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Research Article

Effect of Korean Red Ginseng in individuals exposed to high stress levels: a 6-week, double-blind, randomized, placebo-controlled trial

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ABSTRACT

Background: To investigate the neurobiological evidence supporting the adaptogenic effects of Korean Red Ginseng in reducing the harmful consequences of stress using a double-blind, placebo-controlled trial.

Method: Sixty-three subjects with high stress levels were randomized to receive an orally administered, double-blind, 6-week treatment with Korean Red Ginseng (n = 32) or placebo (n = 31). All participants underwent a comprehensive psychological evaluation using Beck Depression Inventory and Stress Response Inventory, cognitive evaluation using the continuous performance test, biological evaluation by measuring blood levels of lipids, catecholamines, inflammation markers, and heart rate variability at baseline and after 6 weeks.

Results: At baseline, both groups showed no significant differences in age, sex, years of education, Beck Depression Inventory, and Stress Response Inventory. After 6 weeks, triglyceride levels were significantly increased within the normal limit in the Korean Red Ginseng group ($F = 4.11$, $p = 0.048$), and the epinephrine level was decreased in this group ($F = 4,35$, $p = 0.043$). The triglyceride increase was significantly associated with epinephrine decrease ($B = -0.087$, $p = 0.041$), suggesting that Korean Red Ginseng may stabilize the sympathetic nervous system. In addition, we detected a significant group by time effect in the visually controlled continuous performance test, suggesting positive effects of Korean Red Ginseng on cognition.

Conclusion: Korean Red Ginseng might help to stabilize the sympathetic nervous system and improve cognition in individuals with high stress.

1. Introduction

Korean Red Ginseng (KRG; heat-processed *Panax ginseng*) has long been recognized as a traditional natural medicine for the goodness of physical and mental health in Far East Asia. Traditionally, it is believed to possess equilibrating, tonic, antistress, and adaptogenic actions. It remains one of the best-selling herbal products. Animal and preclinical studies have confirmed the neuromodulatory [1], neuroprotective [2–4], and antiinflammatory effects [5–7], which may be associated with antistress activity. However, there is little biological evidence underlying the adaptogenic effects, with no published double-blind randomized controlled trials (RCTs).

This is the first double-blind RCT to explore the biological evidence supporting the adaptogenic effects of KRG. We compared the perceived stress levels, cognitive functions, and biological markers

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associated with stress in individuals with serious psychological distress (i.e., high-risk group). The high-risk group was randomized to 6 weeks of treatment with KRG or placebo. We investigated if administration of KRG improved the aforementioned variables.

2. Methods

2.1. Participants

We recruited nurses and fire fighters, members of two high-stress occupations, who aged 20–60 years. They responded to an advertisement concerning stress management with KRG. After explaining the purpose and procedures, participants who provided informed consent were included. Women of childbearing potential or those who were pregnant who had serious or unstable medical illness, past history of psychiatric illnesses, premenstrual syndrome, and clinically significant depression defined as Beck Depression Inventory (BDI) score ≥30 were excluded from the study. This study was approved by the Institutional Review Board of the Samsung Medical Center.

After the screening interview, the stress response inventory (SRI) and the BDI were administered to select the high-stress group. The SRI is a widely used and valid measure of psychological, physical, cognitive, and behavioral stress responses in clinical practice [8]. It comprises 26 questions with responses measured on a 5-point Likert scale. The cutoff score to define high-stress individuals is ≥81 points. The BDI [9] is a popular measure to evaluate the severity and patterns of depressive symptoms based on 21 questions. Each question is used to measure the symptom severity on a 4-point Likert scale. We used the standardized Korean translated version [10], which has high sensitivity and reliability. The cutoff score to define high-stress individuals was ≥10 points, which indicates mild depression. Sixty-three of 100 screened participants (57.1% female; mean ± SD age = 40.4 ± 1.5 years) met the criteria for the high-stress group.

