Complementary Therapies in Medicine 48 (2020) 102246

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Efficacy of Korean red ginseng (*Panax ginseng*) for middle-aged and moderate level of chronic fatigue patients: A randomized, double-blind, placebo-controlled trial

Won-Suk Sung[a], Ha-Ra Kang[b], Chan-Yung Jung[c], Seong-Sik Park[d], Seung-Ho Lee[e], Eun-Jung Kim[a,*]

[a] Department of Acupuncture & Moxibustion, Dongguk University Bundang Oriental Hospital, Gyeonggi-do, South Korea
[b] Department of Korean Medicine, Dongguk University Graduate School, Gyeonggi-do, South Korea
[c] Institute of Oriental Medicine, College of Korean Medicine, Dongguk University, South Korea
[d] Department of Sasang Constitutional Medicine, College of Oriental Medicine, Dongguk University, South Korea
[e] Korea Ginseng Corporation, Daejeon, South Korea

ARTICLE INFO

Keywords:
Chronic fatigue
Korean red ginseng
Antioxidants
Cortisol concentration

ABSTRACT

Objectives: Chronic fatigue (CF) is unexplained fatigue lasting more than 6 months. Korean red ginseng (KRG) is known to have higher anti-fatigue substance than white ginseng. However, its efficacy and safety for CF is unknown. The purpose of this study was to investigate the effect of KRG on CF by various measurements and objective indicators.
Design: A randomized, double-blind, clinical trial was conducted on 50 patients with CF.
Intervention: Participants were allocated to KRG or placebo group (1:1 ratio) and visited hospital every 2 weeks during taking 3 g KRG or placebo for 6 weeks and followed up 4 weeks after the treatment.
Main outcome measures: The primary outcome measurement was fatigue VAS. Secondary outcome measurements included FSS, CFSQ, SRI, scales of various fields (Depression: BDI; Sleep: ISI; Quality of life: EQ-5D 5 L), biochemical test (Antioxidants: d-ROMs, TBARS, BAP, and SOD; Cortisol concentration: salivary cortisol), blinding assessment, and adverse events.
Results: The fatigue VAS declined significantly in each group, but there were no significant differences between the groups. The 2 groups also had no significant differences in the secondary outcome measurements and there were no adverse events. Sub-group analysis indicated that patients with initial fatigue VAS below 80 mm and older than 50 years had significantly greater reductions in the fatigue VAS if they used KRG rather than placebo.
Conclusions: By our study, KRG did not show absolute anti-fatigue effect but provided the objective evidence of fatigue-related measurement and the therapeutic potential for middle-aged individuals with moderate fatigue.

1. Introduction

Chronic fatigue (CF) is a poor condition that unexplained fatigue lasts for more than 6 months, and is accompanied by behavioral, emotional, social, and cognitive imbalances.[1] The prevalence of chronic fatigue syndrome (CFS), a type of the CF, generally ranges from 0.4 % to 2.5 % in adult populations, and economic impact is estimated annual 20,000$ loss per person.[2,3] The diagnosis of CF is determined by patients' symptoms with no abnormalities in laboratory or physical tests.

However, the hypothesis about the relationship between CF and metabolism has recently emerged through the development of molecular biology and immunology. There has been a focus on metabolic problems (oxidative stress, altered amino acids, nucleotides, nitrogen, and hormones) and abnormal immune activations (changed NK and T cells), especially oxidative stress and hormonal alterations.[4,5] Several studies demonstrated the role of oxidative stress in CF and suggested the administration of antioxidants as a potential treatment.[6,7] Some study indicated that altered cortisol levels are associated with CF and investigated the relationship by comparing cortisol excretion among CF, depression, and healthy subjects.[8]

In treatment, several therapies for CF have been introduced and the anti-fatigue effects of ginseng (*Panax ginseng Meyer*) have been reported

* Corresponding author at: Dongguk University Bundang Oriental Medicine Hospital, 268, Buljeong-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13601, South Korea.
E-mail address: hanijjung@naver.com (E.-J. Kim).

https://doi.org/10.1016/j.ctim.2019.102246
Received 3 August 2019; Received in revised form 12 October 2019; Accepted 15 November 2019
Available online 19 November 2019

by various studies. For example, several animal studies demonstrated the anti-fatigue effects and possible mechanism of polysaccharides isolated from ginseng.[9,10] Other research reported the anti-fatigue effects of an herbal medicine consisting of ginseng with other herbs, based on measurements of physiological markers.[11] A clinical trial of CF patients confirmed that ginseng administration led to improved scores on a numerical rating scale (NRS) fatigue-related factors including reactive oxygen species (ROS), malondialdehyde (MDA), total glutathione (GSH), and glutathione reductase (GSH-Rd). [12]

Korean red ginseng (KRG), produced by repeatedly washing, steaming, and drying of white ginseng, was known to have 3 folds higher levels of acidic polysaccharides, compounds known to stimulate immune responses, improve physical activity, and regulate oxidative stress.[13] Despite the potential effects of KRG on fatigue, there is limited clinical evidence supporting its use for CF.

The purpose of this randomized, double-blind, placebo-controlled trial was to investigate the effect of KRG on CF patients by various measurements and objective indicators (antioxidants and hormone levels).

