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Original Research

Korean red ginseng for cancer-related fatigue in colorectal cancer patients with chemotherapy: A randomised phase III trial☆

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KEYWORDS
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Abstract ***Background:*** Cancer-related fatigue (CRF) is a common symptom and has a negative impact on prognosis in cancer patients. CRF could be improved by Korean red ginseng (KRG).
Patients and methods: For this randomised and double-blinded trial, colorectal cancer patients who received mFOLFOX-6 were randomly assigned to either KRG 2000 mg/day (n = 219) or placebo (n = 219) for 16 weeks. CRF was evaluated using the mean area under the curve (AUC) change from baseline of brief fatigue inventory (BFI) as the primary endpoint. Fatigue-related quality of life, stress, and adverse events were evaluated as secondary endpoints.
Results: In the full analysis group, KRG up to 16 weeks improved CRF by the mean AUC change from baseline of BFI compared to placebo, particularly in "Mood" and "Walking ability" ($P = 0.038$, $P = 0.023$, respectively). In the per-protocol group, KRG led to improved CRF in the global BFI score compared with the placebo ($P = 0.019$). Specifically, there were improvements in "Fatigue right now," "Mood," "Relations with others," "Walking ability," and "Enjoyment of life" at 16 weeks ($P = 0.045$, $P = 0.006$, $P = 0.028$, $P = 0.003$, $P = 0.036$, respectively). In subgroups of female patients, ≥60 years old, with high compliance (≥80%) or more baseline fatigue, the beneficial effects of KRG were more enhanced than that of placebo. Although neutropenia was more frequent in KRG than placebo, the incidence of all adverse events was similar.
Conclusions: KRG could be safely combined with mFOLFOX-6 chemotherapy in colorectal cancer patients, and reduced CRF compared with placebo.

1. Introduction

Cancer-related fatigue (CRF) that is caused by cancer or by repeated cancer treatments is defined as a subjective feeling of physical, emotional, or cognitive fatigue or exhaustion and that interferes with daily functioning [1–7]. CRF affects disease progression by negatively altering mood, concentration, ability to work, willingness to receive treatment, daily life, and feelings of security [1,5,6]. According to previous studies, 80% of cancer patients treated with either chemotherapy or radiotherapy reported fatigue [3,8]. Patients undergoing chemotherapy experience various symptoms, and those symptoms affect fatigue both directly and indirectly, and can also have a negative impact on prognosis after treatment [7,9,10].

To date, the management of CRF has not been a large focus of research, potentially because fatigue is not a life-threatening condition that requires urgent treatment. However, some studies have suggested that improvement in CRF had a positive effect on the quality of life, and the management of CRF is now being highlighted as an adjunctive cancer treatment [11,12]. Pharmacologic interventions to improve CRF, such as psychostimulants (methylphenidate), donepezil, paroxetine, and dietary supplements (coenzyme Q 10, L-carnitine, guarana) have been studied in several clinical trials [13–20]. Recently, the NCCTG phase II and phase III trials using American ginseng (*Panax quinquefolius* L.) showed significant benefits in fatigue improvement compared to placebo [21,22].

Korean red ginseng (KRG) is a processed product of Asian ginseng (*Panax ginseng* C.A. Meyer) consumed through either powderization after steaming and drying or concentration and fermentation after extraction with water or alcohol. KRG is a well-known health food that has been ingested for many years without safety issues [23]. Previous pilot studies in cancer patients undergoing cancer treatments confirmed the improvement of fatigue with KRG and Asian ginseng [24–26].

Thus, we aimed to show whether KRG improves CRF compared with placebo in colorectal cancer patients undergoing modified FOLFOX-6 (mFOLFOX-6) chemotherapy. We also compared the fatigue-related quality of life, stress, and adverse events with/without KRG.

2. Patients and methods

2.1. Patients

Eligibility criteria were planned administration of the mFOLFOX-6 regimen with adjuvant or palliative intent for at least 6 months. Full inclusion/exclusion criteria are detailed in Data Supplement 1.

2.2. Study scheme

This clinical trial was designed as a randomised, double-blinded, placebo-controlled, parallel, multi-center trial. After screening, patients were randomly assigned to either the KRG or placebo group at a 1:1 ratio. The placebo was the same size, taste, and smell of KRG so that the two could not be distinguished by patients or investigators. Stratified block randomization was used to randomly assign patients using sex (male/female) and type of chemotherapy (adjuvant/palliative) as stratification factors (Data Supplement 2). The baseline severity of CRF was not a stratification factor. Randomly assigned patients were given trial products for 16 weeks (1000 mg of KRG, 500 mg × 2 pills, twice daily vs. placebo with the same schedule) and were asked to visit at Week 4, Week 8, Week 12, and Week 16 for assessment. Other chemotherapy agents aside from the current regimen, systemic steroids (except chemotherapy premedication), medications that impact fatigue, such as mental stimulants and antidepressants (except medications started before participating in this trial, taken at a stable dosage and used throughout the trial), herbal medications, and megestrol acetate were prohibited during the trial period. In terms of chemotherapy regimen, the mFOLFOX-6 regimen was applied, which was the same in patients with the adjuvant setting and in patients with metastatic disease. Written informed consent was obtained from all patients. All protocols and consent forms were approved by the institutional review board of each institution. The trial is registered at ClinicalTrials.gov (NCT02039635). Information regarding KRG is detailed in Data Supplement 3.

2.3. Cancer-related fatigue

Fatigue measurements were completed at each visit using the brief fatigue inventory (BFI) survey developed by Mendoza *et al.* [27]. The global BFI score was calculated by averaging the BFI values of the previous nine questions. Each question was assessed using a 10-point Likert scale (0–10), and scores for all questions were converted to a 100-point scale. Higher AUC indicates a greater improvement in fatigue. The degree of fatigue was evaluated by calculating the area under the curve (AUC), with trapezoidal rule after subtracting the baseline BFI score at each week.

2.4. Fatigue-related quality of life

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue survey (https://www.facit.org/FACITOrg) was used to assess the fatigue-related quality of life at baseline, Week 8, and Week 16. From the survey questions of the FACIT-Fatigue, FACIT-Fatigue Trial Outcome Index scores calculated from questions assessing fatigue and FACIT-General scores calculated from questions assessing the general quality of life. FACIT-Fatigue Trial Outcome Index scores and FACIT-General scores were summed to produce FACIT-Fatigue Total scores at baseline, Week 8, and Week 16.