3. Study process

3.1. Preparation of Korean Red Ginseng

Korean Red Ginseng (KRG) powder was manufactured by Korea Ginseng Corporation, Seoul, Korea, from roots of a 6-year-old red ginseng, *Panax ginseng* Meyer, harvested in the Republic of Korea. KRG was prepared by steaming fresh ginseng at 90–100°C for 3 h and drying at 50–80°C. KRG powder was prepared from ground red ginseng. In our study, we used the KRG capsule (LAX-101), which contains 500 mg of KRG powder per capsule. KRG used in our study was analyzed by high-performance liquid chromatography. KRG extract contained major ginsenosides as follows: Rb1, 6.44 mg/g; Rb2, 2.25 mg/g; Rc, 2.68 mg/g; Rd, 0.50 mg/g; Re, 2.08 mg/g; Rf, 0.89 mg/g; Rg1, 3.21 mg/g; Rg2, 0.29 mg/g; Rg3, 0.18 mg/g; and other minor ginsenosides.

3.1.1. Baseline evaluation

All participants underwent comprehensive psychological, cognitive, and biological evaluations. For the psychological evaluation, the Perceived Stress Scale (PSS) [11] was used to measure the degree of individually perceived stress. The PSS contains 10 questions with responses measured using a 5-point Likert scale. We used the Korean version of PSS [12], which has excellent reliability and validity. The Profile of Mood States [13] was used to evaluate the mood status during the preceding week. The Profile of Mood States is a self-reported questionnaire comprising 65 questions that evaluate six dimensions, including tension or anxiety, anger or hostility, vigor or activity, fatigue or inertia, depression or dejection, and confusion or bewilderment, using a 5-point scale. The Sheehan Disability Scale [14] was used to evaluate the degree of functional impairment. The Sheehan Disability Scale comprises three questions with responses measured using an 11-point Likert scale. The tool explores functional levels at work/school, social, and family life.

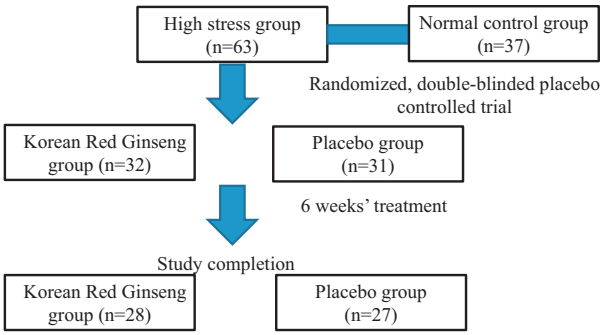

Fig. 1. Study flow diagram.

The cognitive evaluation involved the visual and auditory controlled continuous performance test (CPT), which was administered to evaluate attention and memory. The test takes 10 min to complete. In addition, the subjective cognitive impairment was assessed using the following question that was validated in a previous study [15]: "Do you have complaints about your memory?" Answers were coded in four categories (no; sometimes, but it is no problem; yes, it is a problem; yes, it is a serious problem).

The biological evaluation involved determination of height and weight; vital signs, including blood pressure and heart rate; catecholamines, including norepinephrine and epinephrine; inflammatory factors, including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, IL-12, interferon-gamma, tumor necrosis factor-alpha, and C-reactive protein; lipid levels, including high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol; and fasting blood sugar and HbA1c levels. Blood samples were drawn after 30 min of rest.

3.1.2. Randomization and evaluations (Fig. 1)

Sixty-three participants (57.1% female; mean ± SD age 40.4 ± 1.5 years) were randomly assigned after being considered eligible by a study clinician at the screening visit. Randomization was performed using the Excel program. A research coordinator conducted the randomization process. All study clinicians and participants remained blinded to the assignment for the duration of the study. Participants received treatment (four capsules per day taken twice daily) of either 2 g/day of KRG (LAX-101) or placebo for 6 weeks. We selected the dosage of 2 g/day based on the previous study [16]. Packaging, storing, and handling conditions were identical for both LAX-101 and placebo. The normal control group received neither KRG nor placebo. The aforementioned evaluations were performed at baseline and after 6 weeks.

3.2. Statistical analyses

Descriptive statistics were obtained for the ginseng and placebo groups. The two groups were compared using Student *t* test for continuous variables (age and education level) and by Chi-square test for categorical variables. Mixed model analyses were conducted to assess improvement in measures after 6 weeks of treatment to determine the group effect and group by time effect. For all analyses, two-sided significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 24 software (IBM SPSS Statistics, United States).

