J Ginseng Res 42 (2018) 192–198

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Research article

Effect of high-dose ginsenoside complex (UG0712) supplementation on physical performance of healthy adults during a 12-week supervised exercise program: A randomized placebo-controlled clinical trial

Eon Sook Lee, Yun Jun Yang*, Jun Hyung Lee, Yeong Sook Yoon

Department of Family Medicine, Center for Health Promotion and Clinical Research Center, Ilsan-Paik Hospital, College of Medicine, Inje University, Goyang, Republic of Korea

ARTICLE INFO

Article history:
Received 30 June 2016
Received in Revised form
15 February 2017
Accepted 15 March 2017
Available online 5 April 2017

Keywords:
cardiopulmonary exercise test
ginsenoside
Panax ginseng
randomized controlled trial

ABSTRACT

Background: Ginseng has been used as an ergogenic agent, although evidence for its effectiveness is weak. A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the effect of a ginsenoside complex (UG0712) on changes in exercise performance.

Methods: Sedentary individuals ($n = 117$) were randomly assigned into one of three groups: low-dose ginsenoside supplementation (100 mg/d, $n = 39$), high-dose ginsenoside supplementation (500 mg/d, $n = 39$), or a placebo group (500 mg/d, $n = 39$). All participants underwent a supervised 12-wk aerobic and resistance exercise training course. To assess the effects of supplementation on physical performance, maximal oxygen consumption (VO_2max), anaerobic threshold (AT), lactic acid, and muscle strength of the dominant knee were measured at baseline, every visit, and after the training program.

Results: Both ginsenoside groups showed significant increases in VO_2max and muscular strength during exercise training. There were no definite changes in AT and lactic acid levels over time. After exercise training, there were definite differences in the VO_2max (28.64.9 to 33.7 ± 4.9 ml/kg/min in high-dose group vs. 30.4 ± 6.7 to 32.8 ± 6.6 ml/kg/min in placebo, $p = 0.029$) and AT (19.3 ± 4.2 to 20.9 ± 3.5 ml/kg/min in high-dose group vs. 20.0 ± 5.1 to 20.0 ± 4.9 ml/kg/min in placebo, $p = 0.038$) between the high-dose ginsenoside and placebo groups. However, there was no difference in VO_2max between the low-dose ginsenoside and placebo groups ($p = 0.254$). There were no differences in muscular strength during exercise training among the three groups.

Conclusion: High-dose ginsenoside supplementation (UG0712) augmented the improvement of aerobic capacity by exercise training.

© 2017 The Korean Society of Ginseng, Published by Elsevier Korea LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Ginseng is one of the best-selling herbal medicines in the world. Ginseng preparations are used to improve cognitive function, immunity, and vitality in East Asia [1–4]. They have also been used as ergogenic aids, which enhance physical performance and accelerate postexertional recovery [5,6]. Ginseng products are also commonly used as ergogenic aids for athletes in the USA [7]. There are many studies investigating the ergogenic action of ginseng in experimental animal studies [8,9] and clinical studies, with mixed results [10–12]. Several positive results have shown that ginseng can improve physical performance [13,14]; however, there is minimal research evaluating the dose differences of ginseng's effect.

Liang et al [13] reported that administration of high-dose ginseng (1,350 mg) lowered oxygen requirement at the 24th min during endurance exercise in healthy adults. Most studies exhibiting positive effects of ginseng on physical performance were conducted using a high-dose ginseng regimen [10–12,15], which was suggested originally by Bucci [16]. It is difficult to compare the effects of ginseng directly because the amount, quality, and

* Corresponding author. Department of Family Medicine, Center for Health Promotion and Clinical Research Center, Ilsan-Paik Hospital, College of Medicine, Inje University, 170, Juhwa-ro, Ilsanseo-gu, Goyang-si 10380, Republic of Korea.
E-mail addresses: jyang@paik.ac.kr, tamlaa@naver.com (Y.J. Yang).

http://dx.doi.org/10.1016/j.jgr.2017.03.001
p1226-8453 e2093-4947/$ – see front matter © 2017 The Korean Society of Ginseng, Published by Elsevier Korea LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

composition of ginseng supplements used in previous studies are different [13,16,17]. The various forms of ginseng are also controversial in the assessment of ginseng's influence on physical performance. Ginsenosides, found exclusively in *Panax ginseng*, are the main active components responsible for ginseng's efficacy [18,19]. To clarify the ginseng effect, research using standard complexes such as G115 or ginsenosides (such as Rb1 or Rg3) has been rapidly increasing [20].

