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Research article

Safety and tolerability of Korean Red Ginseng in healthy adults: a multicenter, double-blind, randomized, placebo-controlled trial



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ABSTRACT

Background: Korean Red Ginseng (KRG) has been used in Asia for its various biological effects, but no studies have investigated the safety of its long-term intake. Therefore, the present study evaluated the safety of KRG intake for 24 weeks.

Methods: We randomized 1,000 participants in a 1:1 ratio into two groups, which were treated daily with 2 g of KRG or a placebo for 24 weeks. The primary endpoint was all adverse events and adverse drug reactions (ADRs) that occurred after KRG or placebo administration, which were reported at week 4, 12, and 24 after the baseline visit.

Results: In total, 192 and 211 participants experienced adverse events in the KRG and placebo groups (39.2% and 42.0%, respectively; $p = 0.361$), and 59 and 57 KRG- and placebo-treated individuals reported ADRs (12.0% and 11.4%, respectively; $p = 0.737$). The frequently occurring ADRs were pruritus (2.0%), headache (1.6%), diarrhea (1.4%), and dizziness (1.2%) in the KRG group and pruritus (2.0%), headache (1.8%), dizziness (1.6%), rash (1.4%), and diarrhea (1.2%) in the placebo group. Discontinuation of drug administration due to ADRs was reported in 13 participants, six (1.2%) and seven (1.4%) in the KRG and placebo groups, respectively ($p = 0.814$). No significant abnormal changes were revealed by anthropometric, laboratory, and vital sign measurements in the KRG group compared with those in the placebo group.

Conclusion: The present study confirms the safety and tolerability of daily intake of 2 g of KRG for 24 weeks by healthy adults.

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1. Introduction

Ginseng is one of the most popular herbs worldwide. It has been used in many countries for several thousands of years in traditional medicine and as a nutritional supplement that improves the well-being and quality of life and promotes longevity [1,2]. Of the many ginseng species identified, Asian ginseng (*Panax ginseng* Meyer), which is found throughout East Asia and Russia and has been harvested in other parts of Asia, is the most commonly consumed species and is well established as a therapeutic herb [3]. Various processing methods and formulations of Asian ginseng have been developed for maintaining or improving the original ingredients of fresh ginseng. Korean Red Ginseng (KRG), a processed formulation of Asian ginseng, is produced by steaming fresh ginseng with water vapor and then allowing it to dry. KRG is used in various traditional oriental medicine formulations and as a nutritional supplement in Asian countries despite its specific processing method and related high cost.

Several studies have reported the positive biological effects of KRG, including blood pressure regulation [4], plasma glucose control [5], neurological improvement [6], hepatoprotection [7], as well as anticancer [8] and antioxidant properties [9]. KRG is rich in biologically active ginsenosides [10] because the steaming process stabilizes ginseng metabolism and transforms its active constituents into more lipophilic compounds with a higher bioavailability [1].

Although its efficacy and usefulness have been established, KRG and other similar herbal formulations contain various components, which make it difficult to predict their toxicity after administration. Thus, the safety of KRG intake is a major concern, and safety-related evaluations are needed. However, few studies have reported the safety of KRG intake [11], and no studies have been conducted on the safety of its long-term intake. Therefore, the present study aimed to evaluate the health-related safety of KRG intake for 24 weeks in a multicenter, double-blind, randomized, placebo-controlled trial.

2. Materials and methods

2.1. Study population

The study participants were adults who visited one of 13 medical centers in South Korea. The inclusion criteria were adults aged 19 years or above, who consented to participate in this study and voluntarily signed the written informed consent form. The exclusion criteria were as follows: (1) pregnancy or breastfeeding; (2) a history of hypersensitivity to ingredients of KRG; (3) renal dysfunction (≥ 1.5 times the normal upper limit of serum creatinine levels); (4) elevated serum aspartate aminotransferase or alanine aminotransferase levels ($>$ three times the normal upper limit); (5) medical conditions that could affect the study outcomes, including cardiovascular and gastrointestinal diseases or malignancies; (6) autoimmune diseases; (7) uncontrolled hypertension (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg) and related conditions, such as diabetes (glycated hemoglobin $\geq 8.0\%$) or dyslipidemia (low-density lipoprotein cholesterol ≥ 160 mg/dL); (8) the use of sulfonylureas and insulin as antidiabetic agents; (9) thyroid dysfunction; (10) neurological or psychiatric disorders or the use of an antipsychotic medication for at least 2 weeks within 4 weeks before the screening visit; (11) the use of steroids within 1 week before the screening visit; (12) the use of traditional herbs within 4 weeks before the screening visit; and (13) the use of dietary supplements other than vitamins and minerals within 2 weeks before the randomization. The study was

approved by the institutional review board at each participating site and registered at [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT02428998).