2. Materials and methods

2.1. Study design

This study was a randomized, double-blind, clinical trial with 2 parallel groups conducted at Dongguk University Bundang Oriental Hospital (South Korea). The study protocol was planned according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guideline and procedures were conducted on the base of the rules of the Helsinki Declaration. This study was approved by the Institutional Review Board (IRB) of Dongguk University Bundang Oriental Hospital on January 06, 2016 (IRB No.: DUBOH 2016-0001) and also registered at the Clinical Research Information Service (CRIS, KCT0001935).

2.2. Sample size calculation

The sample size was calculated by previous study that evaluated the anti-fatigue effects of 2 g doses of *P. ginseng* by measuring the VAS change from baseline to treatment completion (week-4) in individuals given KRG or placebo.[12] This previous study reported that the difference in the VAS change was 1.6 and the standard deviation was 1.8. Using these data, we calculated 20 participants per group with 0.80 power (1-β) at the 0.05 α level of significance. Assuming 20 % drop out rate, we enrolled 25 participants per group.

2.3. Study participants

The 50 patients with CF were assessed for eligibility by predefined inclusion/exclusion criteria by citing Wyller's diagnosis period.[14] All patients were 19 ~ 65 years old, had repetitive or continuous fatigue over 6 months with unknown cause and had no abnormal clinical findings of blood pressure, blood chemistry, urine chemistry, thyroid gland function, radiology, and electrocardiography. Patients were excluded if they worked at night, took medication, or were pregnant. After voluntarily signing the informed consent form, participants were randomly allocated to the experimental or control group (1:1 ratio) using block randomization with a block size of 4. The random sequence was generated by the independent practitioner who was not involved in this trial by using Microsoft Excel 2010 (Microsoft Inc., USA). During the study, double-blind design was kept by making investigators and subjects blinded. The random codes were sealed envelopes and this envelope was delivered to the institution that prepared the medication. The institution made and packaged the medication according to the code and delivered to the hospital. The pharmacist provided the subjects the trial medication which was same as the randomization number. Also, KRG and placebo capsule was identical in the appearance and the number of capsules. The random code was kept in an independent practitioner who was not involved in this trial. There was no interaction between sponsor officials and clinical researchers, and the participants were educated to be prevented from unnecessary talks between the researchers or other subjects.

Participants in the experimental group took KRG powder (KRGP) capsules twice per day for 6 weeks. 3 g of KRGP capsules/day contained the ginsenosides Rb1 (4.79 mg/g), Rc (1.90 mg/g), Rb2 (1.54 mg/g), Rg3(S) (0.18 mg/g), Rf (0.98 mg/g), Rg3(R) (0.10 mg/g), Rg1 (3.0 mg/g), Re(1.48 mg/ml), Rh(0.17 mg/ml), Rg2(S) (0.15 mg/ml), and Rd (0.26 mg/g). The KRG formulation 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 complied with the quality control criteria for the acceptable levels of pesticides and contaminants. The capsules were produced by KRGP (0.5 g per capsules) and were yellow-brown in color. The control group took placebo capsules on the same schedule. The placebo capsule contained corn starch and cellulose with the KRG flavor and color, and the total content was the same as that of the KRGP capsule. The KRGP capsules were produced by Korea Ginseng Corporation (South Korea) *via* Good Manufacturing Practices while the placebo capsules were made by Natural F&P (South Korea). The assessor and researcher were blinded to group allocation until the end of the trial. In addition, blinding of participants was assessed using a blinding assessment questionnaire. 4 weeks after taking KRG or placebo, participants were asked to visit the hospital and answer the questionnaire.

2.4. Outcome measurements

The primary outcome measurement was fatigue VAS.[15] This method has an advantage that is valid and convenient and participant requires minimal reading skills, time, and effort.[16] Participants were asked to score their fatigue using a 100 mm VAS from 0 (absence of fatigue) to 100 (the worst fatigue imaginable). There were several secondary outcome measurements.[17] The fatigue severity scale (FSS) has 9 questions about fatigue severity during the previous week and asks subjects to answer their agreement using a Likert-type scale from 1 to 7 points. The total scores are calculated as the average, and higher score indicates greater fatigue.[18] The Chalder fatigue severity questionnaire (CFSQ) has 11 questions, (7 for physical symptoms and 4 for mental symptoms), it is measured by 10 points from 0 (no fatigue-related symptoms) to 9 (too severe to tolerate).[19] The stress response inventory (SRI)-short form has 22 questions (9 for somatization, 8 for depression, and 5 for anger) for measurement of the stress responses. Subjects respond their experiences during the previous week and the total scores are calculated.[20] The Beck depression inventory (BDI) has 21 questions regarding cognitive, emotional, and physical symptoms of depression.[21] The total scores are calculated by 4 scales from 0 to 3. The insomnia severity index (ISI) is a questionnaire that measures the severity of insomnia. The 2014 version has 5 questions and the answers are scored from 0 (absence of insomnia) to 4 (worst possible insomnia).[22] The five-level EuroQol-5 Dimension (EQ-5D 5 L) scale is a newly established measurement to improve the sensitivity by increasing the level from 3 to 5. It has 2 parts: EQ-VAS evaluates the health-related quality of life and is scored from 0 (lowest) to 100 (highest healthy level) and EQ-5D evaluates mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[23,24] Biochemical tests were used to measure antioxidants and cortisol concentration. Based on the previous article and experiment, antioxidants including derivatives of reactive oxygen metabolites (d-ROMs), thiobarbituric acid reactive species (TBARS), biological antioxidant potential (BAP), and superoxide dismutase (SOD) were assessed.[25,26] Cortisol was collected in saliva immediately 4 times (within 30 min after awakening, 11 ~ 13, 16 ~ 18, and 22 ~ 24 o'clock) a day and measured by using the area under the curve (AUC).[27,28] To assess blinding, participants were asked to guess the