UG0712 is a new standardized ginsenoside complex with 10% protopanaxadiol ginsenosides Rg3, Rg5, and Rk1, which is higher than the content in Korean white ginseng root (0.35%). Due to its high concentration of ginsenosides, UG0712 is thought to have a better ergogenic effect than other ginseng products.

This 12-wk randomized, placebo-controlled trial was aimed at evaluating the efficacy and safety of daily UG0712 intake (100 mg or 500 mg), as an adjunct to aerobic and muscular exercise training, in improving the physical performance of healthy sedentary adults.

Our hypothesis is that UG0712 might get a better augmentation effect on maximal oxygen consumption (VO_2max) change by exercise training compared to placebo.

2. Participants and methods

2.1. Study design

A randomized, double-blind, placebo-controlled trial was conducted at a sports center located in the university hospital. After screening, 117 participants were randomly assigned to one of three groups: high-dose ginsenoside complex ($n = 39$); low-dose ginsenoside complex ($n = 39$); or a placebo ($n = 39$), according to a computer-generated randomization code that was provided by an independent research organization (LSK Global PS). Block randomization was used. Drug labels were applied to the capsule bottles at the distribution center to make sure all study personnel were blinded to the participant's study group. After randomization and baseline evaluation of physical performance, all participants visited hospital three times for follow-up exercise test. The follow-up interval was 4 wk with a 7-d window period. This trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines [21]. The study protocol was approved by the University Hospital Institutional Review of Board (approval number IB-0708-046). All participants provided written informed consent. Double blinding was conducted for all study participants and investigators including clinicians, exercise supervisors, exercise specialists for testing, and pharmacists.

2.2. Participants

The participants, who were aged > 20 yr with a sedentary lifestyle, were enrolled via a standardized advertisement. We defined a sedentary lifestyle as no regular exercise or sport participation in the last 3 mo. There were 123 volunteers screened according to the exclusion criteria. Their sociodemographic factors and past medical history were noted, and physical performance tests were performed. We excluded those with obesity (body mass index > 30 kg/m^2), cardiovascular disease such as myocardial infarction and previous cardiac surgery, osteoarthritis, respiratory disease [Chronic obstructive pulmonary disease (COPD), asthma], and other conditions that could make exercise difficult. Participants were also free of hypothyroidism, renal disorders, hepatic disorders, pregnancy, breast-feeding, and diabetes mellitus. Participants who took drugs known to have an influence on exercise performance or recovery from postexercise fatigue (e.g., thyroxine or carnitine) 1 wk before the study entry were excluded.

The sample size was calculated based on study of Pipat and Kanyarat [6]. They reported the effect of 8-wk therapy of ginseng with exercise training on change in VO_2max. Based on this result, the number of participants was generated using two-sample t test so that the study may be able to compare each of UG0713 dose groups with placebo group in terms of difference between their pre- and post-treatment levels. With 27 per group, a total of 81 participants for this study was calculated to be required for analysis of ginseng effect. Considering a 30% withdrawal rate, 117 participants were recruited, and 81 participants completed the study.

Hypothesis: $H_0 : \varepsilon = 0$ versus $H_\alpha : \varepsilon \neq 0$, where $\varepsilon = \mu_2 - \mu_1$
Significance level $\alpha = 0.05$
Test power $1 - \beta = 0.8$
Change in VO_2max of control group in comparison to its pretreatment level

$$\mu_1 \pm \sigma_1 = 114.5 \pm 4.3(\%)$$

Change in VO_2max of test group in comparison to its pretreatment level

$$\mu_2 \pm \sigma_2 = 124.5 \pm 3.7(\%)$$

Pooled sample variance

$$\sigma^2 = s_p^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2} = \frac{(11-1)14.26^2 + (10-1)11.70^2}{11 + 10 - 2} = 171.8677$$

Sample size

$$n_1 = n_2 = \frac{2\left(z_{\alpha/2} + z_\beta\right)^2 \sigma^2}{\varepsilon^2} = \frac{2(1.96 + 0.84)^2 171.87}{(124.5 - 114.5)^2} \approx 27$$

2.3. Intervention

Eligible participants were randomly allocated into one of three groups: high-dose ginsenoside complex (UG0712, 500 mg/d), low-dose ginsenoside complex (UG0712, 100 mg/d), or a placebo (carboxy methyl cellulose, CMC 500 mg) group. The three study drugs were identical in color, shape, and taste.