Table 1
Comparisons of basic characteristics between Korean Red Ginseng and placebo groups

Variables	Korean Red Ginseng group (n = 32)		Placebo group (n = 31)		Statistics t or χ^2	p
	Mean	SD	Mean	SD		
Age	39.59	12.36	41.29	11.73	0.56	0.58
Sex (M)	52.8%		47.2%		0.13	0.72
Education level (years)	3.56	0.84	3.61	0.76	0.25	0.80
BMI	22.89	3.66	22.58	2.95	0.37	0.71
SBP	127.16	14.23	123.10	13.64	1.16	0.25
DBP	79.28	9.19	75.74	9.01	1.54	0.13
Heart rate	77.42	12.68	74.39	7.93	1.13	0.26
Alcohol consumption, g/wk	50.03	92.85	59.97	99.03	0.41	0.68
Smoking, pack-year	6.09	19.41	5.66	15.17	0.10	0.92
BDI	20.44	8.90	19.87	9.32	0.25	0.81
SRI	56.88	25.26	54.61	31.76	0.31	0.76

BDI, Beck Depression Inventory; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation; SRI, Stress Response Inventory.

4. Results

The two groups showed no significant baseline differences in age, sex, education levels, body mass index (BMI), systolic and diastolic blood pressure, heart rate, alcohol intake and smoking status, BDI, or SRI (Table 1).

Fifty-five of the randomized participants (87.3%; 28 in the treatment group, 27 in the placebo group) completed the full 6 weeks of treatment. There was no significant difference in dropout rates between the groups ($p > 0.05$).

No significant differences were observed regarding psychological measures (Table 2). In the cognitive function test (Table 3), an interaction effect of group by time was detected between the two groups for correct response time although it did not reach statistical significance ($F = 3.84$, $p = 0.056$). The KRG group showed a shorter correct response time after 6 weeks in visually controlled CPT, whereas the placebo group had longer correct response time at study endpoint.

In the blood measures (Table 4), a significant interaction effect of group by time was observed for triglyceride levels ($F = 4.11$, $p = 0.048$). The KRG group had greater triglyceride levels at study endpoint. However, the increased triglyceride level remained within the normal range, suggesting no harmful cardiovascular side effects. The number of participants whose triglyceride level exceeded normal limit (>200 mg/dL) was not significantly different between two groups ($\chi^2 = 0.25$, $p = 0.61$). Furthermore, a significant group effect and the interaction effect of group by time with a trend toward significance were detected in epinephrine levels: The KRG group showed a trend to decreasing epinephrine after treatment, whereas the placebo group showed increased epinephrine. No significant differences were observed in the other blood measures.

Because epinephrine is involved in triglyceride hydrolysis, we additionally evaluated the correlation between epinephrine and triglyceride levels after adjusting for age and BMI (Table 5). The epinephrine level was significantly associated with triglyceride levels ($\beta = -0.087$, $p = 0.041$). In the KRG group, the mean change of blood epinephrine level was consistently decreased depending on the mean changes of blood triglyceride level, whereas inconsistent patterns of change were observed in the placebo group (Fig. 2).

5. Discussion

This is the first double-blind RCT to explore the biological evidence for an adaptogenic effect of KRG in individuals at high risk for stress. The results provide neurobiological evidence supporting an adaptogenic effect of KRG.

The treatment group tolerated KRG very well, with a dropout rate similar to the placebo group. No significant improvement was detected with regard to subjective measures, including perceived stress level, mood status, and cognitive complaints, possibly because of the characteristics of the study participants. They all had highly stressful jobs, which were directly associated with greater psychological distress and high risk of mental illness. The 6-week treatment period might not have been long enough to produce an effect. In addition, a few studies suggest that high placebo effect was frequently observed in clinical trials of nutraceuticals [17] although evidence for this effect is mixed [18]. Expectations of a trial outcome [19] and treatment received [20] are likely to have a significant effect on the degree of placebo response.

Blood parameters, however, suggested potential mechanisms associated with adaptogenic effect of KRG. The treatment group showed a significant increase in triglyceride levels (although still

Table 2
Comparison of psychological distress between Korean Red Ginseng and placebo groups after 6 weeks of treatment