	Study period					
	Enrollment	Intervention				Follow-up
Time point (week)	0	0	2	4	6	10
Time point (visit)	1 (Screening)	2	3	4	5	6
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions:						
Korean red ginseng		—	—	—	—	
Placebo		—	—	—	—	
Assessments:						
Fatigue VAS	X	X	X	X	X	X
FSS, CFSQ, SRI-short form, ISI, EQ-5D 5L		X	X	X	X	X
BDI		X			X	X
Antioxidants, cortisol concentration		X			X	
Adverse events		X	X	X	X	X
Blinding assessment					X	
Compliance					X	

Fig. 1. Study schedule.
BDI, Beck depression inventory; CFSQ, Chalder fatigue severity questionnaire; EQ-5D 5 L, five-level EuroQol-5 Dimension; FSS, fatigue severity index; ISI, insomnia severity index; SRI, stress response inventory; VAS, visual analogue scale.

group to which they were assigned and whether they would recommend the treatment they received to others. Adverse events were checked at every visit, and recorded in detail (Fig. 1).

2.5. Statistical analysis

All statistical analyses were performed by SPSS for windows version 20.0 (SPSS Inc, Chicago, IL, USA). Intent-to-treat analysis was the principle, and missing values were replaced by last observations carried forward (LOCF) analysis. If subjects were in the following cases, LOCF analysis was excluded: 1) the violation of the inclusion/exclusion criteria, 2) subjects did not receive trial medication, 3) subjects did not offer the outcome measurements after randomization. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequency and percentage. The Chi-squared test for categorical variables and the independent two-sample *t*-test for continuous variables were used to analyze demographic data and symptoms. A paired *t*-test or the Wilcoxon signed-rank test was used for comparisons of primary and secondary outcome measurements and repeated measured analysis of variance (RM ANOVA) was used to confirm the effect of time and treatment cross-effects. A paired *t*-test or the Wilcoxon signed-rank test was also used in the analysis of antioxidants and cortisol concentration and the independent-samples *t*-test or the Mann-Whitney test was used to compare the groups. If there were no significant differences, participants were divided according to the demographic items (age and sex) and the initial fatigue VAS which represented the fatigue severity. The Chi-squared test or Fisher's exact test for blinding assessment and the incidences of AEs for safety outcomes were performed. A 95 % confidence interval was calculated, all tests were carried based on two-sided. A p value below 0.05 was considered statistically significant.

3. Results

We recruited 59 CF patients from May 31 to December 16 in 2016 and enrolled 50 patients who met the eligibility criteria. These 50 patients were randomly allocated to KRG or placebo group in a 1:1 ratio. During the study, 3 participants withdrew due to treatment discontinuation after visit 2 (1 in the KRG group and 2 in the placebo group) and 47 patients completed the clinical trial (Fig. 2). All of 3 subjects did not follow up after visit 2 in which randomization and first medication offer were conducted. In the statistical analysis terms, it was judged that we could not perform LOCF analysis, and we exclude the data of 3 subjects. There were no significant differences in age, sex ratio, height, and body weight (Table 1). In addition, the 2 groups had no significant differences in duration of fatigue and initial fatigue VAS.

3.1. Primary outcome measurement

Each group had significant reductions in the fatigue VAS from baseline (week-0, visit 2) to visit 6 ($p < 0.001$ for both comparisons; Table 2). This reduction was greater in the KRG group (33.375 ± 23.171 *vs.* 26.826 ± 23.482), but the difference was not significant.