2.2. Study design

This was a 24-week, randomized, double-blind, placebo-controlled clinical trial conducted to assess the safety of KRG in Korean healthy adults. The volunteers who met the study inclusion and exclusion criteria were allocated at a 1:1 ratio to two groups, KRG- and placebo-administered groups, by the stratified block randomization method. The stratification factors considered were the study site and whether medications were used or not for chronic diseases. Over a 24-week period, the groups received a daily dose of 2 g of KRG or the placebo (2 tablets of 500 mg twice daily 30 minutes before breakfast and dinner to reduce the interaction with food and increase the bioavailability). After the baseline visit, the participants were followed up at week 4, 12, and 24 with clinical evaluations, including recording of adverse events (AEs), measurement of vital signs, physical examination, and anthropometric and laboratory measurements related to AEs.

2.3. Preparation of KRG

The Korean Herbal Pharmacopoeia recommends a daily KRG intake of 1.5–10 g for medicinal purposes, which can be increased up to 30 g; however, for a dietary supplement, the KRG dose is limited to 2.4–80 mg of ginsenosides per day [12]. Therefore, the KRG dose used in this study was 2 g of KRG tablets/day, which contained the ginsenosides Rb1 (8.03 mg/g), Rc (3.29 mg/g), Rb2 (2.80 mg/g), Rg3 (2.50 mg/g), Rf (1.47 mg/g), Re (1.29 mg/g), Rg1 (1.18 mg/g), and Rd (1.0 mg/g). The KRG formulation used in this study was made with steamed 6-year-old *P. ginseng* according to the International Organization for Standardization ISO 19610:2017 requirements. *P. ginseng* and the KRG formulation met the quality control criteria for the acceptable levels of pesticides and contaminants. The KRG tablets were produced by dehydration of a KRG extract (3 g per 2 g of tablets) and were light brown in color. The placebo tablets contained corn starch and cellulose with the KRG flavor and color, and the total content was the same as that of the KRG tablets. The KRG tablets were produced via Good Manufacturing Practices by Korea Ginseng Corporation, South Korea. The placebo tablets were made by Natural F&P, South Korea.

2.4. Safety assessments

AEs were defined as newly developed or worsened unfavorable and unintended signs, symptoms, or diseases that occurred in the participants after administration of KRG or the placebo. Serious AEs (SAEs) were defined as any unanticipated medical occurrence, resulting in a persistent or significant disability or incapacity, hospitalization or prolongation of the existing hospitalization, death, or life-threatening outcomes after administration of KRG or the placebo. Adverse drug reactions (ADRs) were defined as an appreciably harmful or unpleasant reaction, resulting from the administration of KRG or the placebo. The intensity of AEs was assessed based on the following classification: Grade 1 (mild), symptoms that required no intervention and did not limit the daily activities; Grade 2 (moderate), symptoms that improved with minimal intervention and might limit daily activities; Grade 3 (severe), symptoms that led to difficulty in normally performing daily activities; Grade 4 (fatal/disabling), a life-threatening or disabling condition requiring urgent intervention; and Grade 5 (death). The causal relationship between AEs and KRG or placebo administration was assessed as definitely, probably, possibly,

probably not, or definitely not related or was categorized as unassessable.

The primary endpoint was all AEs and ADRs that occurred during the 24-week period after the initial KRG or placebo administration, and the AE and ADR information was assessed through interviews.

The secondary endpoints included all AEs and ADRs reported in the specific AE-related questionnaire, such as headache, diarrhea, itching sensation, dizziness, loss of appetite, insomnia, rash, vaginal bleeding, and mood change symptoms, AEs and ADRs with the intensity of \geq Grade 3, as well as cardiovascular-, gastrointestinal-, and neuropsychiatric-related AEs and ADRs that occurred after KRG or placebo administration.