2.5. Stress index

Stress index was measured at baseline, Week 8, and Week 16 using the perceived stress scale. The perceived stress scale is composed of 10 questions, and scores were calculated with a predefined method [28,29].

2.6. Cortisol and cytokines

Baseline thyroid function tests were performed. Blood cortisol, IL-1, IL-6, IL-2, IL-8, IL-10, and TNF-α levels were measured using laboratory tests at baseline and Week 16 (Data Supplement 4).

2.7. Safety

Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for adverse events (NCI-CTCAE) v4.0. At every visit, adverse events and use of concomitant drugs were assessed. Drug compliance was calculated by counting the remaining drugs. Laboratory studies (blood cell count test, chemistry, coagulation, and urinary analysis) were performed at baseline, Week 8, and Week 16.

2.8. Statistical analysis

The primary endpoint was the mean AUC change from baseline of BFI over 16 weeks. The secondary endpoints were the mean AUC change from baseline of BFI over eight weeks, the change from baseline in FACIT-Fatigue Trial Outcome Index and FACIT-Fatigue total score at Week 8 and Week 16, the change from baseline in perceived stress scale at Week 16, and the change from baseline in blood cytokine (IL-1, IL-6, IL-2, IL-8, IL-10, and TNF-α) and cortisol levels at Week 16. The sample size was calculated by assuming a 6.0 difference between KRG and placebo and a 20% drop-out rate based on Moraska *et al.* [16]. With a significance level of 5% and a power of 80%, a total of 438 subjects (219 subjects per group) were required.

Efficacy results were analyzed using full analysis and per-protocol analysis set. The full analysis set consisted of all randomised patients taking at least one trial product and having at least one post-baseline efficacy measurement, and the per-protocol set consisted of all patients who completed the trial without any major violations. The between-group difference for the mean AUC change from baseline of BFI over 8 weeks and 16 weeks was assessed using a mixed model with time, group, the interaction between time and group, and stratification factors [30]. The mean AUC change from baseline of BFI in each group was calculated by combining the stratum-specific estimates using weights proportionate to the stratum-specific sample sizes. The rank analysis of covariance (rank ANCOVA) model with baseline value and stratification factors as covariates was used to compare treatment groups for the change from baseline in FACIT-Fatigue Trial Outcome Index, FACIT-Fatigue total score, the perceived stress scale, the blood cytokine, and the cortisol levels. The subgroup analyses for the efficacy endpoints were performed in subgroups by age, compliance, sex, chemotherapy type. Safety outcomes were assessed as adverse events in patients who had taken the trial product at least once after randomization. Adverse events were summarised using the number of subjects and the percentages. General statistical analysis was performed with SAS version 9.4 (SAS, Cary, NC, USA).

3. Results

3.1. Patients

A total of 471 patients in 15 centers were enrolled from December 2013 to April 2016, and 438 were randomly assigned to either the KRG (n = 219) or placebo group (n = 219). A CONSORT diagram is shown in Fig. 1. One hundred seventy-two patients (79%) in the KRG group and 176 patients (80%) in the placebo group completed the clinical trial up to Week 16. Full analysis included a total of 409 patients (KRG, n = 206; placebo, n = 203). Per-protocol analysis included a total of 330 patients (KRG, n = 161; placebo, n = 169). Safety data of 427 patents (KRG, n = 215; placebo, n = 212) were collected.

In the full analysis set, the median age was 60 years, and 247 (60%) patients were males. In the majority of patients (362, 89%), adjuvant chemotherapy was included in the treatment plan. Although there were more current alcohol drinkers in the KRG group than in the placebo group (44%, 33%, respectively, $P = 0.041$), there were no significant differences in other baseline characteristics between groups (Table 1).

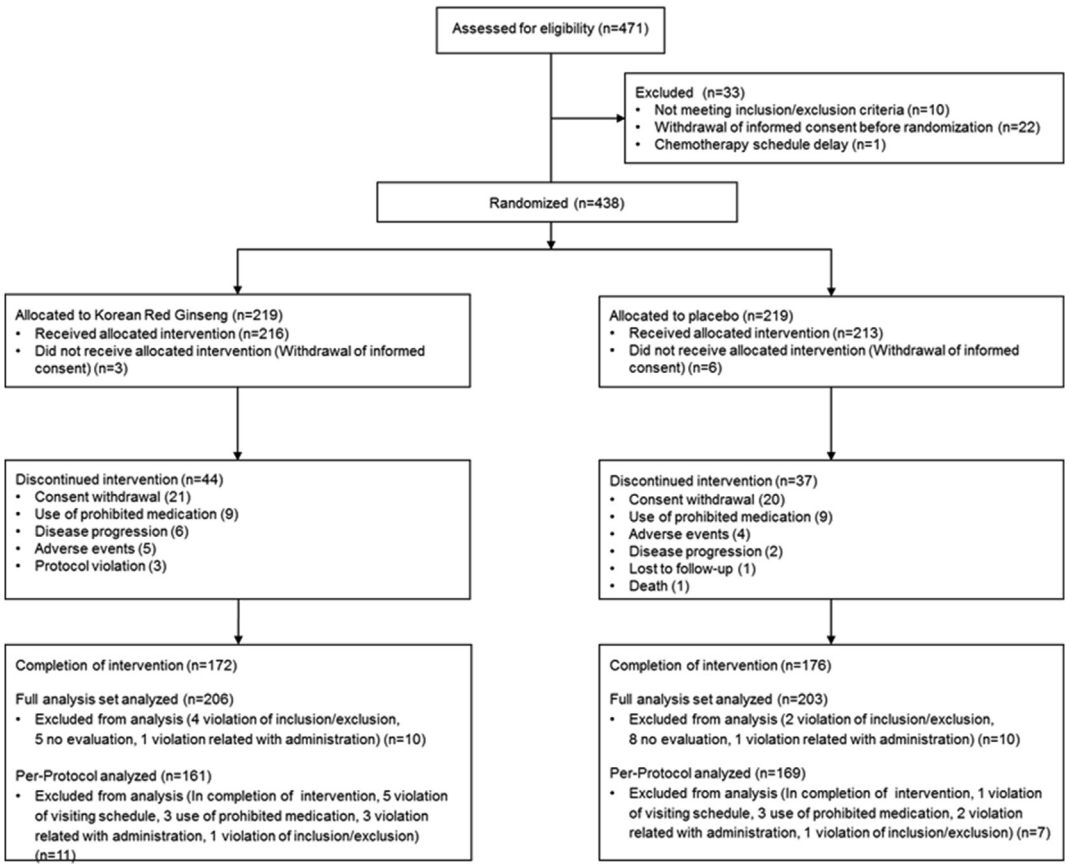


Fig. 1. CONSORT diagram.

