24 (40.00)	48 (40.00)	0.9633 <sup>b</sup>
	1–2 times/wk	15 (25.00)	12 (20.00)	27 (22.50)	
	3–4 times/wk	12 (20.00)	14 (23.33)	26 (21.67)	
	5–6 times/wk	5 (8.33)	5 (8.33)	10 (8.33)	
	Daily	4 (6.67)	5 (8.33)	9 (7.50)	
Smoking n (%)	Non-Smoker	57 (95.00)	56 (93.33)	113 (94.17)	
	Ex-Smoker (no smoking for >6 mo)	0 (0.00)	0 (0.00)	0 (0.00)	
	Smoker	3 (5.00)	4 (6.67)	7 (5.83)	
Amount of smoking (cigarette(s)/d)	For smokers, (___) cigarette(s)/d				1.0000 <sup>a</sup>
	Mean ± SD	7.33 ± 4.62	7.33 ± 2.52	7.33 ± 3.33	
	Min, Max	2.00, 10.00	5.00, 10.00	2.00, 10.00	
Duration of smoking (yr)	For smokers, (___) yr(s)				0.6374 <sup>a</sup>
	Mean ± SD	30.00	18.33 ± 2.58	21.25 ± 11.81	
	Min, Max	30.00	5.00, 30.00	5.00, 30.00	
Drinking n (%)	None	36 (60.00)	31 (51.67)	67 (55.83)	0.6069 <sup>c</sup>
	Stopped	3 (5.00)	3 (5.00)	6 (5.00)	
	Less than 1 bottle/wk	18 (30.00)	19 (31.67)	37 (30.83)	
	1 to 2 bottles/wk	3 (5.00)	7 (11.67)	10 (8.33)	
	More than 3 bottles/wk	0 (0.00)	0 (0.00)	0 (0.00)	
Stress self-assessmentn (%)	None	3 (5.00)	1 (1.67)	4 (3.33)	0.5590 <sup>c</sup>
	Low	39 (65.00)	35 (58.33)	74 (61.67)	
	High	16 (26.67)	21 (35.00)	37 (30.83)	
	Very high	2 (3.33)	3 (5.00)	5 (4.17)	

<sup>a</sup> p-value by Wilcoxon rank-sum test.

<sup>b</sup> p-value by Chi-square test.

<sup>c</sup> p-value by Fisher's exact test.

consumption showed no statistically significant difference between the intake groups.

### 3.2. Adverse reactions

The incidence and number of adverse reactions occurring after consuming the test substance are presented in Table 2. A total of 6

cases occurred in the RHC group, and adverse reactions included gastrointestinal disorders (1.67%), musculoskeletal disorders, connective tissue disorders (1.67%), nervous system disorders (1.67%), genital and breast disorders (1.67%), skin and subcutaneous tissue disorders (1.67%), and vascular disorders (1.67%). A total of 9 adverse reactions occurred in the placebo group, and the main adverse reactions were genital disorders (3.33%), subcutaneous

**Table 2**  
Adverse reactions and symptoms.

System organ class	RHC group N = 60		Placebo group N = 60		Total N = 120	
	n (%)	Case(s)	n (%)	Case(s)	n (%)	Case(s)
Gastrointestinal disorders	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
Gastrointestinal disorder	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
Infections and infestations	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Pneumonia	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Musculoskeletal and connective tissue disorders	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
Rotator cuff syndrome	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
Nervous system disorders	1 (1.67)	1	1 (1.67)	1	2 (1.67)	2
Headache	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Dizziness	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
Renal and urinary disorders	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Hypertonic bladder	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Reproductive system and breast disorders	1 (1.67)	1	2 (3.33)	2	3 (2.50)	3
Postmenopausal hemorrhage	1 (1.67)	1	1 (1.67)	1	2 (1.67)	2
Vaginal hemorrhage	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Skin and subcutaneous tissue disorders	1 (1.67)	1	2 (3.33)	2	3 (2.50)	3
Pruritus	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Rash	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
Acne	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Vascular disorders	1 (1.67)	1	2 (3.33)	2	3 (2.50)	3
Hot flash	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Rectal hemorrhage	0 (0.00)	0	1 (1.67)	1	1 (0.83)	1
Venous hemorrhage	1 (1.67)	1	0 (0.00)	0	1 (0.83)	1
<b>Total<sup>a</sup></b>	<b>6 (10.00)</b>	<b>6</b>	<b>8 (13.33)</b>	<b>9</b>	<b>14 (11.67)</b>	<b>15</b>

<sup>a</sup> Cumulative count (number of cases).

tissue disorders (3.33%), and vascular disorders (3.33%). Others were microbial contamination (1.67%), nervous system disorders (1.67%), and renal and urinary disorders (1.67%). However, there was no statistically significant difference between the administration groups ( $p = 0.5695$ ). No severe adverse reactions occurred in either the RHC or placebo groups, and two patients in the placebo group dropped out due to adverse reactions.