The investigator was responsible for evaluating all AEs based on the date of onset/resolution, duration, intensity, outcome, and the causal relationship to the administration of the study materials. All AEs and SAEs that occurred throughout the study period were recorded on the AE page of the case report form, reported to the institutional review board, and followed up until the participant recovered to the baseline condition or the investigator decided not to perform further monitoring.

In addition, the vital signs (blood pressure, heart rate, and body temperature) were monitored, and physical examinations and clinical laboratory tests were performed at baseline and during the 4-, 12- and 24-week visits, whereas 12-lead electrocardiography (ECG) was conducted at baseline and at 24 weeks. The measurements of blood pressure were performed in a sitting position; the heart rate, body temperature, weight, and height were measured after a rest period of at least 5 minutes. In the case of a significant finding that met the AE definition, the investigators recorded it on the AE page of the case report form. The complete blood count, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and uric acid levels were measured, and urinalysis was performed. The results of the laboratory measurements were classified as normal or abnormal based on the normal range for each study site. The investigators recorded the findings as abnormal when the results were determined to have clinical significance.

2.5. Other

Self-reported information on the age, sex, smoking, alcohol consumption, the amount of physical activity, dietary intake, medical conditions, including past or present medical problems, and a history of surgery were obtained.

2.6. Statistical analysis

For AEs with an incidence of 5%, the number of individuals required to detect an AE showing at least a twofold difference between the KRG and placebo groups was 497 individuals per group, with a two-sided significance level of 0.05 and an 85% statistical power. For AEs with an incidence of 1%, the number of individuals required to detect an AE showing at least a fourfold difference between the KRG and placebo groups was estimated to be 485 individuals per group, with a two-sided significance level of 0.05 and an 85% statistical power. Therefore, the sample size was set to 1,000 participants (500 per group) to obtain an 85% statistical power and a significance level of 0.05.

The safety analyses included all randomized participants who received at least one dose of the KRG or placebo tablets and underwent at least one safety assessment. The demographic characteristics, vital signs, and 12-lead ECG, laboratory test, and physical examination data were compared using an independent *t* test or Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for dichotomous variables. The differences in AE or ADR prevalence in both the groups were analyzed using the chi-square test or Fisher's exact test. Statistical analyses were conducted using the SAS software program (version 9.1.3; SAS Institute, Cary, NC, USA), and a $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

The disposition of participants is shown in Fig. 1. Between October 2014 and November 2015, 1,152 participants were screened