Table 1
Baseline characteristics of patients.

	Korean red ginseng (n = 206)	Placebo (n = 203)	*P* value
Age (y)			
Median (range)	60 (29–84)	60 (27–86)	0.581t
Sex, n (%)			
Male/Female	124 (60)/82 (40)	123 (61)/80 (39)	0.935c
Body mass index (kg/m²)			
Mean (SD)	22.71 (3.18)	22.78 (2.96)	0.661w
Smoking Status, n (%)			
Non-Smoker	104 (50)	111 (55)	0.689c
Ex-Smoker	51 (25)	45 (22)	
Current Smoker	51 (25)	47 (23)	
Drinking Status, n (%)			
Non-Drinker	101 (49)	116 (57)	0.041c
Ex-Drinker	14 (7)	21 (10)	
Current Drinker	91 (44)	66 (33)	
Exercising Status[a], n (%)			
Yes	69 (34)	70 (34)	0.833c
No	137 (67)	133 (66)	
Supplementary Use for Health Functional Food, n (%)			
Yes	3 (1)	0 (0)	0.248f
No	203 (99)	203 (100)	
Stage			
II	46 (22)	40 (20)	0.798c
III	132 (64)	136 (67)	
IV	28 (14)	27 (13)	

SD = standard deviation, comparison of treatment and placebo groups using two-sample t-test (t), Wilcoxon rank-sum test (w), chi-square test (c), or Fisher's exact test (f).

[a] Exercise status means whether subject is currently doing physical exercise or not.

3.2. Drug compliance

Mean drug compliance with the trial product protocol by counting the remaining drugs throughout the 16 weeks was 88%. In the full analysis set, mean compliance was 87% in the KRG group and 89% in the placebo group. In the per-protocol set, mean compliance was 90% in the KRG group and 91% in the placebo group (Supplementary Table S1).

3.3. BFI

For the mean AUC change from baseline of BFI over 16 weeks in the full analysis set, the KRG group showed a benefit compared to the placebo group for all questions (AUC difference and *P*-value: 1.71 and 0.331 in "Fatigue right now"; 1.65 and 0.336 in "Usual fatigue"; 0.59 and 0.763 in "Worst fatigue"; 1.41 and 0.428 in "General activity"; 3.49 and 0.038 in "Mood"; 2.72 and 0.158 in "Normal work"; 2.65 and 0.144 in "Relations with others"; 4.03 and 0.023 in "Walking ability"; 3.51 and 0.065 in "Enjoyment of life"; 2.41 and 0.119 in "Global BFI score," respectively) (Fig. 2a, Supplementary Table S2). CRF was significantly improved, calculated by the mean AUC change from baseline of BFI regarding "Mood" and "Walking ability" compared to placebo (P = 0.038 and P = 0.023, respectively). In the per-protocol group, KRG led to improved CRF in the global BFI score compared with the placebo (P = 0.019). Specifically, there were improvements in "Fatigue right now" (P = 0.045), "Mood" (P = 0.006), "Relations with others" (P = 0.028), "Walking ability" (P = 0.003), and "Enjoyment of life" (P = 0.036) at 16 weeks ($P = 0.045$, $P = 0.006$, $P = 0.028$, $P = 0.003$, $P = 0.036$, respectively, Fig. 2b).

The results of mean AUC change from baseline of BFI over 8 weeks were similar to the results over 16 weeks (Supplementary Table S2). In the full analysis set, BFI regarding "Waking ability" was significantly improved. Per-protocol analysis revealed significant fatigue improvement in the KRG group for "Fatigue right now," "Usual fatigue," 'Mood," "Relations with others," "Walking ability" and "Global BFI score" ($P = 0.023$, $P = 0.021$, $P = 0.006$, $P = 0.027$, $P = 0.003$, $P = 0.013$, respectively).

3.4. Fatigue-related quality of life

In the full analysis set, although the KRG group had less deterioration of the FACIT-Fatigue Trial Outcome Index score from baseline compared to the placebo group, the difference between the two groups was not significant (Week 8; $P = 0.153$, Week 16; $P = 0.552$). In the per-protocol analysis set, changes in the FACIT-Fatigue Trial Outcome Index score from baseline to Week 8 were significantly better in the KRG group ($P = 0.015$, Table 2).

In the full analysis set, although KRG also showed less deterioration of FACIT-Fatigue Total score from baseline to Week 8 and Week 16 than the placebo group, the difference between the two groups was not significant (Week 8; $P = 0.546$, Week 16; $P = 0.700$). In the per-protocol set, changes in FACIT-Fatigue Total score from baseline to Week 8 and Week 16 were not significant between the two groups (Week 8; $P = 0.088$, Week 16; $P = 0.165$, Table 2).