The symptom severity of adverse reactions and their relevance to the test substance are in Table S1. In investigating the severity of adverse reactions during the study period, 6 cases in the RHC group and 9 cases in the placebo group were mild. In terms of the relevance to the test substance, 1 case of “probably related” and 5 cases of “not related” were reported by subjects in the RHC group, and 2 cases of “probably related,” 1 case of “possibly related,” and 6 cases of “not related” were reported by subjects. There was no statistically significant difference between the two groups ( $p = 0.7363$ ).

Table S2 shows the adverse reactions that cannot be excluded from the relevance to the test substance. Based on the table, the RHC group has one case of gastrointestinal disorder, while the placebo group has one case each of gastrointestinal, nervous system, skin and subcutaneous tissue, and vascular disorders. In the RHC group, one subject fully recovered from gastrointestinal disorder without receiving a related treatment. In addition, one subject with pruritus and hot flash and another subject with headache fully recovered after discontinuation of administration in the placebo group. It is noteworthy that no severe adverse reactions were observed in this study.

### 3.3. Clinical pathology test

A clinical pathology test was performed during the baseline and 12th wk of administration. In addition, hematologic and blood chemistry tests were carried out (Tables 3 and 4).

**Table 3**  
Hematologic examination.

		RHC group		Placebo group		p-value
		N = 60		N = 60		
		n	Mean ± SD	n	Mean ± SD	
Red blood cell ( $10^6/\mu\text{L}$ )	Baseline (Visit 1)	60	4.38 ± 0.29	60	4.35 ± 0.35	0.6228 <sup>a</sup>
	12 wk (Visit 4)	54	4.31 ± 0.31	54	4.32 ± 0.34	
	Change from baseline	54	-0.08 ± 0.16	54	-0.04 ± 0.23	0.2273 <sup>a</sup>
	p-value <sup>c</sup>		0.0002		0.2287	
Hemoglobin (g/dL)	Baseline (Visit 1)	60	13.27 ± 0.78	60	13.15 ± 0.90	0.4363 <sup>a</sup>
	12 wk (Visit 4)	54	13.12 ± 0.87	54	13.14 ± 0.89	
	Change from baseline	54	-0.16 ± 0.55	54	-0.01 ± 0.61	0.1621 <sup>a</sup>
	p-value <sup>c</sup>		0.0312		0.9296	
Hematocrit (%)	Baseline (Visit 1)	60	39.22 ± 2.28	60	38.88 ± 2.55	0.4341 <sup>a</sup>
	12 wk (Visit 4)	54	38.28 ± 2.43	54	38.66 ± 2.52	
	Change from baseline	54	-1.00 ± 1.54	54	-0.17 ± 1.87	0.0136 <sup>a</sup>
	p-value <sup>c</sup>		<0.0001		0.5004	
White blood cell ( $10^6/\mu\text{L}$ )	Baseline (Visit 1)	60	5.23 ± 1.39	60	5.46 ± 1.46	0.5340 <sup>b</sup>
	12 wk (Visit 4)	54	5.19 ± 1.01	54	5.36 ± 1.24	
	Change from baseline	54	-0.04 ± 0.80	54	-0.11 ± 1.23	0.6873 <sup>b</sup>
	p-value <sup>d</sup>		0.8219		0.4826	
Platelet ( $10^6/\mu\text{L}$ )	Baseline (Visit 1)	60	253.77 ± 59.66	60	247.47 ± 49.22	0.7528 <sup>b</sup>
	12 wk (Visit 4)	54	246.74 ± 58.51	54	248.50 ± 51.38	
	Change from baseline	54	-5.04 ± 25.82	54	0.87 ± 20.82	0.1934 <sup>a</sup>
	p-value <sup>c</sup>		0.1575		0.7599	
Neutrophil (%)	Baseline (Visit 1)	60	50.37 ± 7.66	60	52.94 ± 7.49	0.0653 <sup>a</sup>
	12 wk (Visit 4)	54	49.11 ± 8.72	54	51.43 ± 7.45	
	Change from baseline	54	-0.74 ± 7.87	54	-0.96 ± 7.51	0.8839 <sup>a</sup>
	p-value <sup>c</sup>		0.4902		0.3510	
Lymphocyte (%)	Baseline (Visit 1)	60	39.37 ± 7.45	60	36.57 ± 7.26	0.0391 <sup>a</sup>
	12 wk (Visit 4)	54	40.52 ± 8.49	54	38.15 ± 7.03	
	Change from baseline	54	0.68 ± 7.56	54	1.14 ± 6.77	0.7412 <sup>a</sup>
	p-value <sup>c</sup>		0.5128		0.2236	
Monocyte (%)	Baseline (Visit 1)	60	7.13 ± 1.69	60	7.14 ± 1.39	0.7408 <sup>b</sup>
	12 wk (Visit 4)	54	7.27 ± 1.47	54	6.78 ± 1.31	
	Change from baseline	54	0.03 ± 1.53	54	-0.31 ± 1.14	0.1548 <sup>b</sup>
	p-value		0.7890 <sup>d</sup>		0.0539 <sup>c</sup>	
Eosinophil (%)	Baseline (Visit 1)	60	2.47 ± 1.71	60	2.70 ± 2.00	0.7210 <sup>b</sup>
	12 wk (Visit 4)	54	2.30 ± 1.45	54	2.90 ± 2.67	
	Change from baseline	54	-0.09 ± 1.31	54	0.08 ± 2.55	0.9485 <sup>b</sup>
	p-value <sup>c</sup>		0.6348 <sup>c</sup>		0.5725 <sup>d</sup>	
Basophil (%)	Baseline (Visit 1)	60	0.66 ± 0.40	60	0.64 ± 0.36	0.8743 <sup>b</sup>
	12 wks (Visit 4)	54	0.79 ± 0.37	54	0.74 ± 0.36	
	Change from baseline	54	0.12 ± 0.35	54	0.06 ± 0.36	0.4178 <sup>a</sup>
	p-value <sup>c</sup>		0.0153		0.1875	
Mean corpuscular volume (fl.)	Baseline (Visit 1)	60	89.64 ± 3.42	60	89.06 ± 4.85	0.6180 <sup>b</sup>
	12 wk (Visit 4)	54	88.99 ± 3.14	54	89.27 ± 3.96	
	Change from baseline	54	-0.57 ± 1.46	54	0.53 ± 4.07	0.0046 <sup>b</sup>
	p-value		0.0063 <sup>c</sup>		0.6590 <sup>d</sup>	

<sup>a</sup> Compared between groups, p-value for two-sample t-test.  
<sup>b</sup> Compared between groups; p-value for Wilcoxon rank-sum test.  
<sup>c</sup> Compared within groups, p-value for paired t-test.  
<sup>d</sup> Compared within groups; p-value for Wilcoxon signed-rank test.