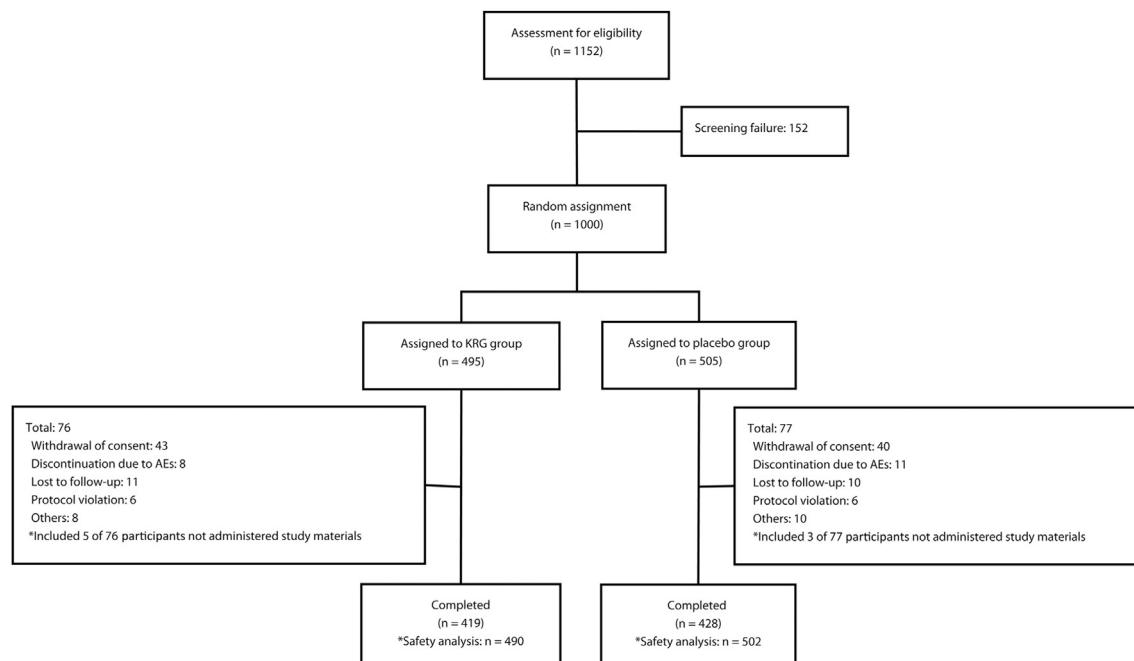


Fig. 1. Study design for evaluating the health-related safety and tolerability of the intake of Korean Red Ginseng for 24 weeks. AEs, adverse events; KRG, Korean Red Ginseng.

across 13 centers. Subsequently, 1,000 participants were randomized into two groups, the KRG- and placebo-treated groups ($n = 495$ and $n = 505$, respectively), and finally, 992 participants (490 and 502 from the KRG and placebo groups, respectively) were included in the safety analysis; eight participants were excluded because of nonadministration of KRG or placebo after randomization. A total of 847 participants (419 and 428 from the KRG and placebo groups, respectively) completed this study (completion rate: 84.7%). The reasons for the 153 discontinuations were as follows: withdrawal ($n = 83$), loss to follow-up ($n = 21$), intolerable AEs ($n = 19$), protocol violation ($n = 12$), and others ($n = 18$).

The demographic and baseline characteristics did not differ between the KRG and placebo groups (Table 1). The average $\geq 80\%$ compliance rate with the intake of the study materials was 84.5% (84.3% and 84.7% in the KRG and placebo groups, respectively).

3.2. Safety

3.2.1. Primary outcome

The AEs and ADRs occurring after KRG or placebo administration are shown in Table 2. Overall, 734 AEs occurred in 403 (40.6%) of the 992 participants. Of those, 192 (39.2%) and 211 (42.0%) participants were in the KRG and placebo groups, respectively, and no significant difference in the prevalence of AEs between the groups was observed ($p = 0.361$). The incidence rate of SAEs did not significantly differ between the KRG and placebo groups either ($p = 0.964$), and no AEs leading to death were reported. A total of 184 ADRs occurred in 116 (11.7%) of the 992 participants, including 59 (12.0%, 92 events) and 57 (11.4%, 92 events) participants in the KRG and placebo groups, respectively, and the proportion of participants with ADRs did not differ significantly between the groups ($p = 0.737$). The permanent discontinuation of administration due to AEs was reported in 19 participants (8 and 11 in the KRG and placebo groups, respectively), and no significant difference was found between the groups ($p = 0.521$). Thirteen participants

Table 1
Baseline characteristics and treatment compliance of study participants

Variables	KRG ($n = 490$)	Placebo ($n = 502$)	Total ($n = 992$)	p
Age (yr)	45.8 \pm 13.2	46.3 \pm 13.6	46.1 \pm 13.4	0.431
Sex (Male)	133 (27.1)	135 (26.9)	268 (27.0)	0.929
Height (cm)	162.6 \pm 8.1	162.0 \pm 8.8	162.3 \pm 8.5	0.180
Weight (kg)	61.3 \pm 10.7	61.9 \pm 11.6	61.6 \pm 11.1	0.499
Body mass index (kg/m^2)	23.1 \pm 2.9	23.5 \pm 3.1	23.3 \pm 3.0	0.137
Waist circumference (cm)	80.5 \pm 9.0	81.5 \pm 9.6	81.0 \pm 9.3	0.087
Current smoking				
Yes	28 (5.7)	36 (7.2)	64 (6.4)	0.267
Alcohol drinking				
Yes	276 (56.3)	261 (52.0)	537 (54.1)	0.182
Exercise				
Yes	273 (55.7)	273 (54.4)	546 (55.0)	0.673
Intake of dietary supplements				
Yes	13 (2.6)	14 (2.8)	27 (2.7)	0.895
Chronic diseases				
Yes	221 (45.1)	211 (42.0)	432 (43.5)	0.329
Medication	101 (20.6)	109 (21.7)	210 (21.2)	0.671
Study materials				
Overall compliance $\geq 80\%$	413 (84.3)	425 (84.7)	838 (84.5)	0.870
Total dose (tablets)	583.2 \pm 158.7	576.1 \pm 165.5	579.6 \pm 162.1	0.423
Treatment duration (days)	162.0 \pm 35.5	160.5 \pm 35.7	161.2 \pm 35.6	0.748

Values are expressed as n (%) for dichotomous variables and mean \pm standard deviation for continuous variables
KRG, Korean Red Ginseng

Table 2
Summary of the safety profiles of the study materials.