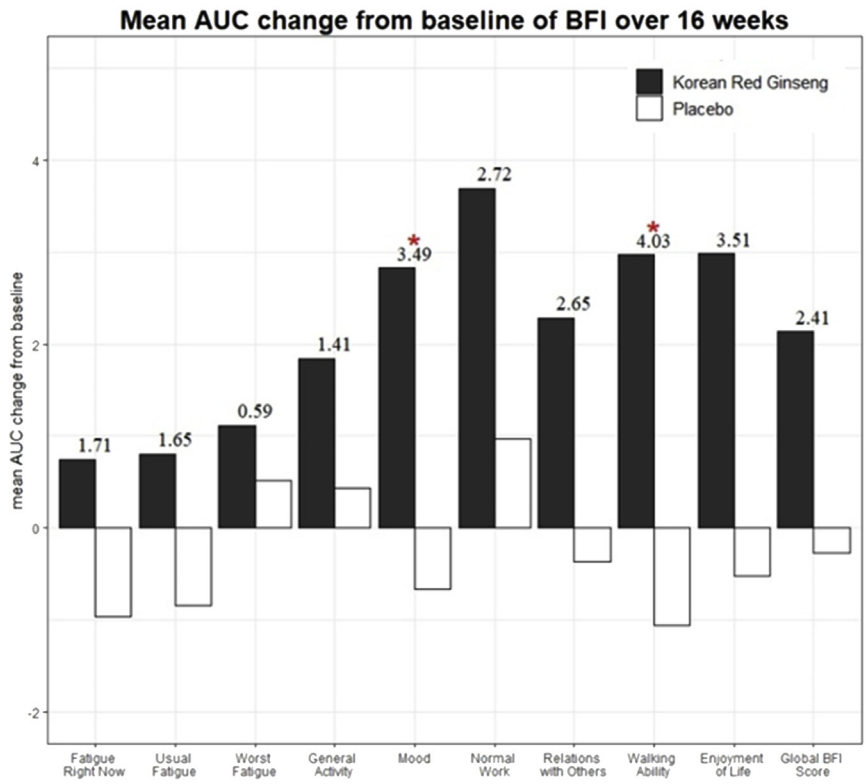
3.5. Perceived stress scale

Change in perceived stress scale from baseline to Week 16 in the full analysis set was -1.26 ± 6.47 for the KRG group and -0.25 ± 6.26 for the placebo group (Table 2). Although the stress index appeared to be reduced in the KRG group, this difference was not significant ($P = 0.147$). However, in per-protocol set analysis, KRG significantly reduced the perceived stress scale at Week 16 ($P = 0.024$, Table 2).

3.6. Subgroup analysis

Planned subgroup analysis was performed according to age (<60 years, ≥60 years), compliance (≥80%), sex

a. Full analysis set



b. Per protocol set

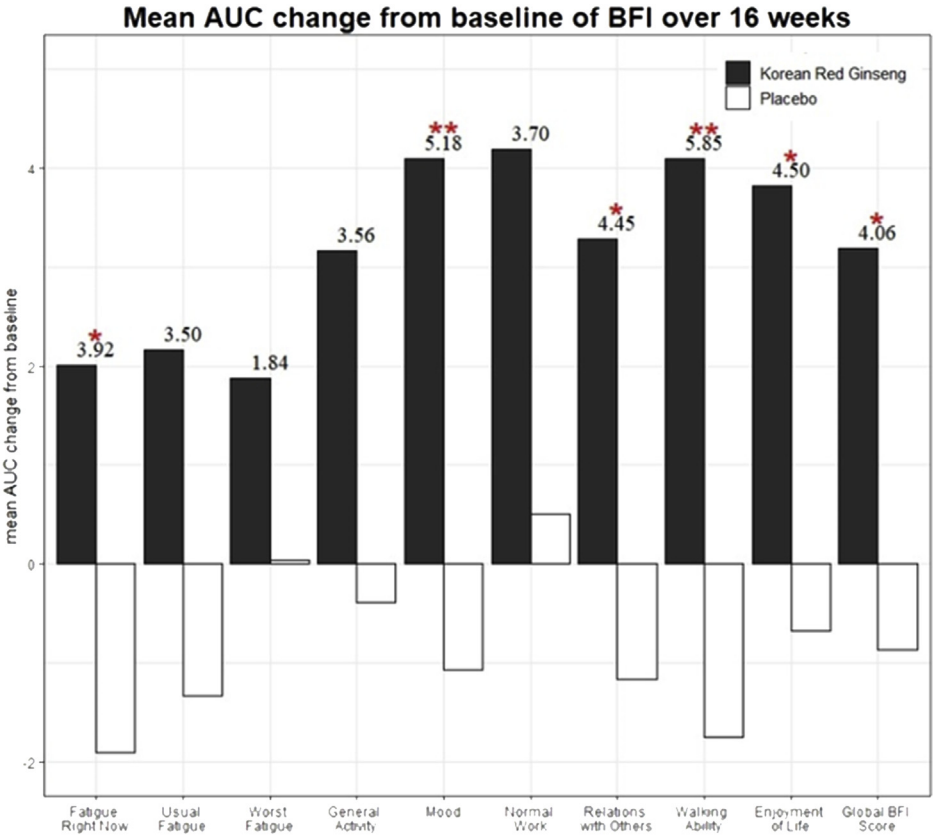


Fig. 2. The difference in cancer-related fatigue between Korean red ginseng and placebo over 16 weeks. **A)** Full analysis set. **B)** Per-protocol set. $*P < 0.05$, $**P < 0.01$, comparing treatment and placebo groups.

Table 2
Change from baseline in the functional assessment of chronic illness therapy (FACIT)-fatigue trial outcome index, FACIT-fatigue and perceived stress scale.

	Full analysis set			Per-protocol set		
	Korean red ginseng (n = 206)	Placebo (n = 203)	*P* value[a]	Korean red ginseng (n = 161)	Placebo (n = 169)	*P* value[a]
FACIT-fatigue trial outcome index						
Baseline	78.41 (16.52)	79.07 (17.32)		78.90 (16.37)	80.09 (16.58)	
Week 8	77.35 (19.92)	75.44 (18.85)		79.40 (18.76)	76.23 (18.54)	
Week 16	75.56 (18.85)	73.85 (20.35)		77.56 (17.90)	74.58 (19.89)	
Change from baseline at Week 8	−1.15 (18.33)	−3.69 (16.54)	0.153	0.50 (16.69)	−4.00 (15.38)	0.015
Change from baseline at Week 16	−2.95 (18.85)	−5.19 (18.40)	0.552	−1.34 (17.81)	−5.51 (17.19)	0.155
FACIT-fatigue total score						
Baseline	114.67 (22.11)	115.37 (23.61)		115.45 (22.45)	116.80 (22.76)	
Week 8	112.84 (27.15)	111.79 (24.71)		115.58 (25.71)	112.77 (24.26)	
Week 16	110.90 (25.36)	108.78 (26.63)		113.70 (24.23)	109.68 (26.09)	
Change from baseline at Week 8	−2.01 (23.59)	−3.66 (22.43)	0.546	0.13 (21.09)	−4.23 (21.45)	0.088
Change from baseline at Week 16	−3.96 (24.18)	−6.48 (23.55)	0.700	−1.75 (22.41)	−7.12 (22.38)	0.165
Perceived stress scale						
Baseline	16.07 (5.63)	15.90 (5.77)		15.86 (5.63)	15.53 (5.73)	
Week 16	14.66 (6.15)	15.58 (6.00)		14.07 (6.04)	15.38 (5.87)	
Change from baseline at Week 16	−1.26 (6.47)	−0.25 (6.26)	0.147	−1.79 (6.29)	−0.15 (6.00)	0.024

Data are presented as mean (standard deviation).
[a] Comparing treatment and placebo groups (rank ANCOVA model with ranked baseline value, sex and type of chemotherapy as covariates).