3.2. Secondary outcome measurements

Each group had significant improvements in all secondary outcome

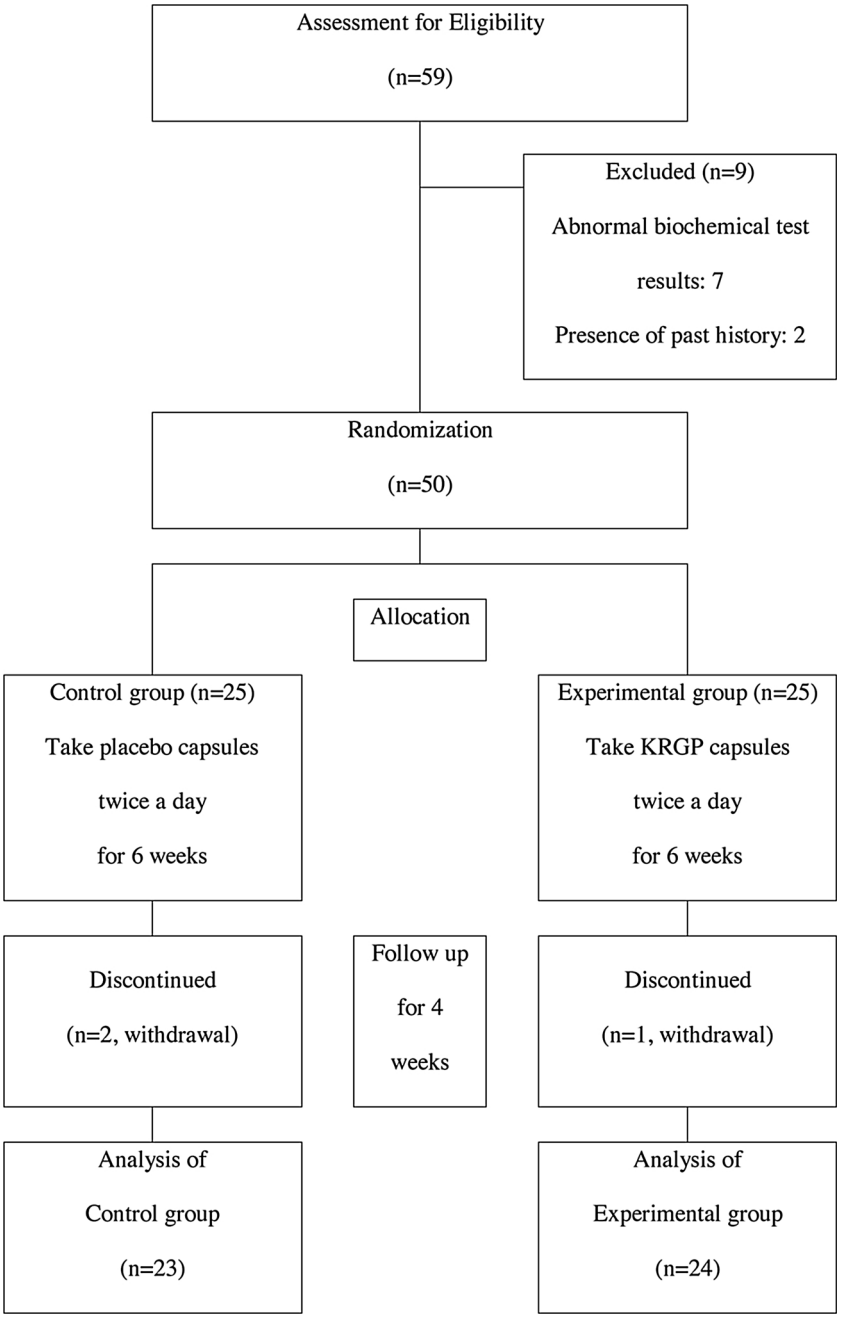

Fig. 2. CONSORT flow diagram.
KRGP, Korean red ginseng powder

Table 1
Patient characteristics at visit 1.

Variable		KRG group (n = 24)	Placebo group (n = 23)
Age (years)		49.000 ± 8.351	47.087 ± 10.795
Sex N (%)	Male	9 (19.149)	5 (10.638)
	Female	15 (31.915)	18 (38.298)
Height (cm)		162.625 ± 9.300	163.739 ± 7.244
Weight (kg)		58.042 ± 10.323	57.696 ± 9.938
Duration of CF (year)		6.038 ± 7.686	5.730 ± 7.055
Fatigue VAS (mm)		79.083 ± 10.261	79.913 ± 6.660

CF, chronic fatigue; KRG, Korean red ginseng; VAS, visual analogue scale.

measurements ($p < 0.05$ for all comparisons; Table 3). The KRG group showed more improvements in the SRI-short form (19.791 ± 18.180 *vs.* 15.652 ± 26.008), BDI (6.250 ± 6.783 *vs.* 5.521 ± 7.279), and EQ-5D 5 L (25.250 ± 20.600 *vs.* 19.826 ± 24.-099 in EQ-VAS, 1.583 ± 2.083 *vs.* 1.565 ± 2.710 in EQ-5D). However, none of the differences between the groups were significant.

3.3. Biochemical tests

None of the within-group or between group changes in markers of antioxidants (d-ROMs, TBARS, BAP, and SOD; Fig. 3) or cortisol concentration (Fig. 4) were significantly different. In antioxidants, the KRG group showed more reduction of d-ROMs (4.041 ± 33.705 *vs.* 2.391 ± 56.085), and TBARS (0.041 ± 0.265 *vs.* 0.017 ± 0.221) than the placebo group, which meant the reduction of radicals and oxidative

Table 2
Fatigue VAS at baseline, week-6, and week-10.

	KRG group (n = 24)		Placebo group (n = 23)		Main Effects		Interaction
	Mean	SD	Mean	SD	Within-group F	Between-group F	Group × Time F
VAS (mm)							
Baseline	79.041	11.418	77.173	10.473	34.447	1.453	0.874
Week-6	42.375	16.730	49.608	21.385			
Week-10	45.666	19.685	50.347	22.434			
Mean change	−33.375	23.171	−26.826	23.482			
***p* value**	< **.001****		< **.001****		< **.001**††	.234	.480

*Wilcoxon signed-rank test was used for intra-group comparison, † RM ANOVA.
KRG, Korean red ginseng; VAS, visual analogue scale.

Table 3
Secondary outcome measurements at baseline, week-6, and week-10.