	KRG ($n = 490$)	Placebo ($n = 502$)	Total ($n = 992$)	p
Participants				
With all AEs	192 (39.2)	211 (42.0)	403 (40.6)	0.361
With SAEs	7 (1.4)	7 (1.4)	14 (1.4)	0.964
Discontinued due to AEs	8 (1.6)	11 (2.2)	19 (1.9)	0.521
With ADRs	59 (12.0)	57 (11.4)	116 (11.7)	0.737
Discontinued due to ADRs	6 (1.2)	7 (1.4)	13 (1.3)	0.814
With serious ADRs	0 (0.0)	0 (0.0)	0 (0.0)	–
Discontinued due to serious ADRs	0 (0.0)	0 (0.0)	0 (0.0)	–
Died	0 (0.0)	0 (0.0)	0 (0.0)	–
Events				
All AEs	345	389	734	–
SAEs	7	7	14	–
ADRs	92	92	184	–
Serious ADRs	0	0	0	–

Values are expressed as n (%) or as n

ADRs, adverse drug reactions; AEs, adverse events; KRG, Korean Red Ginseng; SAEs, serious adverse events

discontinued the study material administration because of ADRs, including six (1.2%) in the KRG group and seven (1.4%) in the placebo group, with no significant difference between the groups ($p = 0.814$). The AEs and ADRs leading to study material discontinuation are shown in Table 3.

As shown in Fig. 2, nasopharyngitis (5.1%) was the most frequently reported AE in the KRG group, followed by upper respiratory tract infection (4.9%), headache (4.3%), diarrhea (3.5%), and pruritus (3.1%). The most commonly occurred AEs in the placebo group were nasopharyngitis (5.4%), followed by upper respiratory tract infection (5.0%), headache (4.6%), diarrhea (3.6%), dizziness (3.6%), and pruritus (3.4%).

The most commonly occurring ADRs in the KRG group were pruritus (2.0%), followed by headache (1.6%), diarrhea (1.4%), and dizziness (1.2%). Pruritus (2.4%) was the most frequently reported ADR in the placebo group, followed by headache (1.8%), dizziness (1.6%), rash (1.4%), and diarrhea (1.2%) (Fig. 3).

3.2.2. Secondary outcomes

According to the AE intensity, 208 and 137 of 345 AEs in the KRG group were Grade 1 and 2, respectively. In the placebo group, 236, 152, and one out of 389 AEs were Grade 1, 2, and 3, respectively. Of the 184 ADRs, 92 and 91 reactions were Grade 1 or 2 in the KRG and placebo group, respectively, and one ADR in the placebo group was Grade 3 (Table 4).

The incidence rates of AEs reported in the specific AE-related questionnaire were 13.5% and 15.3% in the KRG and placebo groups, respectively ($p = 0.402$). The ADR incidences reported in the AE-related questionnaire were 6.3% and 7.4% in the KRG and placebo groups, respectively ($p = 0.515$). The frequencies of cardiovascular-, gastrointestinal-, and neuropsychiatric-related AEs and ADRs did not significantly differ between the KRG and placebo groups (Supplementary Table 1).

3.2.3. Anthropometric and laboratory measurements and physical examination

Based on the laboratory tests, the total bilirubin level was lower in the KRG group than in the placebo group at the 24-week visit, but no other significant differences were observed between the KRG and placebo groups. Changes in the vital signs and ECG data did not differ between the groups (Supplementary Table 2). The information on abnormal changes in anthropometric and laboratory data as well as physical examination parameters after administration of the study materials is presented in Supplementary Table 3.