(male, female), and chemotherapy type (adjuvant, palliative). In a subgroup of the per-protocol set ≥60 years of age, CRF was significantly improved in the KRG group compared with the placebo group based on the mean AUC change from baseline of the global BFI score over 16 weeks ($P = 0.005$) and 8 weeks ($P = 0.011$) in full analysis set and to 16 weeks ($P < 0.001$) and 8 weeks ($P < 0.001$) in per-protocol set (Table 3). Less deterioration of fatigue-related quality of life and stress index was also observed in the KRG group in a subgroup ≥60 years of age (Supplementary Table S3). In the per-protocol analysis of subgroups with high compliance (≥80%) or those that were female, the KRG group showed significant improvement in fatigue based on the mean AUC change from baseline of the global BFI over 16 weeks and 8 weeks compared with the placebo group (Table 3). In palliative and adjuvant subgroups of the per-protocol set, KRG also significantly improved FACIT-fatigue total score at Week 8 and perceived stress scale at Week 16 from baseline compared with placebo, respectively ($P = 0.034$, $P = 0.033$, respectively, Supplementary Table S3). On the other hand, patients with more baseline fatigue (<median, 78.89) showed improvement of global BFI score at Week 8 and Week 16 compared with baseline in both groups. In contrast, patients with less baseline fatigue (≥median, 78.89) showed worse fatigue at Week 8 and Week 16 compared with baseline in both groups. In patients with more baseline fatigue (<median, 78.89), there was more improvement of global BFI score for patients with KRG than placebo at Week 8 and Week 16 (P = 0.048 and P = 0.060, respectively in full analysis set; P = 0.006 and P = 0.010, respectively) (Supplementary Table S4). However, this efficacy of KRG compared with placebo was not identified in patients with less baseline fatigue (≥median, 78.89).

3.7. Cortisol and cytokines

Although the blood cortisol level was significantly higher at Week 16 in the KRG group compared to the placebo group, the difference was within the normal physiological range and was not considered clinically significant. There were no significant changes in blood cytokines IL-1α, IL-1β, IL-6, or TNF-α at Week 16 in either group (Supplementary Table S5).

3.8. Safety

Adverse events of any grade were observed in a total of 366 patients (KRG, 86%; placebo, 86%). The incidence rates of adverse events were not significantly different between groups ($P = 0.937$) (Table 4). There were only 86 adverse events (6%) that were reported to be related to the trial product. The most frequently observed adverse events were nausea in 128 patients (KRG, 28%; placebo, 32%) and neutropenia in 62 subjects (KRG, 19%; placebo, 10%) (Table 4). Regarding concerns related to hypertensive crises at high doses of KRG, G3 hypertension was reported in 3 cases (1.40%), but in the placebo group, 1 patient (0.47%) also had G2 hypertension. However, mean and median systolic and diastolic blood pressures were not altered according to the treatment group or time frame (Supplementary Table S6). Severe adverse events (≥grade 3) occurred rarely and equally in both groups, except neutropenia. Neutropenia ≥ grade 3 was more frequent in the KRG

Table 3
Subgroup analysis: Global brief fatigue inventory score.

			Full analysis set		*P* value[a]	Per-protocol set		*P* value[a]
			Korean red ginseng (n = 206)	Placebo (n = 203)		Korean red ginseng (n = 161)	Placebo (n = 169)	
Global brief fatigue inventory score								
Age	<60 y (n = 194)	Week 4	1.50 (23.64)	2.97 (18.17)		2.89 (23.36)	3.11 (18.78)	
		Week 8	0.16 (23.58)	2.27 (18.48)		0.18 (24.36)	3.23 (18.63)	
		Week 12	−0.32 (25.27)	0.74 (20.05)		−1.11 (24.88)	0.94 (20.21)	
		Week 16	1.21 (24.16)	1.92 (21.74)		0.23 (23.42)	2.06 (21.83)	
		AUC (8 wks)	0.70 (1.34)	2.11 (1.33)		1.55 (1.56)	2.34 (1.46)	
		AUC (16 wks)	0.08 (1.54)	1.72 (1.52)		0.57 (1.77)	2.05 (1.65)	
		AUC diff.(8 wks)	−1.41 (1.89) [−5.12, 2.30]		0.455	−0.79 (2.14) [−4.98, 3.40]		0.712
		AUC diff.(16 wks)	−1.65 (2.16) [−5.88, 2.59]		0.446	−1.48 (2.43) [−6.23, 3.28]		0.543
	≥60 y (n = 215)	Week 4	6.29 (24.05)	1.12 (19.12)		9.42 (21.87)	−0.35 (18.71)	
		Week 8	4.63 (22.39)	−4.12 (22.30)		5.51 (22.28)	−5.82 (21.70)	
		Week 12	4.36 (25.53)	−3.11 (22.71)		4.72 (25.96)	−5.48 (21.11)	
		Week 16	2.77 (24.80)	−6.43 (25.05)		3.56 (24.77)	−7.02 (24.29)	
		AUC (8 wks)	4.28 (1.29)	−0.43 (1.34)		6.07 (1.40)	−1.62 (1.43)	
		AUC (16 wks)	3.93 (1.54)	−2.20 (1.58)		5.34 (1.70)	−3.74 (1.73)	
		AUC diff.(8 wks)	4.72 (1.86) [1.07, 8.36]		0.011	7.69 (2.01) [3.76, 11.62]		0.000
		AUC diff.(16 wks)	6.14 (2.20) [1.82, 10.45]		0.005	9.07 (2.43) [4.32, 13.83]		0.000
Compliance	≥80% (n = 324)	Week 4	4.33 (23.47)	1.59 (18.39)		6.84 (21.78)	1.01 (18.34)	
		Week 8	2.89 (23.43)	−1.00 (20.23)		2.98 (23.93)	−1.42 (20.03)	
		Week 12	2.57 (25.19)	−2.20 (21.08)		2.33 (25.29)	−3.43 (20.17)	
		Week 16	2.56 (24.50)	−1.94 (23.23)		2.59 (24.15)	−2.11 (22.83)	
		AUC (8 wks)	2.83 (1.05)	0.57 (1.04)		4.17 (1.12)	0.17 (1.09)	
		AUC (16 wks)	2.45 (1.23)	−0.63 (1.22)		3.37 (1.32)	−1.20 (1.28)	
		AUC diff.(8 wks)	2.26 (1.48) [−0.64, 5.16]		0.127	4.00 (1.57) [0.93, 7.08]		0.011
		AUC diff.(16 wks)	3.08 (1.73) [−0.31, 6.47]		0.075	4.56 (1.84) [0.95, 8.17]		0.013
Sex	Male (n = 247)	Week 4	2.55 (23.43)	2.20 (17.93)		4.19 (22.23)	2.12 (18.69)	
		Week 8	1.38 (22.48)	−1.71 (19.46)		2.06 (23.02)	−1.60 (20.06)	
		Week 12	1.72 (25.65)	−0.60 (19.01)		1.50 (25.40)	−1.31 (18.86)	
		Week 16	1.24 (23.33)	−3.69 (22.38)		1.29 (22.38)	−3.43 (22.40)	
		AUC (8 wks)	1.61 (1.17)	0.67 (1.17)		2.62 (1.32)	0.66 (1.31)	
		AUC (16 wks)	1.40 (1.36)	−0.51 (1.36)		2.11 (1.53)	−0.63 (1.52)	
		AUC diff.(8 wks)	0.94 (1.66) [−2.32, 4.19]		0.572	1.96 (1.86) [−1.69, 5.61]		0.293
		AUC diff.(16 wks)	1.91 (1.92) [−1.86, 5.68]		0.321	2.74 (2.16) [−1.49, 6.97]		0.204
	Female (n = 162)	Week 4	6.24 (24.59)	1.73 (19.87)		10.18 (23.20)	0.20 (18.96)	
		Week 8	4.29 (23.85)	0.33 (22.55)		4.79 (23.90)	−0.85 (21.70)	
		Week 12	2.93 (25.28)	−2.22 (24.91)		3.02 (26.02)	−3.74 (23.59)	
		Week 16	3.37 (26.29)	−0.31 (25.83)		3.30 (26.94)	−1.13 (25.10)	
		AUC (8 wks)	4.12 (1.54)	0.99 (1.60)		6.48 (1.74)	−0.25 (1.65)	
		AUC (16 wks)	3.27 (1.84)	0.01 (1.87)		5.18 (2.10)	−1.41 (1.99)	
		AUC diff.(8 wks)	3.13 (2.23) [−1.24, 7.49]		0.160	6.73 (2.41) [2.00, 11.46]		0.005
		AUC diff.(16 wks)	3.25 (2.63) [−1.90, 8.40]		0.216	6.59 (2.90) [0.90, 12.28]		0.023