Variables	Korean Red Ginseng group (n = 32)		Placebo group (n = 31)		Group effect		Group by time effect	
	Baseline	6 weeks	Baseline	6 weeks	F	p	F	p
Profile of Mood States score (K-POMS) [mean (SD)]								
Total score	98.59 (37.33)	87.55 (36.77)	71.71 (30.18)	66.35 (32.39)	1.17	0.287	0.11	0.737
Depression	18.59 (9.43)	15.65 (10.45)	9.00 (7.19)	10.00 (8.65)	0.21	0.653	0.89	0.352
Vigor	24.65 (2.38)	27.06 (2.98)	24.25 (2.20)	23.20 (2.75)	0.76	0.389	0.40	0.531
Anxiety	14.71 (2.10)	7.59 (1.86)	11.95 (1.93)	8.15 (1.72)	0.41	0.525	0.64	0.431
Anger	14.12 (9.57)	9.47 (9.81)	12.70 (8.30)	7.95 (8.39)	0.45	0.507	0.01	0.980
Fatigue	18.35 (7.39)	13.00 (7.52)	15.90 (7.31)	11.70 (7.59)	1.18	0.286	0.11	0.743
Confusion	8.18 (4.89)	5.59 (3.18)	7.10 (4.71)	5.35 (4.84)	0.39	0.539	0.16	0.688
Perceived Stress Scale (PSS) [mean (SD)]								
Total score	17.52 (4.14)	14.00 (6.26)	18.26 (4.21)	15.81 (6.33)	1.51	0.224	0.28	0.600
Positive	9.04 (2.72)	8.44 (3.90)	9.11 (2.64)	8.59 (4.25)	0.02	0.881	0.004	0.949
Negative	8.48 (2.82)	5.56 (4.04)	9.15 (3.61)	7.22 (3.97)	2.25	0.140	0.66	0.420
Sheehan Disability Scale (SDS) [mean (SD)]								
Total score	10.38 (7.72)	6.54 (5.18)	11.96 (6.90)	9.70 (7.56)	2.41	0.127	0.49	0.487
Occupational	3.33 (2.58)	2.63 (1.97)	3.60 (2.84)	3.64 (2.66)	1.22	0.275	0.74	0.395
Family	3.17 (2.75)	2.75 (2.03)	3.76 (2.40)	3.32 (2.32)	0.93	0.339	<0.01	0.971
Interpersonal	2.62 (2.48)	1.96 (1.69)	4.25 (2.36)	4.00 (2.34)	1.96	0.007	0.69	0.411

SD, standard deviation.

Table 3
Comparison of cognitive measures between Korean Red Ginseng and placebo groups after 6 weeks of treatment

Variables	Korean Red Ginseng group (n = 32)		Placebo group (n = 31)		Group effect		Group by time effect	
	Baseline	6 weeks	Baseline	6 weeks	*F*	*p*	*F*	*p*
Visually controlled continuous performance test (CPT) [mean (SD)]								
Number of correct response	59.68 (8.16)	61.72 (3.97)	60.96 (5.97)	61.75 (1.82)	0.29	0.594	0.39	0.538
Omission error	3.24 (8.19)	1.08 (3.00)	2.04 (5.97)	1.25 (1.82)	0.20	0.660	0.46	0.500
Commission error 1	0.56 (1.81)	0.60 (2.06)	2.96 (8.35)	1.46 (4.64)	1.72	0.197	1.36	0.249
Commission error 2	2.52 (10.95)	0.36 (0.64)	2.17 (9.36)	0.54 (0.88)	<0.01	0.953	0.03	0.857
Correct response time	0.455 (0.10)	0.439 (0.09)	0.461 (0.10)	0.475 (0.10)	0.75	0.393	3.84	0.056
Auditory controlled CPT [mean (SD)]								
Number of correct response	60.48 (2.49)	59.56 (3.87)	59.38 (4.34)	58.46 (4.63)	1.47	0.232	<0.01	0.998
Omission error	2.52 (2.49)	3.24 (3.64)	3.63 (4.34)	4.54 (4.63)	1.82	0.184	0.02	0.879
Commission error 1	1.88 (1.81)	1.92 (2.00)	3.88 (7.01)	3.75 (5.48)	2.42	0.127	0.03	0.860
Commission error 2	0.16 (0.37)	0.12 (0.33)	1.67 (6.30)	0.21 (0.51)	1.58	0.215	1.26	0.268
Correct response time	0.659 (0.09)	0.649 (0.09)	0.674 (0.09)	0.647 (0.08)	0.61	0.437	1.15	0.290

SD, standard deviation.

within the normal limit) and a trend toward decreased levels of epinephrine. Lower lipid levels have been associated with depression [21], impulsivity [22,23], and suicidal attempts [24,25] probably due to the impact of lipids on the structure and function of neuronal membranes [26]. In addition, epinephrine stimulates the sympathetic nervous system, which mediates the stress response.