	KRG group (n = 24)		Placebo group (n = 23)		Main Effects		Interaction
	Mean	SD	Mean	SD	Within-group F	Between-group F	Group × Time F
FSS							
Baseline	43.833	8.800	46.087	10.710	19.153	0.038	0.280
Week-6	32.875	9.488	32.434	11.915			
Week-10	32.500	12.676	32.652	12.426			
Mean change	−11.333	11.020	−13.434	18.117			
p value	< **.001****		**.002****		< **.001**††	.846	.891
CFSQ							
Baseline	31.375	4.585	31.782	5.884	22.122	0.028	0.533
Week-6	23.958	5.344	22.260	7.040			
Week-10	24.083	7.575	24.217	6.067			
Mean change	−7.291	8.426	−7.565	9.213			
p value	**.001****		**.001****		< **.001**††	.867	.589
SRI							
Baseline	40.708	16.493	38.652	16.546	22.394	0.068	0.338
Week-6	18.041	14.198	19.652	18.224			
Week-10	20.916	17.534	23.000	18.347			
Mean change	−19.791	18.180	−15.652	26.008			
p value	< **.001****		**.006****		< **.001**††	.796	.852
BDI							
Baseline	17.875	7.011	16.826	7.094	22.433	0.029	1.833
Week-6	10.791	9.596	13.260	7.915			
Week-10	11.625	9.938	11.304	7.911			
Mean change	−6.250	6.783	−5.521	7.279			
p value	< **.001****		**.002****		< **.001**††	.866	.166
ISI							
Baseline	10.583	5.837	12.043	5.121	11.008	0.168	0.817
Week-6	8.375	5.969	8.173	3.880			
Week-10	7.625	6.405	8.869	5.119			
Mean change	−2.958	5.094	−3.173	5.104			
p value	**.012***		**.007****		< **.001**††	.684	.516
EQ-VAS							
Baseline	29.458	8.905	33.173	12.119	17.893	0.639	1.056
Week-6	56.416	20.213	54.391	20.979			
Week-10	54.708	20.950	53.000	20.371			
Mean change	25.250	20.600	19.826	24.099			
p value	< **.001****		**.001****		< **.001**††	.428	.380
EQ-5D							
Baseline	8.333	1.948	8.826	2.386	14.921	0.222	1.014
Week-6	6.625	1.789	6.869	1.841			
Week-10	6.750	1.594	7.260	2.359			
Mean change	−1.583	2.083	−1.565	2.710			
p value	**.003****		**.013***		< **.001**††	.640	.401

BDI, Beck depression inventory; CFSQ, Chalder fatigue severity questionnaire; EQ-5D, EuroQol-5 Dimension; FSS, fatigue severity index; EQ-VAS, EuroQol visual analogue scale; ISI, insomnia severity index; KRG, Korean red ginseng; SRI, stress response inventory.
* Wilcoxon signed-rank test was used for intra-group comparison, † RM ANOVA.

damage, but there was no significant difference. The KRG showed less reduction of BAP (24.041 ± 412.465 *vs.* 86.608 ± 260.157), which meant the maintenance of antioxidant ability, but there was no significant difference. In cortisol concentration, the KRG group showed higher AUC with respect to ground (AUC_G) and AUC with respect to the increase (AUC_i) levels than the placebo group, which meant the improvement of cortisol secretion, but there was also no significant difference.

3.4. Sub-group analysis

Due to the lack of statistical significance, we performed sub-group analysis. Some fatigue-related studies defined moderate fatigue under 8 of 10[29] and focused on the middle-aged people at the age of 50 and the

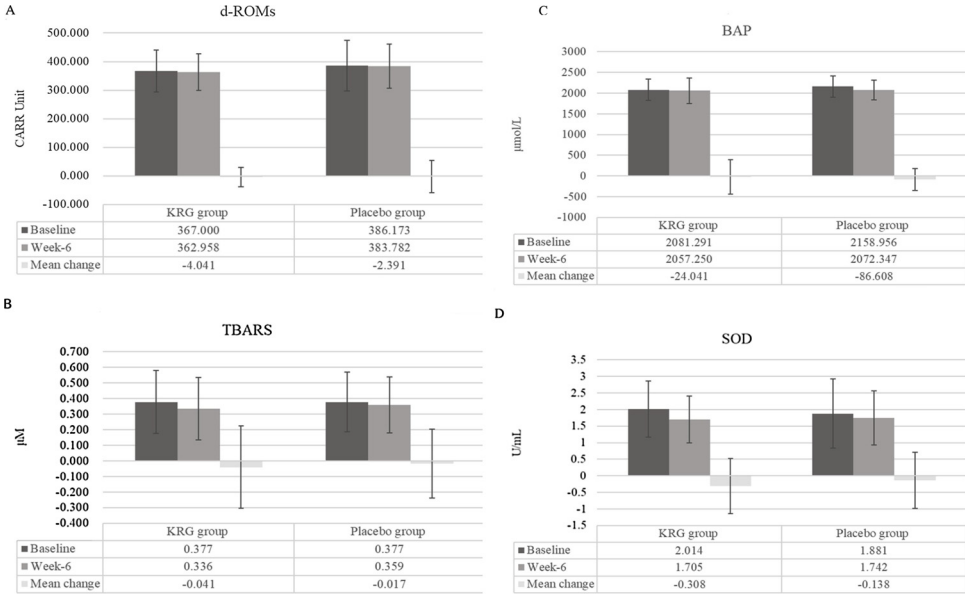

Fig. 3. Antioxidants levels at baseline and week-6 A. d-ROMs, B. TBARS, C. BAP, D. SOD. Wilcoxon signed-rank test was used for intra-group comparisons and the Mann-Whitney test for inter-group comparisons.
*Data were missing for one case in the KRG group due to lack of samples.
BAP, biological antioxidant potential; d-ROMs, derivatives of reactive oxygen metabolites; KRG, Korean red ginseng; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive species.