Table 3
Incidences of AEs and ADRs leading to discontinuation of the study materials

	AEs		ADRs	
	KRG (n = 490)	Placebo (n = 502)	KRG (n = 490)	Placebo (n = 502)
Total participants	8 (1.6)	11 (2.2)	6 (1.2)	7 (1.4)
Total events	12	17	10	13
Gastrointestinal disorder				
Nausea	2	1	2	1
Abdominal pain	1	0	1	0
Diarrhea	0	1	0	1
Dyspepsia	0	1	0	1
Hematochezia	0	1	—	—
Vomiting	0	1	0	1
Nervous system disorder				
Dizziness	1	3	1	3
Headache	1	2	1	2
Skin and subcutaneous tissue disorder				
Pruritus	1	1	1	1
Rash	1	1	1	1
Hyperhidrosis	1	0	1	0
Cardiac disorder				
Palpitations	1	1	1	0
Eye disorder				
Dry eye	0	1	—	—
General disorder				
Decreased appetite	0	2	0	2
Fatigue	1	0	1	0
Obstetric and gynecologic condition				
Pregnancy	2	1	—	—

Values are expressed as n (%) or n
ADRs, adverse drug reactions; AEs, adverse events; KRG, Korean Red Ginseng

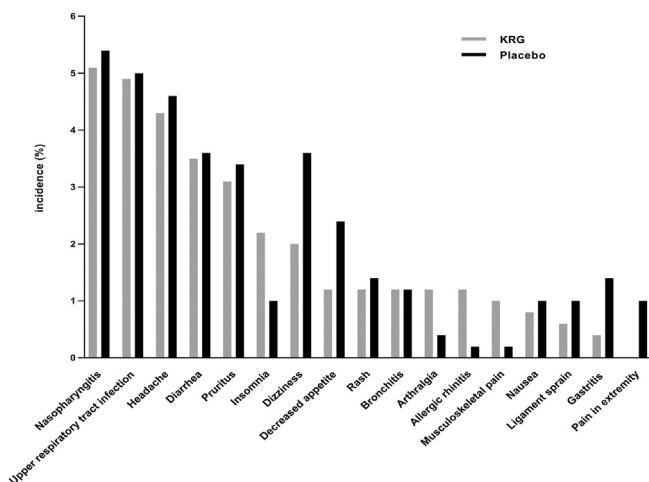


Fig. 2. Incidence rate of frequently occurred adverse events. Frequently occurred adverse events were defined as events with an occurrence of $\geq 1\%$ in each group. KRG, Korean Red Ginseng.

4. Discussion

We investigated the safety profile of KRG after administration of the preparation to healthy Korean adults for 24 weeks. In the present study, the daily intake of 2 g of KRG (equivalent to 3 g of KRG extract) resulted in no significant differences in the number of total AEs and the proportion of the participants who reported AEs compared with those recorded after daily intake of the placebo. There was no difference in the incidence of SAEs between the KRG and placebo groups, and none of the SAEs observed were related to the study material intake. The treatment-related ADRs, the numbers of ADR events, and the numbers of participants with ADRs were similar after KRG and placebo intake, both of which induced

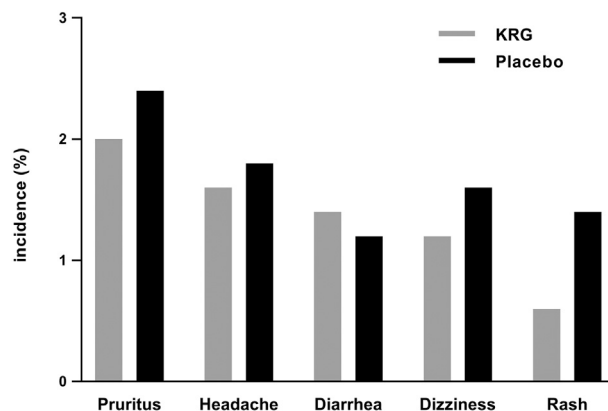


Fig. 3. Incidence rate of frequently occurred adverse drug reactions. Frequently occurred adverse drug reactions were defined as events with an occurrence of $\geq 1\%$ in each group. KRG, Korean Red Ginseng.