Interestingly, epinephrine levels in the KRG group showed a negative correlation with triglyceride levels ($\beta = -0.087, p = 0.041$); increased triglyceride levels were associated with decrease in epinephrine after adjusting for age and BMI. Epinephrine stimulated triglyceride hydrolysis in adipocytes [27]. In line with this finding, an animal study showed that saponin, a compound abundant in KRG, inhibited catecholamine secretion stimulated by cholinergic stimulation [28].

Chronic stress increases cortisol levels by activating the hypothalamic–pituitary–adrenal axis via catecholamine hormones including epinephrine. Increased cortisol level exacerbates the risk of metabolic syndrome associated with decreased urinary epinephrine output (20), suggesting complex interactions between lipid metabolism and the sympathoadrenal systems. In another study, individuals at risk of metabolic syndrome showed lower plasma epinephrine levels, which were negatively correlated with triglyceride (21).

Taken together, the results suggest that KRG might stabilize the central nervous system, autonomic nervous system, and hypothalamic–pituitary–adrenal axis via complex effects on lipid metabolism and sympathoadrenal systems.

Although subjective cognitive complaints were not improved, the KRG group also showed improvement in correct response time of visually controlled CPT, probably due to improved cognitive function.

Ginsenosides, the triterpene glycosides (saponins), are the constituents found almost exclusively in ginseng. More than 100 ginsenosides have been isolated from *P. ginseng*, and protopanaxadiol and protopanaxatriol are the main structural components of the aglycone moiety of ginsenosides [29]. KRG is heat-processed *P. ginseng*. The processed red ginseng comprises unique

Table 4
Comparison of blood parameters between Korean Red Ginseng and placebo groups after 6 weeks of treatment

Variables	Korean Red Ginseng group (n = 32)		Placebo group (n = 31)		Group effect		Group by time effect	
	Baseline	6 weeks	Baseline	6 weeks	*F*	*p*	*F*	*p*
Lipid battery [mean (SD)]								
HDL (mg/dL)	62.66 (17.23)	60.65 (17.78)	63.58 (15.47)	65.63 (17.22)	0.67	0.42	1.87	0.18
LDL (mg/dL)	103.59 (28.44)	110.92 (26.62)	111.45 (31.61)	105.75 (25.71)	0.23	0.63	2.53	0.12
Triglyceride (mg/dL)	117.97 (67.51)	149.65 (81.68)	124.07 (68.83)	111.21 (54.26)	0.38	0.54	4.11	0.048*
Total cholesterol (mg/dL)	176.03 (30.73)	185.73 (26.78)	187.26 (31.43)	179.50 (24.44)	0.59	0.45	3.65	0.06
Catecholamine [mean (SD)]								
Norepinephrine (pg/dL)	296.48 (139.40)	307.21 (177.87)	289.83 (119.15)	314.24 (119.45)	0.002	0.97	0.21	0.65
Epinephrine† (pg/dL)	29.17 (1.72)	27.87 (1.91)	30.60 (1.80)	35.00 (2.02)	4.35	0.043*	2.96	0.093
Interleukin (IL) [mean (SD)]								
IL-1β	0.64 (0.52)	0.50 (0.53)	1.38 (0.51)	0.96 (0.53)	0.68	0.41	0.88	0.36
IL-2	0.87 (0.87)	1.36 (0.88)	1.78 (0.85)	1.34 (0.90)	0.14	0.71	1.43	0.24
IL-4	0.47 (0.38)	0.79 (0.40)	0.73 (0.36)	1.20 (0.43)	0.56	0.46	0.05	0.82
IL-6	0.71 (0.48)	1.38 (0.50)	0.82 (0.50)	0.59 (0.55)	0.41	0.53	0.94	0.34
IL-10	1.07 (1.79)	1.09 (2.08)	3.59 (1.79)	0.96 (2.28)	0.35	0.56	0.46	0.50
IL-12	1.73 (1.24)	4.56 (1.29)	0.51 (1.21)	0.48 (1.41)	3.71	0.059	1.43	0.24
IFN-α	3.18 (1.57)	6.08 (1.75)	0.78 (1.55)	1.27 (1.90)	3.52	0.065	0.70	0.41
TNF-α	8.98 (1.70)	11.08 (1.95)	10.65 (1.70)	9.04 (2.14)	0.08	0.93	1.24	0.27
C-reactive protein (mg/dL) (mean (SD)	0.14 (0.25)	0.10 (0.15)	0.07 (0.09)	0.07 (0.08)	1.68	0.20	0.84	0.36
Fasting blood sugar (mg/dL) (mean (SD)	114.19 (47.87)	123.65 (52.42)	104.73 (14.36)	107.42 (34.19)	1.29	0.26	0.56	0.81
HbA1c (mean (SD)	5.38 (0 .31)	5.33 (0.35)	5.47 (0.38)	5.31 (0.34)	2.68	0.11	0.95	0.34