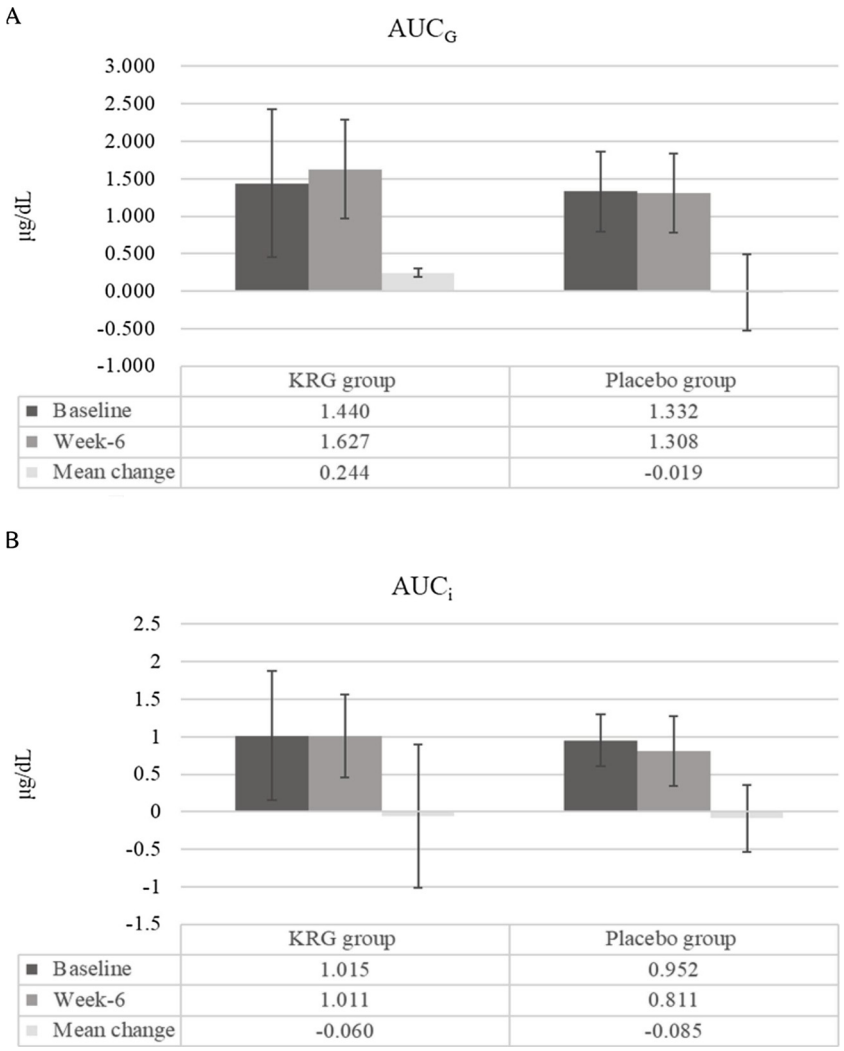

Fig. 4. Cortisol at baseline and week-6.
A. AUC_G, B. AUC_i
Wilcoxon signed-rank test was used for intra-group comparisons and the Mann-Whitney test for inter-group comparisons.
*Data were missing in 3 cases in the placebo group and 1 case in the KRG group due to lack of samples.
AUC_G, Area Under the Curve with respect to ground; AUC_i, Area Under the Curve with respect to the increase; KRG, Korean red ginseng.

Table 4a
Fatigue VAS at baseline, week-6, and week-10 in patients with initial fatigue VAS below 80 mm (top) and older than 50 years (bottom).

Initial fatigue VAS below 80 mm	KRG group (n = 12)		Placebo group (n = 12)		Main Effects		Interaction
	Mean	SD	Mean	SD	Within-group F	Between-group F	Group × Time F
VAS (mm)							
Baseline	71.500	7.229	74.333	3.700	15.967	4.742	0.960
Week-6	39.916	8.659	53.500	22.199			
Week-10	44.666	13.040	50.833	20.211			
Mean change	−26.833	12.769	−23.500	19.602			
p value	< **.001****		< **.001****		< **.001**††	**.040**†	.434
Older than 50 years	**KRG group (n = 11)**		**Placebo group (n = 13)**		**Main Effects**		**Interaction**
	Mean	**SD**	**Mean**	**SD**	**Within-group F**	**Between-group F**	**Group × Time F**
VAS (mm)							
Baseline	74.545	14.548	74.230	12.228	11.617	4.542	0.897
Week-6	39.909	11.631	55.923	19.185			
Week-10	45.181	19.727	55.307	18.121			
Mean change	−29.363	23.337	−18.923	18.580			
p value	< **.001****		< **.001****		< **.001**††	**.044**†	.469

*Wilcoxon signed-rank test was used for intra-group comparison, † RM ANOVA.
KRG, Korean red ginseng; VAS, visual analogue scale.