**Table 4**  
Blood chemistry test.

		RHC group		Placebo group		p-value
		N = 60		N = 60		
		n	Mean ± SD	n	Mean ± SD	
AST (GOT)(IU/L)	Baseline (Visit 1)	60	28.15 ± 8.75	60	29.33 ± 12.12	0.8725 <sup>b</sup>
	12 wk (Visit 4)	54	27.89 ± 8.10	54	28.81 ± 10.65	
	Change from baseline	54	-0.46 ± 9.79	54	-1.09 ± 11.51	
	p-value <sup>d</sup>		0.9212		0.5273	
ALT (GPT) (IU/L)	Baseline (Visit 1)	60	25.18 ± 16.94	60	23.38 ± 18.29	0.1269 <sup>b</sup>
	12 wk (Visit 4)	54	21.98 ± 10.97	54	22.78 ± 18.37	
	Change from baseline	54	-3.85 ± 18.41	54	-0.46 ± 9.63	
	p-value <sup>d</sup>		0.3172		0.4576	
Protein (g/dL)	Baseline (Visit 1)	60	7.62 ± 0.36	60	7.58 ± 0.34	0.5667 <sup>a</sup>
	12 wk (Visit 4)	54	7.51 ± 0.41	54	7.57 ± 0.38	
	Change from baseline	54	-0.10 ± 0.29	54	-0.02 ± 0.40	
	p-value <sup>c</sup>		0.0145		0.6570	
Albumin (g/dL)	Baseline (Visit 1)	60	4.29 ± 0.14	60	4.32 ± 0.18	0.4055 <sup>b</sup>
	12 wk (Visit 4)	54	4.27 ± 0.15	54	4.31 ± 0.21	
	Change from baseline	54	-0.02 ± 0.15	54	-0.02 ± 0.19	
	p-value		0.5343 <sup>d</sup>		0.3865 <sup>c</sup>	
Glucose (mg/dL)	Baseline (Visit 1)	60	98.02 ± 8.32	60	98.18 ± 13.20	0.3182 <sup>b</sup>
	12 wk (Visit 4)	54	97.89 ± 8.25	54	97.94 ± 10.72	
	Change from baseline	54	-0.02 ± 8.78	54	-0.50 ± 10.56	
	p-value		0.9877 <sup>c</sup>		0.7287 <sup>d</sup>	
Total bilirubin (mg/dL)	Baseline (Visit 1)	60	0.63 ± 0.22	60	0.73 ± 0.30	0.1374 <sup>b</sup>
	12 wk (Visit 4)	54	0.62 ± 0.23	54	0.70 ± 0.26	
	Change from baseline	54	-0.02 ± 0.25	54	-0.03 ± 0.24	
	p-value		0.6162 <sup>c</sup>		0.7565 <sup>d</sup>	
Na (mEq/L)	Baseline (Visit 1)	60	140.77 ± 1.24	60	140.78 ± 1.79	0.8480 <sup>b</sup>
	12 wk (Visit 4)	54	140.57 ± 1.31	54	140.57 ± 1.35	
	Change from baseline	54	-0.24 ± 1.41	54	-0.11 ± 1.94	
	p-value <sup>d</sup>		0.1758		0.4306	
K (mEq/L)	Baseline (Visit 1)	60	4.19 ± 0.28	60	4.19 ± 0.39	0.8928 <sup>b</sup>
	12 wk (Visit 4)	54	4.15 ± 0.25	54	4.15 ± 0.30	
	Change from baseline	54	-0.03 ± 0.31	54	-0.03 ± 0.29	
	p-value		0.4838 <sup>c</sup>		0.9274 <sup>d</sup>	
Cl (mEq/L)	Baseline (Visit 1)	60	104.62 ± 1.70	60	104.08 ± 1.75	0.1034 <sup>b</sup>
	12 wk (Visit 4)	54	104.80 ± 1.68	54	104.59 ± 2.11	
	Change from baseline	54	0.09 ± 1.85	54	0.59 ± 2.00	
	p-value <sup>d</sup>		0.5831		0.0550	
Ca (mg/dL)	Baseline (Visit 1)	60	9.30 ± 0.30	60	9.35 ± 0.37	0.3839 <sup>b</sup>
	12 wk (Visit 4)	54	9.24 ± 0.31	54	9.35 ± 0.39	
	Change from baseline	54	-0.06 ± 0.30	54	-0.01 ± 0.37	
	p-value		0.3328 <sup>d</sup>		0.8535 <sup>c</sup>	
CK (IU/L)	Baseline (Visit 1)	60	87.28 ± 35.60	60	95.85 ± 71.32	0.8563 <sup>b</sup>
	12 wk (Visit 4)	54	113.70 ± 150.00	54	93.98 ± 52.60	
	Change from baseline	54	25.41 ± 146.22	54	-3.61 ± 72.04	
	p-value <sup>d</sup>		0.2407		0.9409	
Creatinine (mg/dL)	Baseline (Visit 1)	60	0.68 ± 0.10	60	0.69 ± 0.10	0.8398 <sup>b</sup>
	12 wk (Visit4)	54	0.68 ± 0.09	54	0.68 ± 0.09	
	Change from baseline	54	-0.01 ± 0.07	54	-0.01 ± 0.07	
	p-value <sup>c</sup>		0.3523		0.2152	
BUN (mg/dL)	Baseline (Visit 1)	60	14.41 ± 3.33	60	13.71 ± 3.24	0.2365 <sup>b</sup>
	12 wk (Visit 4)	54	13.69 ± 3.16	54	13.79 ± 3.31	
	Change from baseline	54	-0.65 ± 3.00	54	-0.08 ± 2.91	
	p-value <sup>c</sup>		0.1198		0.8489	
Uric acid (mg/dL)	Baseline (Visit 1)	60	4.36 ± 0.77	60	4.40 ± 0.92	0.8215 <sup>a</sup>
	12 wk (Visit 4)	54	4.17 ± 0.71	54	4.29 ± 0.85	
	Change from baseline	54	-0.21 ± 0.61	54	-0.08 ± 0.48	
	p-value <sup>c</sup>		0.0153		0.2102	
γ-GTP (IU/L)	Baseline (Visit 1)	60	24.65 ± 21.52	60	24.03 ± 16.34	0.9706 <sup>b</sup>
	12 wk (Visit 4)	54	23.78 ± 19.22	54	27.33 ± 19.42	
	Change from baseline	54	-1.56 ± 9.91	54	2.69 ± 9.66	
	p-value <sup>d</sup>		0.6154		0.0612	