Chemotherapy type	Adjuvant (n = 362)	Week 4	4.10 (24.14)	1.89 (18.25)		6.53 (22.58)	1.49 (18.33)	
		Week 8	2.13 (22.92)	−0.84 (21.01)		2.73 (23.26)	−0.93 (20.93)	
		Week 12	1.37 (25.79)	−1.33 (21.52)		1.24 (25.86)	−2.05 (21.09)	
		Week 16	2.09 (24.46)	−1.57 (23.80)		2.20 (24.04)	−1.56 (23.46)	
		AUC (8 wks)	2.55 (1.00)	0.75 (1.00)		3.99 (1.11)	0.49 (1.06)	
		AUC (16 wks)	1.85 (1.17)	−0.25 (1.16)		2.95 (1.30)	−0.58 (1.25)	
		AUC diff.(8 wks)	1.80 (1.41) [−0.96, 4.57]		0.201	3.50 (1.54) [0.49, 6.51]		0.023
		AUC diff.(16 wks)	2.11 (1.65) [−1.12, 5.33]		0.201	3.52 (1.81) [−0.02, 7.07]		0.052
	Palliative (n = 47)	Week 4	3.70 (22.75)	3.17 (22.20)		5.86 (24.45)	−0.16 (23.79)	
		Week 8	5.27 (23.96)	−1.61 (18.12)		5.99 (24.29)	−5.32 (17.73)	
		Week 12	8.39 (22.26)	−0.42 (21.78)		8.70 (22.71)	−4.92 (18.59)	
		Week 16	1.78 (25.02)	−10.67 (22.81)		0.86 (25.65)	−13.02 (21.71)	
		AUC (8 wks)	3.09 (2.77)	1.28 (3.01)		4.83 (3.46)	−1.93 (3.94)	
		AUC (16 wks)	4.43 (3.20)	−0.90 (3.47)		5.91 (3.91)	−5.08 (4.45)	
		AUC diff.(8 wks)	1.81 (4.13) [−6.29, 9.91]		0.662	6.76 (5.30) [−3.63, 17.15]		0.202
		AUC diff.(16 wks)	5.33 (4.76) [−4.01, 14.66]		0.263	10.99 (6.00) [−0.77, 22.74]		0.067

AUC (8 wks) and AUC (16 wks) represent the mean AUC change from baseline of global BFI score over 8 weeks and 16 weeks. AUC diff. represents the difference of mean AUC change from baseline of global BFI score between treatment groups.

[a] Comparing between treatment and placebo groups (mixed model with time, group, the interaction of time by group, and stratification factors). The change from baseline of global BFI score at each week is presented as mean (standard deviation). The mean AUC change from baseline of global BFI score and the difference between treatment groups are presented as mean (standard error) and mean (standard error) [95% confidence interval].

group than in the placebo group (13% vs. 7%). Adverse events resulting in trial product discontinuation occurred in 9 patients (KRG, 2%; placebo, 2%). Adverse events resulting in death occurred in one patient in the placebo group.

4. Discussion

We assessed the efficacy and safety of KRG compared with placebo for improving fatigue in patients with colorectal cancer receiving the mFOLFOX-6 regimen. Per-protocol set analysis showed significant improvement of fatigue in the KRG group compared with the placebo group based on the mean AUC change from baseline of BFI over 8 weeks and 16 weeks. The efficacy of KRG for improving fatigue was greater over 16 weeks than over 8 weeks. Additionally, the analysis of fatigue-related quality of life and stress index showed less deterioration from baseline in the KRG group. This study suggests that KRG could improve fatigue, reduce deterioration of fatigue-related quality of life, and decrease stress in patients with colorectal cancer receiving chemotherapy.

Because CRF is continuous and also fluctuates, it is difficult to identify the change in CRF through the simple comparison of two time points. Indeed, in this study, the simple comparison between baseline and Week 8 (or Week 16) did not demonstrate a difference between groups. For compensating this issue, the mean AUC change from baseline of the BFI was analyzed in this study, as in previous studies [16,22].