Table 4b
Fatigue VAS at baseline, week-6, and week-10 in males (top) and females (bottom).

Male	**KRG group (n = 9)**		**Placebo group (n = 5)**		**Main Effects**		**Interaction**
	Mean	**SD**	**Mean**	**SD**	**Within-group F**	**Between-group F**	**Group × Time F**
VAS (mm)							
Baseline	79.333	5.958	77.800	11.344	10.242	1.054	0.504
Week-6	44.444	13.342	54.600	25.559			
Week-10	45.555	17.292	50.800	27.824			
Mean change	−33.777	18.952	−27.000	25.485			
p value	**.008****		**.080**		< **.001**††	.325	.733
Female	**KRD group (n = 15)**		**Placebo group (n = 18)**		**Main Effects**		**Interaction**
	Mean	**SD**	**Mean**	**SD**	**Within-group F**	**Between-group F**	**Group × Time F**
VAS (mm)							
Baseline	78.866	13.922	77.000	10.560	22.838	0.888	0.585
Week-6	41.133	18.806	41.133	18.806			
Week-10	45.733	21.581	45.733	21.581			
Mean change	−33.133	26.013	−26.777	23.680			
p value	**.001****		**.001****		< **.001**††	.353	.674

*Wilcoxon signed-rank test was used for intra-group comparison, † RM ANOVA.
KRG, Korean red ginseng; VAS, visual analogue scale.

sex.[30,31] With these reasons, we conducted sub-group analysis of patients with initial fatigue VAS below 80 mm, older than 50 years (Table 4a), and males and females (Table 4b). For patients with initial fatigue VAS below 80 mm, there was a greater decline of the fatigue VAS in the KRG group than the placebo group ($F = 4.742$, $p = 0.040$). For patients older than 50 years, there was also a greater decline of the fatigue VAS in the KRG group than the control group ($F = 4.542$, $p = 0.044$). However, sex had no impact on the decline of fatigue VAS.

3.5. Blinding assessment and adverse events

The 2 groups had no significant differences in guessing the group to which they belonged nor in recommending the treatment for others, indicating adequate maintenance of patient blinding (Table 5). There were no adverse events associated with KRG intaking.

Table 5
Two-question analysis for blinding assessment.

Guessed the group allocation	KRG group (n = 24)		Placebo group (n = 23)		*p* value*
	N	%	N	%	
KRG	12	25.5	8	17.0	0.576
Placebo	2	4.3	2	4.3	
Unknown	10	21.3	13	27.7	
Recommended the received treatment for others	**KRG group (n = 24)**		**Placebo group (n = 23)**		***p* value***
	N	**%**	**N**	**%**	
Yes	21	44.7	15	31.9	0.072
No	3	6.4	8	17.0	

KRG, Korean red ginseng.
* Fisher's exact test.

4. Discussion

Researchers first proposed the term CFS in 1988 to describe patients with a complex set of symptoms with chronic or recurrent debilitating fatigue of unknown cause.[32] In 1994, Fukuda et al. proposed new diagnostic criteria for CFS.[33] According to that criteria, CF patients may be further categorized into 4 sub-groups. First, they are classified as 'Explained' or 'Unexplained' CF, depending on the identification of a medically explainable cause. Patients with 'Explained' CF are divided into having 'Physical' or 'Psychological' CF, according to the main cause; patients with 'Unexplained' CF are divided into having 'Idiopathic' CF (ICF) or 'CFS'. Since then, the diagnosis of CFS has greatly

increased over time. Various studies estimated the prevalence of 0.075 ~ 0.267 % in 1995, and it rose to 1.67 % in 2007, and 2.5 % in 2009.[34,35,2]

The physiological basis of CF is still unclear. However, our study focused on the possible role of antioxidants and hormones, based on several previous studies. Kennedy et al. reported decreased high-density lipoprotein (HDL), increased oxidized low-density lipoprotein (oxLDL), and increased F2 α-isoprostane levels in CFS patients relative to healthy subjects, and they also identified a relationship between isoprostane levels and CFS symptoms (joint pain and discomfort after exercise).[36] Vecchiet et al. found that elevated TBARS, decreased Lag phase, vitamin E had significant correlations with fatigue.[37] Demitrack et al. examined hormones in the hypothalamic-pituitary-adrenal (HPA) axis and reported decreased cortisol excretion in CFS patients.[38] Cleare et al. measured urinary free cortisol secretion and suggested that hypocortisolism contributes to CFS.[39] These results motivated us to measure antioxidants and cortisol levels in assessing the effect of KRG for CF.

Except for 1 animal study, which showed that KRG more effectively alleviated psychological than physical fatigue, very few studies have documented the effect of KRG on CF.[40] Thus, we compared our study results with previous studies that examined the use of KRG or ginseng for the treatment of other diseases.