AST, aspartate aminotransferase; GOT, glutamic-oxaloacetic transaminase; ALT, alanine aminotransferase; GPT, glutamic pyruvic transaminase; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; CK, creatine kinase; BUN, blood urea nitrogen; γ-GTP, gamma-glutamyl transpeptidase.

- <sup>a</sup> Compared between groups, p-value for two-sample *t*-test.
- <sup>b</sup> Compared between groups, p-value for Wilcoxon rank-sum test.
- <sup>c</sup> Compared within groups, p-value for paired *t*-test.
- <sup>d</sup> Compared within groups; p-value for Wilcoxon signed-rank test.

The result of analysis of the amount of hematocrit change in the hematologic test shows that after 12 wk of consumption, hematocrit levels decreased by  $1.00\% \pm 1.54\%$  in the RHC group ( $p < 0.0001$ ) and decreased by  $0.17\% \pm 1.87\%$  in the placebo group ( $p = 0.5004$ ), showing a statistically significant difference between the groups ( $p = 0.0136$ ). Meanwhile, the analysis of the change in the mean corpuscular volume showed that after 12 wk of consumption, it decreased by  $0.57 \pm 1.46$  fL in the RHC group ( $p = 0.0063$ ) and increased by  $0.53 \pm 4.07$  fL in the placebo group ( $p = 0.6590$ ), indicating that there was no statistically significant difference between the groups ( $p = 0.0046$ ). Thus, the change was within the normal range, and there was no statistically significant difference between the groups after 12 wk of consumption in other hematologic and blood chemistry test measurements.

### 3.4. Vital signs and weight

Table S3 shows the analysis results of vital signs (blood pressure and pulse) and body weight. In the systolic blood pressure change analysis, the observed pressure decreased by  $3.53 \pm 8.71$  mmHg ( $p = 0.0054$ ) in the RHC group and  $5.40 \pm 10.35$  mmHg ( $p = 0.0003$ ) in the placebo group, showing no statistically significant difference between the two groups, after the 6-wk drug administration. However, after 12 wk of consumption, the pressure increased by  $1.56 \pm 11.08$  mmHg ( $p = 0.2999$ ) in the RHC group, while it decreased by  $3.70 \pm 10.83$  mmHg ( $p = 0.0151$ ) in the placebo group, indicating a statistically significant difference between the groups ( $p = 0.0136$ ). All changes were within the normal range, and there was no statistically significant difference between the two groups after 6 and 12 wk of consumption in the results of the pulse, diastolic blood pressure, and body weight analyses.

Meanwhile, the changes in E2, FSH, and LH levels showed no significant difference in both groups after 12 wk compared to baseline (Table 5), and there was no statistically significant difference between the groups. As for the amount of change in endometrial thickness at baseline and 12 wk, there were no significant differences between baseline and 12 wk for each group and between the RHC and placebo groups.