HbA1c, hemoglobin A1C; HDL-C, high-density lipoprotein-cholesterol; IFN, interferon; IL, interleukin; LDL-C, low-density lipoprotein-cholesterol; SD, standard deviation; TNF-α, tumor necrosis factor-alpha.
Linear mixed model analysis *$p < 0.05$, † Generalized estimating equation.

Table 5
Variation of plasma epinephrine level with age, BMI, and triglycerides: a multiple linear regression analysis

Variables	B coefficient	SE	*p*
[1)]Triglyceride, mg/dL	−0.087	0.040	0.041*
BMI	−0.479	0.516	0.361
Age, yr	0.110	0.156	0.486

BMI, body mass index; SE, standard error.
[1)] Mean changes of triglyceride levels from baseline to 6 months after Korean Red Ginseng treatment.

constituents and is reported to exhibit antidiabetic, immune-modulating, anticancer, and antiinfection activities [30].

There are several caveats to be considered in the interpretation of the study findings. First, we evaluated limited numbers of biological markers. Therefore, it is premature to confirm the association between KRG and autonomic nervous system. Second, no significant difference was observed in subjective psychological distress between the KRG and placebo groups. As mentioned previously, strong placebo effects may occur in clinical trials of nutraceuticals, perhaps in part due to expectations on the part of study participants to receive nutraceutical therapy rather than placebo or other comparator [20]. Third, 6 weeks might not be enough to evaluate psychological changes induced by administration of Korean Red Ginseng. In particular, changes in other biological markers, particularly inflammatory cytokines, may also take as long as 8–12 weeks to manifest. Considering that most nutraceuticals are consumed for a long time, additional studies are needed to determine the long-term effect of KRG. Fourth, all study participants had very stressful professions, so their response to KRG may vary from that of individuals with less stressful jobs. Finally, cognitive function was not evaluated using a comprehensive test that evaluated a wide range of cognitive function.

Notwithstanding these limitations, this study provides biological evidence that may be associated with an adaptogenic effect of KRG. In this randomized, double-blind RCT, KRG decreased epinephrine levels, which was associated with increased, but still normal, triglyceride levels. Decreased catecholamines and increased triglycerides may contribute to stabilization of the autonomic nervous system and neural membranes. KRG additionally improved the cognitive process. The study result suggests that KRG might play a role in autonomic nervous system, which is associated with its adoptogenic effect. Further studies are warranted to determine the appropriate treatment dosage and duration of KRG.

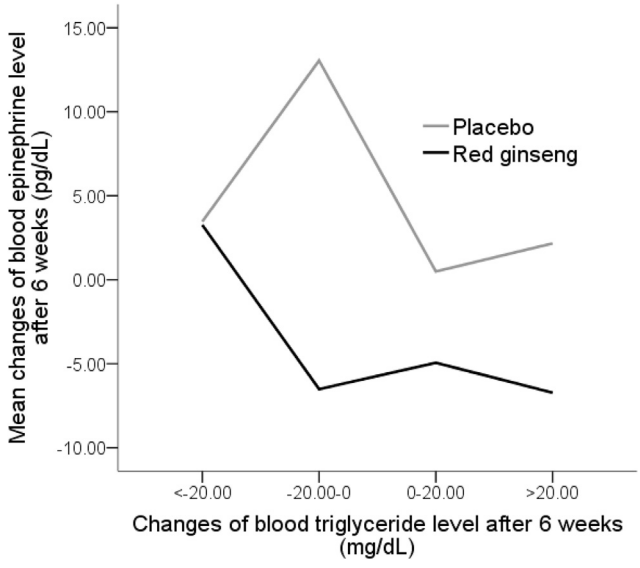

Fig. 2. Mean change of blood epinephrine level after 6 weeks' treatment depending on the triglyceride level changes.

Conflicts of interest

All authors reported no conflict 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.2018.03.001.

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