Previous study performed a randomized controlled trial (RCT) to examine the anti-fatigue effects of KRG by allocating ICF patients into placebo, 1 g, or 2 g ginseng group (30 participants per group).[12] They measured fatigue (using VAS and NRS) and antioxidants levels after 4 weeks of taking medication. The 2 g ginseng group had significantly lower levels of mental fatigue, ROS, MDA, and GSH. This study showed significant improvements using lower doses of KRG (1 or 2 g) than our study (3 g). However, previous study examined ICF patients, which could be considered milder than CFS, whereas our study examined patients with CF that includes ICF and CFS. Thus, KRG might be effective in the treatment of moderate CF (or ICF), as also indicated by our sub-analysis of patients with low initial fatigue VAS.

Several previous studies have examined the anti-oxidant effects of KRG. For example, Kim et al. performed RCT to examine the anti-oxidant effects of KRG by allocating healthy subjects into placebo, 3 g, or 6 g KRG group (19 participants per group) and measured SOD and catalase activity after 8 weeks of taking medication.[41] The 6 g KRG group had a significant difference compared with the baseline ($p < 0.05$) and placebo group while 3 g KRG group did not show either. Seo et al. conducted RCT by allocating postmenopausal women into placebo or 3 g KRG group (41 participants per group) and measured SOD, glutathione peroxidase, and MDA after 12 weeks of taking medication.[42] The KRG group showed a significant difference in SOD and MDA relative to baseline, and SOD compared with placebo group. Our study offered 3 g of KRG for 6 weeks, and enrolled 50 participants (less than previous studies). It might be considered that the dose, treatment period, and the number of participants were insufficient, resulting in the insignificant KRG improvement to reduce the oxidative damage and maintain the antioxidant ability.

There is some evidence that KRG can affect cortisol level. Previous study conducted RCT by allocating 6 ~ 15 years old children with attention deficit hyperactivity disorder (ADHD) to placebo (n = 37) or 2 g KRG group (n = 33), and measured salivary cortisol and dehydroepiandrosterone (DHEA) levels at 4 and 8 weeks of taking medication.[43] Their KRG group had a significant decrease in DHEA and an increase of salivary cortisol, but there were no significant changes in the placebo group. But This study demonstrated that KRG had an effect on the adrenal function, referring to the need for larger sample size, longer dosing period, and sampling time. This study also found that individuals had notable variations in cortisol response. Thus, in addition to one study,[44] which found that salivary concentrations of cortisol differed significantly among individuals, the large inter-individual variations in cortisol levels among our patients may explain our resulting the insignificant KRG improvement on cortisol level.

As the above comparison with the outcome measurements of our study and the results of previous studies, we concentrated on the dosage and treatment period. In the dosage, Barton DL et al. examined the anti-cancer-related fatigue effect of 8 week American ginseng intake by allocating 282 cancer patients into 0 mg, 750 mg, 1000 mg, and 2000 mg group.[45] In the treatment period, Hartz AJ et al. conducted RCT about the anti-fatigue effect of Siberian ginseng and checked the fatigue-related outcome measurements each month during the 4 month of treatment period.[46] Through the sufficient options of dosage and treatment period, each study obtained specific dosage and duration that showed significant improvement (1000 ~ 2000 mg and 2 months at partial group). In the accordance with the review of Kim et al., which reported KRG powder dose used in various studies as 0.9 ~ 6 g and recommended more than 12 weeks to investigate the efficacy and safety of ginseng,[47] study with diverse dosage and treatment period would be needed.

Our sub-group analysis indicated that KRG benefited 2 groups of patients with CF: those more than 50 years old and those with initial fatigue VAS below 80 mm. One study suggested that the frequency of fatigue might increase with age,[48] so our finding of a significant effect in those older than 50 years suggests that KRG has potential as a therapy for middle-aged patients with CF. Our finding of a significant effect of KRG in those with initial fatigue VAS below 80 mm is in line with a previous study that documented the effectiveness of KRG in ICF treatment with low dose (2 g) ginseng.[12] Despite the limitations inherent to sub-group analysis, these results suggest that KRG may be useful for the treatment of a subset of patients with CF.

There were some limitations to our study. First, all patients were from a single institution. Based on a previous study that evaluated cancer-related fatigue in 438 patients with colorectal cancer at 15 different institutions, there may be large variations among institutions.[49] Second, the insignificant amelioration of CF due to KRG may be because of our small sample size or the short treatment duration. Some previous studies examined the impact of a 6-month ginseng treatment with 5-year follow-up.[50] In addition, although we supplemented with several fatigue-related scales, there would be inaccuracy of the fatigue VAS used as the primary outcome measurement. However, the strengths of our study are that it was the first double-blind RCT to investigate the efficacy and the safety of KRG for CF patients, and to also examine the effect of KRG on multiple secondary outcome measurements (several questionnaires, chemical test, and salivary test). Further long-term studies with larger sample sizes appear to be necessary.

Funding

This research was supported by a 2016 grant of The Korean Society of Ginseng.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgement

This work was supported by a 2016 grant from the Korean Society of Ginseng. Eun-Jung Kim just received payment as a research assistant and the Korean Society of Ginseng did not have any involvement in the review, editing, or the submission of the manuscript for publication. A report of the findings of this review was submitted to the Korean Society of Ginseng upon completion. Seung-Ho Lee, as a researcher of Korea Ginseng Corporation, only cooperated methodology and medication (KRG and placebo). He did not involve in other process for publication, and all authors declare that they have no competing interests.

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