**Table 5**  
Changes in estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and endometrial thickness.

		RHC group		Placebo group		p-value
		N = 60		N = 60		
		n	Mean $\pm$ SD	n	Mean $\pm$ SD	
E2 (pg/mL)	Baseline (Visit 2)	60	27.82 $\pm$ 32.60	60	38.27 $\pm$ 48.18	0.4162 <sup>b</sup>
	12 wk (Visit4)	54	28.72 $\pm$ 29.84	54	35.89 $\pm$ 47.40	
	Change from baseline	54	0.73 $\pm$ 42.73	54	-3.10 $\pm$ 52.88	0.2272 <sup>b</sup>
	p-value <sup>c</sup>		0.3855		0.5176	
FSH (mIU/mL)	Baseline (Visit 2)	60	74.29 $\pm$ 25.40	60	74.38 $\pm$ 32.03	0.9862 <sup>a</sup>
	12 wk (Visit 4)	54	75.61 $\pm$ 23.56	54	75.98 $\pm$ 30.05	
	Change from baseline	54	1.50 $\pm$ 25.98	54	1.43 $\pm$ 16.47	0.6896 <sup>b</sup>
	p-value		0.6739 <sup>c</sup>		0.5235 <sup>4</sup>	
LH (mIU/mL)	Baseline (Visit 2)	60	39.35 $\pm$ 17.58	60	35.64 $\pm$ 16.73	0.2636 <sup>b</sup>
	12 wk (Visit 4)	54	36.08 $\pm$ 10.10	54	35.54 $\pm$ 11.18	
	Change from baseline	54	-3.38 $\pm$ 15.44	54	-0.36 $\pm$ 8.57	0.1745 <sup>b</sup>
	p-value <sup>c</sup>		0.0787		0.8886	
Endometrial thickness (mm)	Baseline (Visit 2)	60	2.52 $\pm$ 0.81	60	2.87 $\pm$ 1.85	0.8253 <sup>b</sup>
	12 wk (Visit4)	54	2.58 $\pm$ 1.32	54	3.04 $\pm$ 1.85	
	Change from baseline	54	0.09 $\pm$ 1.54	54	0.19 $\pm$ 1.75	0.3530 <sup>b</sup>
	p-value <sup>c</sup>		0.6805		0.5573	

E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

<sup>a</sup> Compared between groups, p-value for two-sample t-test.

<sup>b</sup> Compared between groups, p-value for the Wilcoxon rank sum test.

<sup>c</sup> Compared within groups; p-value for Wilcoxon signed-rank test.

## 4. Discussion

In this study, the safety of RHC, a mixture of red ginseng and herb extract, which has been proven to be effective for menopausal symptoms, was assessed. Safety was confirmed by menopausal women's daily consumption of 2 g RHC for 12 wk. As for the number of adverse reactions during the study period, six adverse reactions were reported in the RHC group and nine adverse reactions in eight placebo group subjects. However, there was no statistically significant difference between the groups, and there were no severe adverse reactions in either group. In the RHC group, there was only one case of an adverse reaction that could not be excluded from the relevance to the test substance, gastrointestinal disorder, which was naturally improved. In the placebo group, three cases were reported, and it was confirmed that all of them were fully cured. Hematocrit and systolic blood pressure were significantly decreased in both groups at 12 wk, but all changes were within the normal range. There were no other changes in hematologic tests, endometrial ultrasonography, and female hormone level measurement. The average postmenopause period accounts for more than one-third of a woman's lifespan, and the loss of ovarian function causes physical and psychological changes due to the decrease in sex hormones, and some overlook menopause symptoms as part of the aging process. Currently, the number of women at least 60 yr old with symptoms of menopause is increasing significantly due to an increase in the elderly population because of worldwide aging. Considering that life expectancy will be further extended in the future, treatment of menopausal symptoms in the menopausal period is essential for maintaining health and quality of life for women [19]. Because menopausal symptoms occur when female hormones are no longer produced due to the loss of ovarian function, the treatment method that includes a supplement of "female hormones" made of drugs is known as "hormone replacement therapy." Hormone replacement therapy has been used globally to treat menopausal symptoms for the past 40 yr. However, an increasing number of patients seek complementary and alternative therapies because of the risk of developing breast cancers and other harmful effects on the cardiovascular system when used long-term [20]. As a complementary and

alternative therapy, various products containing plant estrogens, also called phytoestrogens, are consumed by women. Phytoestrogens have a chemical structure similar to that of the female hormone estrogen and act similarly to estrogen in the body. Examples include isoflavones, abundantly found in soybeans and ingredients extracted from *C. heracleifolia*, evening primrose, red clover, and pomegranate [21]. Although red ginseng does not contain phytoestrogens, it is effective for menopausal symptoms as it can reduce the KL, which scores menopausal symptoms like hot flashes, sweating, and depression without affecting female hormones [18] and improved sexual function [22].