Briefly, ginseng leaf extract was purchased from Hongju Biotech Co., Ltd. (Yanbian, China). UG0712 contained partially hydrolyzed ginseng leaf extract under acidic conditions by optimizing the blending ratio of Rd and Rg3 derivatives. It was standardized to contain > 5% ginsenoside Rd, and > 10% ginsenoside Rg3 derivatives (Rg3, Rg5, and Rk1) which are higher than in usual ginseng. UG0712 was supplied by Unigen, Inc (Cheonan, Chugnam, Korea) [22–24]. Placebo drug was CMC (500 mg). All participants were scheduled to take the drug twice/d (UG0712 250 mg twice/d in high-dose ginsenoside group, UG0712 50 mg twice per day in low-dose ginsenoside group, or CMC 250 mg twice/d in placebo group).

The drug compliance rate was measured by a pill count method by one pharmacist. Participants with drug compliance < 80% were removed from the study. The participants were not allowed to concurrently use the drugs prohibited at entry during whole period of this study.

2.4. Exercise training

A 12-wk supervised exercise program was provided to all study participants. They visited a single designated training center for the

exercise program. The exercise intervention consisted of the programmed exercise for 60 min/session, three times/wk. Their activities were taught and supervised by the experienced trainers according to the study guidelines. The exercise program was comprised of both aerobic and muscular strengthening exercises. Moderate intensity aerobic exercise (70% of estimated VO_2max) was comprised of treadmill and cycle ergometer exercise for 30–40 min per session. The goal of each exercise was modified by measured VO_2max at every visit.

Muscular strengthening exercise was comprised of seven types of progressive resistance training such as chest press, rowing, lateral pull-down, leg press, leg extension, leg curl, and a multi-hip exercise. After one repetition maximum of each muscle strength of was measured, all participants started training with a weight with 60–65% of one repetition maximum for eight times and training weight was increased when the participant gained the muscular strength to endure 15 repetitions with the weight. Exercise adherence was measured using frequency of exercise at the training center. If participants had < 50% of exercise compliance (<6 times/4 wk) at each visit, they were dropped from the study. The final physical performance evaluation was requested for all participants regardless of the drop out status.

2.5. Physical performance evaluations

For assessment of the ginsenoside complex's effect on physical performance, we compared the changes of the physical performance measurements among the three groups. Four-time physical performance evaluations were done at baseline and at each monthly visit. Cardiopulmonary function, muscular strength of the knee, and serum levels of lactic acid were the components of the physical performance test. For cardiopulmonary function, VO_2max and anaerobic threshold (AT) were measured by a modified Bruce protocol using a treadmill exercise test. It consisted of two stages of warm-up, stages of exercise, and a cool down. The increment between the exercise stages was 1–1.5 metabolic equivalents. The goal was eliciting a submaximal exercise effect with the heart rate that was approximately 85% of the age-predicted maximum (220 minus age) at the end of the test. The test was terminated when the participants achieved the expected heart rate goal or could no longer continue exercise due to leg pain, dizziness, chest pain, systolic blood pressure drop (> 10 mmHg), ST elevation, or ventricular rhythm. The heart rate response to each exercise stage was monitored using an electrocardiography monitoring system (CH2000; Cambridge Heart, Cambridge, MA, USA). Oxygen uptake (VO_2; ml/kg/min) was measured via open circuit spirometry using an automated gas analysis system (Quark b2; Cosmed, Pavona di Albano, Italy) after being calibrated with standard gases. VO_2 data were collected using breath-by-breath method during a treadmill exercise test. VO_2max was calculated by the linear extrapolation of the slope of submaximal VO_2 and heart rate value to an estimated maximal heart rate [25]. AT was automatically measured using the V-slope method (Quark b2).