Table 4
Intensity of AEs and ADRs and relationship to study material administration

		KRG (n = 490)	Placebo (n = 502)	Total (n = 992)
AEs	Participants	192 (39.2)	211 (42.0)	403 (40.6)
	Events	345	389	734
	Relationship of AEs to study materials			
	Definitely related	0	0	0
	Probably related	3	1	4
	Possibly related	49	64	113
	Probably not related	230	273	503
	Definitely not related	23	24	47
	Unassessable	40	27	67
	Intensity			
Grade 1	208	236	444	
Grade 2	137	152	289	
Grade 3	0	1	1	
Grade 4	0	0	0	
Grade 5	0	0	0	
SAEs	Participants	7 (1.4)	7 (1.4)	14 (1.4)
	Events	7	7	14
	Relationship of SAEs to study materials			
	Definitely related	0	0	0
	Probably related	0	0	0
	Possibly related	0	0	0
	Probably not related	1	3	4
	Definitely not related	6	4	10
	Unassessable	0	0	0
	Intensity			
Grade 1	3	2	5	
Grade 2	4	5	9	
Grade 3	0	0	0	
Grade 4	0	0	0	
Grade 5	0	0	0	
ADRs	Participants	59 (12.0)	57 (11.4)	116 (11.7)
	Events	92	92	184
	Relationship of ADRs to study materials			
	Definitely related	0	0	0
	Probably related	3	1	4
	Possibly related	49	64	113
	Probably not related	0	0	0
	Definitely not related	0	0	0
	Unassessable	40	27	67
	Intensity			
Grade 1	57	65	122	
Grade 2	35	26	61	
Grade 3	0	1	1	
Grade 4	0	0	0	
Grade 5	0	0	0	

Values are expressed as n (%) or n
Intensity of AEs and ADRs is classified as Grades 1 (mild), 2 (moderate), 3 (severe), 4 (fatal/disabling), and 5 (death)
ADRs, adverse drug reactions; AEs, adverse events; KRG, Korean Red Ginseng; SAEs, serious adverse events

no serious ADRs. No significant abnormal changes were observed in the anthropometric and laboratory test results or in the physical examination parameters in the KRG group compared with those in the placebo group.

Despite the various biological effects of KRG [4–9], no clinical studies have investigated the safety profile of its long-term intake. Siegel et al [13] have reported the effects of long-term use of ginseng, which were described as “ginseng abuse syndrome” and included symptoms such as elevated blood pressure, nervousness, insomnia, skin rash, and diarrhea. However, the outcome was unclear because it was not reported whether the ginseng products were quality controlled and whether they contained ingredients other than ginseng or the problems were due to overuse. Furthermore, no studies have investigated the long-term safety of ginseng, particularly KRG, to date.

In the present study, the various symptoms described as “ginseng abuse syndrome” were reported with no differences between the treatment and control groups. In addition, no significant changes in the complete blood count, hepatic function test, uric acid levels, blood pressure, and body temperature were found after 24 weeks of KRG intake. The outcomes of the safety evaluation of KRG were assumed to be the result of an appropriate dose of KRG, which was 2 g of KRG tablets daily. Thus, 2 g of KRG daily can be safely administered to healthy adults for up to 24 weeks.

This study has some limitations. First, the enrollment was restricted to individuals living in South Korea. Second, the dose used in this study was 2 g of KRG daily as a tablet, which was equivalent to a 3-g dose of a KRG extract, and therefore, the safety of higher dosages of KRG was not found. Further studies are needed to evaluate the safety of KRG intake in other ethnic populations and at various dosages. In addition, the data of secondary efficacy outcomes, such as the changes in the quality-of-life index, Chalder fatigue scale, biological age, and exploratory laboratory measurements are currently unavailable and will be analyzed and presented in a separate publication.

To the best of our knowledge, the present study is the first multicenter, double-blind, randomized, placebo-controlled trial to examine the safety of KRG intake over a 6-month period in healthy Korean adults. No difference in AEs and ADRs was found between the KRG and placebo control groups, and the permanent discontinuation rates of KRG and placebo intake due to AEs or ADRs were significantly similar. The compliance rates for the study material intake were high and similar in both the groups. From this perspective, the intake of KRG can be considered both safe and generally well tolerated in healthy adults.

In conclusion, the intake of KRG as a dietary supplement at a daily dose of 2 g for 24 weeks was safe and well tolerated in

healthy Korean adults. These findings provide supportive and objective information on the safety and tolerability of long-term KRG intake.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jgr.2018.07.002>.

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