Moreover, among various diseases developed after menopause, red ginseng has been proven to be effective for improving cardiovascular disease [18], reducing cholesterol [23], reducing oxidative stress [24], and treating mental disorders by reducing stress hormones [25]. Red ginseng shows various effects because it contains ginsenosides, polysaccharides, peptides, alkaloids, phenols and phenolic compounds, essential oils, and polyacetylenes. These components interact with each other to maintain homeostasis in the body [26]. In addition, red ginseng is thought to alleviate menopausal symptoms due to hormonal imbalance by maintaining the body's homeostasis during the menopausal period as these components work together. Even natural substances with tremendous effects are useless if they cause side effects. As with all pharmaceuticals, safety is the most important consideration. Therefore, as a traditional complementary and alternative therapy that can alleviate menopausal symptoms, 12 wk of RHC consumption may be considered safe for the human body. In general, there are many studies on the safety of intake of red ginseng and dietary supplements for 12 wk, but this study was conducted with less than 120 subjects and observations for a short period of 12 wk.

## 5. Conclusion

In conclusion, the intake of RHC as a traditional complementary and alternative therapy of menopausal syndrome at a daily dose of 2 g for 12 wk was safe in menopausal women. However, further research is needed on the safety of RHC intake for a long period in large-scale menopausal subjects.

## Acknowledgements

All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgements and have given us their written permission to be named. If we have not included an Acknowledgements, then that indicates that we have not received substantial contributions from non-authors.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgr.2021.11.008>.