CRF can be divided into disease-related fatigue and treatment-related fatigue [7]. Cancer treatment is well known to produce and worsen fatigue. In particular, chemotherapy is a major risk factor in the development of severe fatigue [6,31,32]. Because fatigue characteristics and management may vary according to the cause of fatigue, subgroup analysis by the cause of fatigue should be conducted in clinical trials on CRF. Based on the results of this study, KRG could ameliorate chemotherapy-related fatigue. In particular subgroups (≥60 years old, those with high compliance (≥80%), or female sex), the KRG group showed greater improvement in fatigue. Patients who were ≥60 years old or female who had more fatigue symptoms in the placebo group may be especially vulnerable to chemotherapy-related fatigue. Moreover, in these groups, KRG could be more beneficial than in other groups.

A consistent link among CRF, inflammation, and dysregulation of the hypothalamic-pituitary-adrenal axis has been established in several preclinical studies [33,34]. Ginseng can downregulate inflammatory pathways, decrease inflammation, modulate cortisol, and decrease the impact of chronic stress on the hypothalamic-pituitary-adrenal axis [35–38]. In this study, there were no significant changes in blood cytokine IL-1α, IL-1β, IL-6, and TNF-α at Week 16 for

Table 4
Incidence of frequently occurring (≥5%) treatment-emergent adverse events.

	Korean red ginseng (n = 215)		Placebo (n = 212)	
	Grade 1/2	≥ Grade 3	Grade 1/2	≥ Grade 3
Nausea	50 (23)	11 (5)	56 (26)	11 (5)
Decreased appetite	38 (18)	1 (0)	30 (14)	3 (1)
Neutropenia	13 (6)	28 (13)	6 (3)	15 (7)
Diarrhea	25 (12)	5 (2)	28 (13)	1 (0)
Aspartate aminotransferase increase	23 (11)	0 (0)	24 (11)	0 (0)
Alanine aminotransferase increase	25 (12)	0 (0)	22 (10)	0 (0)
Fatigue	20 (9)	0 (0)	20 (9)	0 (0)
Constipation	20 (9)	0 (0)	15 (7)	0 (0)
Thrombocytopenia	15 (7)	2 (1)	14 (7)	0 (0)
Peripheral neuropathy	33 (15)	1 (0)	41 (19)	0 (0)
Leukopenia	16 (7)	2 (1)	9 (4)	1 (0)
Insomnia	13 (6)	0 (0)	11 (5)	0 (0)
Dyspepsia	12 (6)	0 (0)	10 (5)	0 (0)
Stomatitis	9 (4)	1 (0)	11 (5)	1 (0)
Cough	10 (5)	0 (0)	11 (5)	0 (0)
Headache	15 (7)	1 (0)	4 (2)	0 (0)
Vomiting	11 (5)	2 (1)	6 (3)	0 (0)
Upper respiratory tract infection	12 (6)	0 (0)	4 (2)	0 (0)

Data are presented as the number of subjects (%).

either group. Since blood cortisol and cytokine levels vary for many reasons, it is difficult to define the mechanism of action of KRG in this clinical trial by comparing baseline and Week 16 only.

In the full analysis set, the efficacy of KRG for CRF was not dramatic and in the per-protocol set, KRG was more efficacious than in full analysis set. This is a limitation to interpret the result of this study. However, this study was initially designed to analyze the results in both full analysis set and per-protocol set. All results were analyzed in both the full analysis set and the per-protocol set. When it was considered that KRG was just an adjunctive to chemotherapy, a compliance issue for efficacy would be important. This finding of better efficacy in the per-protocol set was in accordance with a subgroup analysis of high compliance (≥80%). On the other hand, the efficacy of KRG could be different according to the baseline fatigue status. In this study, the efficacy of KRG was enhanced in patients with more baseline fatigue. Therefore, patients' selection according to baseline fatigue status would be important in clinical application and further studies for improving fatigue, although this study did not select patients according to baseline fatigue status.

In contrast to previous trials of American ginseng, laboratory tests were performed to monitor adverse events attributed to concurrent chemotherapy. Neutropenia was observed more frequently in the KRG than in the placebo group. While this difference could not be explained, withdrawal from the study due to neutropenia occurred equally in both groups, and all adverse events were tolerable and manageable. Most adverse events were thought to be associated with mFOLFOX-6 chemotherapy, and adverse events in the KRG group did not appear to be associated with trial product intake. Therefore, there are no specific safety issues related to KRG administration in patients with cancer receiving active chemotherapy. Whether KRG interferes with or acts synergistically with chemotherapeutics remains to be elucidated. Future studies should obtain additional information related to the dose intensity of chemotherapy, disease-free survival, and overall survival.

5. Conclusions

KRG intake showed more effective fatigue improvement over placebo in patients with colorectal cancer receiving mFOLFOX-6 chemotherapy. Furthermore, fatigue-related quality of life and stress index deteriorated less from baseline in the KRG group than in the placebo group. In subgroups of female patients, ≥60 years old, with high compliance (≥80%) or more baseline fatigue, KRG administration had a stronger effect on fatigue. KRG intake for 16 weeks was safe and, although neutropenia was observed more frequently in the KRG group than in the placebo group, all adverse events were tolerable and manageable.

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Role of the funding source

The funder was involved in the design and conduct of the study. But the funding source had no role in the collection, management, analysis and interpretation of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

Contributors' statement

Y.H.K. designed the study. J.W.K., S.W. H., J.Y.C., I.J.C., J.G.K., K.H.L., K.U.P., S.K.B., S.C.O., M.A.L., D.O., B.S., J.B.A., D.S., and Y.H.K. collected study data. Data analysis and interpretation was performed by J.W.K., J.W.L. and Y.H.K. Manuscript draft by J.W.K. and Y.H.K. S.W. H., J.Y.C., I.J.C., J.G.K., K.H.L., K.U.P., S.K.B., S.C.O., M.A.L., D.O., B.S., J.B.A., D.S., and J.W.L. critically appraised the manuscript. All authors agreed with the submission of the final version of the article.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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References