## References

- Takahashi TA, Johnson KM. Menopause. *Med Clin North Am* 2015;99(3):521–34. <https://doi.org/10.1016/j.mcna.2015.01.006>.
- Kim YH, Ha EH, Shin SJ. A study on the menopausal symptoms and quality of life in middle aged women. *J Kor Acad Nurs* 2003;33(5):601–8. <https://doi.org/10.4040/jkan.2003.33.5.601> (In Korean).
- Posadzki P, Lee MS, Moon TW, Choi TY, Park TY, Ernst E. Prevalence of complementary and alternative medicine (CAM) use by menopausal women: a systematic review of surveys. *Maturitas* 2013;75(1):34–43. <https://doi.org/10.1016/j.maturitas.2013.02.005>.
- Huntley AL, Ernst E. A systematic review of herbal medicinal products for the treatment of menopausal symptoms. *Menopause* 2003;10(5):465–76. <https://doi.org/10.1097/01.GME.0000058147.24036.B0>.
- Chen L-R, Ko N-Y, Chen K-H. Isoflavone supplements for menopausal women: a systematic review. *Nutrients* 2019;11(11):2649. <https://doi.org/10.3390/nu11112649>.
- Fritz H, Seely D, McGowan J, Skidmore B, Fernandes R, Kennedy DA, Cooley K, Wong R, Sagar S, Balneaves LG, et al. Black cohosh and breast cancer: a systematic review. *Integr Cancer Ther* 2014;13(1):12–29. <https://doi.org/10.1177/1534735413477191>.
- Al-Akoum M, Maunsell E, Verreault R, Provencher L, Otis H, Dodin S. Effects of *Hypericum perforatum* (St. John's wort) on hot flashes and quality of life in perimenopausal women: a randomized pilot trial. *Menopause* 2009;16(2):307–14. <https://doi.org/10.1097/gme.0b013e31818572a0>.
- Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomson CA, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *J Am Med Assoc* 2003;289(24):3243–53. <https://doi.org/10.1001/jama.289.24.3243>.
- Holmberg L, Iversen O-E, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, Jassem J, Dobaczewska D, Fjosne E, Peralta O, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* 2008;100(7):475–82. <https://doi.org/10.1093/jnci/djn058>.
- Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. *J Am Med Assoc* 2004;291(13):1610–20. <https://doi.org/10.1001/jama.291.13.1610>.
- Brekhman II, Dardymov IV. New substances of plant origin which increase non-specific resistance. *Annu Rev Pharmacol* 1968;8:419–30. <https://doi.org/10.1146/annurev.pa.09.040169.002223>.
- Patela S, Rauf A. Adaptogenic herb ginseng (*Panax*) as medical food: status quo and future prospects. *Biomed Pharmacother* 2017;85:120–7. <https://doi.org/10.1016/j.biopha.2016.11.112>.
- Korea Ministry of Food and Drug Safety. Health functional food code. 2021. p. 66–7. <https://www.mfds.go.kr>.
- Shim M-K, Lee Y-J. Estrogen receptor is activated by Korean Red Ginseng in vitro but not in vivo. *J Ginseng Res* 2012;36(2):169–75. <https://doi.org/10.5142/jgr.2012.36.2.169>.
- Ji S-M, Lee Y-J. Estrogen, androgen, and retinoic acid hormone activity of ginseng saponin. *J Ginseng Res* 2003;27(3):93–7. <https://doi.org/10.5142/JGR.2003.27.3.093>.