[1] Arndt V, Stegmaier C, Ziegler H, Brenner H. A population-based study of the impact of specific symptoms on quality of life in women with breast cancer 1 year after diagnosis. Cancer 2006; 107(10):2496–503.
[2] Bower JE, Ganz PA, Desmond KA, Bernaards C, Rowland JH, Meyerowitz BE, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer 2006;106(4):751–8.
[3] Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5(5):353–60.
[4] Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors–a systematic review. Int J Psychiatr Med 2010; 40(2):163–81.
[5] Molassiotis A, Zheng Y, Denton-Cardew L, Swindell R, Brunton L. Symptoms experienced by cancer patients during the first year from diagnosis: patient and informal caregiver ratings and agreement. Palliat Support Care 2010;8(3):313–24.
[6] Purcell A, Fleming J, Bennett S, McGuane K, Burmeister B, Haines T. A multidimensional examination of correlates of fatigue during radiotherapy. Cancer 2010;116(2):529–37.
[7] Wang XS, Woodruff JF. Cancer-related and treatment-related fatigue. Gynecol Oncol 2015;136(3):446–52.
[8] Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. Support Care Cancer 2008;16(7):791–801.
[9] Minton O, Alexander S, Stone PC. Identification of factors associated with cancer related fatigue syndrome in disease-free breast cancer patients after completing primary treatment. Breast Cancer Res Treat 2012;136(2):513–20.
[10] Minton O, Strasser F, Radbruch L, Stone P. Identification of factors associated with fatigue in advanced cancer: a subset analysis of the European palliative care research collaborative computerized symptom assessment data set. J Pain Symptom Manag 2012;43(2):226–35.
[11] Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. Ann Oncol 2000;11(8):971–5.
[12] Fulton C, Knowles G. Cancer fatigue. Eur J Cancer Care (Engl) 2000;9(3):167–71.
[13] Bruera E, El Osta B, Valero V, Driver LC, Pei BL, Shen L, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2007;25(23):3475–81.
[14] Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006; 24(13):2073–8.
[15] Conklin HM, Reddick WE, Ashford J, Ogg S, Howard SC, Morris EB, et al. Long-term efficacy of methylphenidate in enhancing attention regulation, social skills, and academic abilities of childhood cancer survivors. J Clin Oncol 2010;28(29): 4465–72.
[16] Moraska AR, Sood A, Dakhil SR, Sloan JA, Barton D, Atherton PJ, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. J Clin Oncol 2010;28(23):3673–9.
[17] Morrow GR, Hickok JT, Roscoe JA, Raubertas RF, Andrews PL, Flynn PJ, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the university of rochester cancer center community clinical oncology program. J Clin Oncol 2003;21(24):4635–41.
[18] de Oliveira Campos MP, Riechelmann R, Martins LC, Hassan BJ, Casa FB, Del Giglio A. Guarana (Paullinia cupana) improves fatigue in breast cancer patients undergoing systemic chemotherapy. J Altern Complement Med 2011;17(6):505–12.
[19] Cruciani RA, Dvorkin E, Homel P, Culliney B, Malamud S, Lapin J, et al. L-carnitine supplementation in patients with advanced cancer and carnitine deficiency: a double-blind, placebo-controlled study. J Pain Symptom Manag 2009;37(4): 622–31.
[20] Lesser GJ, Case D, Stark N, Williford S, Giguere J, Garino LA, et al. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. J Support Oncol 2013;11(1):31–42.
[21] Barton DL, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. J Natl Cancer Inst 2013;105(16):1230–8.
[22] Barton DL, Soori GS, Bauer BA, Sloan JA, Johnson PA, Figueras C, et al. Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. Support Care Cancer 2010;18(2):179–87.
[23] Baeg IH, So SH. The world ginseng market and the ginseng (Korea). J Ginseng Res 2013;37(1):1–7.
[24] Kim S, Kim J, Lee Y, Seo MK, Sung DJ. Anti-fatigue effects of acute red ginseng intake in recovery from repetitive anaerobic exercise. Iran J Public Health 2016;45(3):387–9.
[25] Choi JY, Woo TS, Yoon SY, Ike Campomayor Dela P, Choi YJ, Ahn HS, et al. Red ginseng supplementation more effectively alleviates psychological than physical fatigue. J Ginseng Res 2011; 35(3):331–8.
[26] Yennurajalingam S, Reddy A, Tannir NM, Chisholm GB, Lee RT, Lopez G, et al. High-dose asian ginseng (panax ginseng) for cancer-related fatigue: a preliminary report. Integr Cancer Ther 2015;14(5):419–27.
[27] Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. Cancer 1999;85(5):1186–96.
[28] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385–96.
[29] Lee EH. Review of the psychometric evidence of the perceived stress scale. Asian Nurs Res (Korean Soc Nurs Sci) 2012;6(4): 121–7.
[30] Bell ML, King MT, Fairclough DL. Bias in area under the curve for longitudinal clinical trials with missing patient reported outcome data: summary measures versus summary statistics. SAGE 2014;4(2):1–12.
[31] Dhruva A, Dodd M, Paul SM, Cooper BA, Lee K, West C, et al. Trajectories of fatigue in patients with breast cancer before,

during, and after radiation therapy. Cancer Nurs 2010;33(3):201–12.
[32] Donovan KA, Jacobsen PB, Andrykowski MA, Winters EM, Balducci L, Malik U, et al. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. J Pain Symptom Manag 2004;28(4):373–80.
[33] Thornton LM, Andersen BL, Blakely WP. The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Health Psychol 2010;29(3):333–7.
[34] Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. Brain Behav Immun 2007;21(4):413–27.
[35] Lee HJ, Cho SH. Therapeutic effects of Korean red ginseng extract in a murine model of atopic dermatitis: anti-pruritic and anti-inflammatory mechanism. J Korean Med Sci 2017;32(4):679–87.
[36] Yang Y, Lee J, Rhee MH, Yu T, Baek KS, Sung NY, et al. Molecular mechanism of protopanaxadiol saponin fraction-mediated anti-inflammatory actions. J Ginseng Res 2015;39(1):61–8.
[37] Yu T, Rhee MH, Lee J, Kim sH, Yang Y, Kim HG, et al. Ginsenoside rc from Korean red ginseng (panax ginseng C.A. Meyer) attenuates inflammatory symptoms of gastritis, hepatitis and arthritis. Am J Chin Med 2016;44(3):595–615.
[38] Hong M, Lee YH, Kim S, Suk KT, Bang CS, Yoon JH, et al. Anti-inflammatory and antifatigue effect of Korean Red Ginseng in patients with nonalcoholic fatty liver disease. J Ginseng Res 2016;40(3):203–10.