- Hien TT, Kim ND, Pokharel YR, Oh SJ, Lee MY, Kang KW. Ginsenoside Rg3 increases nitric oxide production via increases in phosphorylation and expression of endothelial nitric oxide synthase: essential roles of estrogen receptor-dependent PI3-kinase and AMP-activated protein kinase. *Toxicol Appl Pharmacol* 2010;246:171–83. <https://doi.org/10.1016/j.taap.2010.05.008>.
- Kim H-R, Cui Y, Hong S-J, Shin S-J, Kim D-S, Kim N-M, So S-H, Lee S-K, Kim E-C, Chae S-W, et al. Effect of ginseng mixture on osteoporosis in ovariectomized rats. *Immunopharmacol Immunotoxicol* 2008;30(2):333–45. <https://doi.org/10.1080/08923970801949125>.
- Kim SY, Seo SK, Choi YM, Jeon YE, Lim KJ, Cho S, Choi YS, Lee BS. Effects of red ginseng supplementation on menopausal symptoms and cardiovascular risk factors in postmenopausal women: a double-blind randomized controlled trial. *Menopause* 2012;19(4):461–6. <https://doi.org/10.1097/gme.0b013e3182325e4b>.
- Shorey S, Ng ED. The experiences and needs of Asian women experiencing menopausal symptoms: a meta-synthesis. *Menopause* 2019;26(5):557–69. <https://doi.org/10.1097/gme.0000000000001269>.
- Paciuc J. Hormone therapy in menopause. *Adv Exp Med Biol* 2020;1242:89–120. [https://doi.org/10.1007/978-3-030-38474-6\\_6](https://doi.org/10.1007/978-3-030-38474-6_6).
- Sirotkin AV, Harrath AH. Phytoestrogens and their effects. *Eur J Pharmacol* 2014;741:230–6. <https://doi.org/10.1016/j.ejphar.2014.07.057>.
- Oh K-J, Chae M-J, Lee H-S, Hong H-D, Park K. Effects of Korean Red Ginseng on sexual arousal in menopausal women: placebo-controlled, double-blind crossover clinical study. *J Sex Med* 2010;7:1469–77. <https://doi.org/10.1111/j.1743-6109.2009.01700.x>.
- Kwon Y-J, Jang S-N, Liu K-H, Jung D-H. Effect of Korean Red Ginseng on cholesterol metabolites in postmenopausal women with hypercholesterolemia: a pilot randomized controlled trial. *Nutrients* 2020 Nov 8;12(11):3423. <https://doi.org/10.3390/nu12113423>.
- Seo SK, Hong Y, Yun BH, Chon SJ, Jung YS, Park JH, Cho S, Choi YS, Lee BS. Antioxidative effects of Korean Red Ginseng in postmenopausal women: a double-blind randomized controlled trial. *J Ethnopharmacol* 2014;154(3):753–7. <https://doi.org/10.1016/j.jep.2014.04.051>.
- Tode T, Kikuchi Y, Hirata J, Kita T, Nakata H, Nagata I. Effect of Korean Red Ginseng on psychological functions in patients with severe climacteric syndromes. *Int J Gynaecol Obstet* 1999;67(3):169–74. [https://doi.org/10.1016/s0020-7292\(99\)00168-x](https://doi.org/10.1016/s0020-7292(99)00168-x).
- Hyun SH, Kim SW, Seo HW, Youn SH, Kyung JS, Lee YY, In G, Park C-K, Han C-K. Physiological and pharmacological features of the non-saponin components in Korean Red Ginseng. *J Ginseng Res* 2020;44(4):527–37. <https://doi.org/10.1016/j.jgr.2020.01.005>.