To measure the muscular strength, the isokinetic muscle strength of the dominant knee was used, because it is the main muscle of human body. Quadriceps muscle torque at 60° was assessed during flexion and extension of their dominant knee using an isokinetic torque machine (Cybex770 Norm; Lumex, Brooklyn, NY, USA). Serum lactic acid was measured before the treadmill test and at 20 min after the treadmill test to identify the accumulation of lactic acid during exercise. Serum lactic acid measurements (Lactate 2 generation; Roche, Basel-Stadt, Switzerland) were done at every visit. All these tests were performed in the morning, at the room that maintain the desired temperature level (22°) and desired humidity level (65%).

Smoking and alcohol or caffeine intake were prohibited before each test. Heavy exercise was not allowed from one day before an exercise test to eliminate any confounding effects of the exercise. Adverse effects of UG0712 and placebo were monitored during the study period.

2.6. Statistical analysis

One-way analysis of variance and a Chi-square test were used to examine the difference of the baseline characteristics among the three groups. The VO_2max and AT change over time of each group were evaluated by a repeated measures (RM) one-way analysis of variance . RM analysis of covariance was used to assess differences in VO_2max and AT changes among the three groups. The level of physical performance at baseline was included as a covariate. Dunnett's multiple comparison tests were done as a *posthoc* analysis to evaluate differences in physical performance between two groups. Quadriceps muscle torque and level of serum lactic acid were also evaluated using the same analysis. VO_2max, AT, and muscle strength were assessed by both intention-to-treat (ITT) and per-protocol (PP) analysis. A two-sided p value < 0.05 was considered to be statistically significant. Statistical analyses were done using SAS (version 9.1.3; SAS Institute, Inc., Cary, NC) or STATA (version 12 IC; Stata Corporation, College Station, TX, USA).

3. Results

Figure 1 shows the process of this study. Among 123 volunteers, six were excluded by the exclusion criteria and 117 participated at entry. The participants were 85 women and 32 men with mean age 40.7 ± 8.1 yr (range, 22–60 yr; Table 1). Of the 117 participants, 87% did no exercise at all at entry. Out of the 117 participants, 17 withdrew their consent (high-dose group = 4, low-dose group = 6, and placebo group = 7). Another 19 participants dropped out during the study period because of adverse drug events ($n = 2$), low compliance of drug intake ($n = 5$) and exercise ($n = 3$), and increased serum creatine kinase ($n = 2$). Finally, 81 (69.2%) participants completed the study and were included in the PP analysis set (high-dose group = 30, low-dose group = 27, and placebo group = 24). Sex, age, education, and health behavior of the three groups were not significantly different at baseline, but alcohol intake was different at baseline (Table 1).

VO_2max of both high- and low-dose ginsenoside groups significantly improved during exercise training period (from 28.6 ± 4.9 to 33.7 ± 4.9 ml/kg/min, $p < 0.001$ in high-dose group($n = 39$), from 29.1 ± 4.7 to 33.3 ± 6.0 mL/kg/min, $p = 0.005$ in low-dose group ($n = 39$), but no significant change was observed in VO_2max of the placebo group (from 30.4 ± 6.7 to 32.8 ± 6.6 mL/kg/min, $p = 0.474$, $n = 39$; Table 2). The improvement pattern over time were also observed in quadriceps muscle torque of high- and low-dose ginsenoside groups but not in the placebo group. There were no definite AT changes during exercise in all three groups (from 19.3 ± 4.2 to 20.9 ± 3.5 mL/kg/min, $p = 0.238$ in high-dose group, from 18.8 ± 3.5 to 19.0 ± 3.7 mL/kg/min, $p = 0.972$ in low-dose group, and from 20.0 ± 5.1 to 20.0 ± 4.9 mL/kg/min, $p = 0.366$, in placebo, Table 2). No changes over time were observed in serum lactic acid after exercise among three groups. There was no interaction between time and group (F 1.25, $p = 0.28$) in RM analysis of variance model. The interaction variable was excluded in the final model.

The RM analysis of covariance with Dunnett's multiple comparison tests showed the difference in VO_2max increase from baseline of three groups at each step. VO_2max increase from baseline of the high-dose group was significantly higher than the placebo group after adjusting for baseline VO_2max ($p = 0.029$; Table 2). Although changes over time in AT of three group were

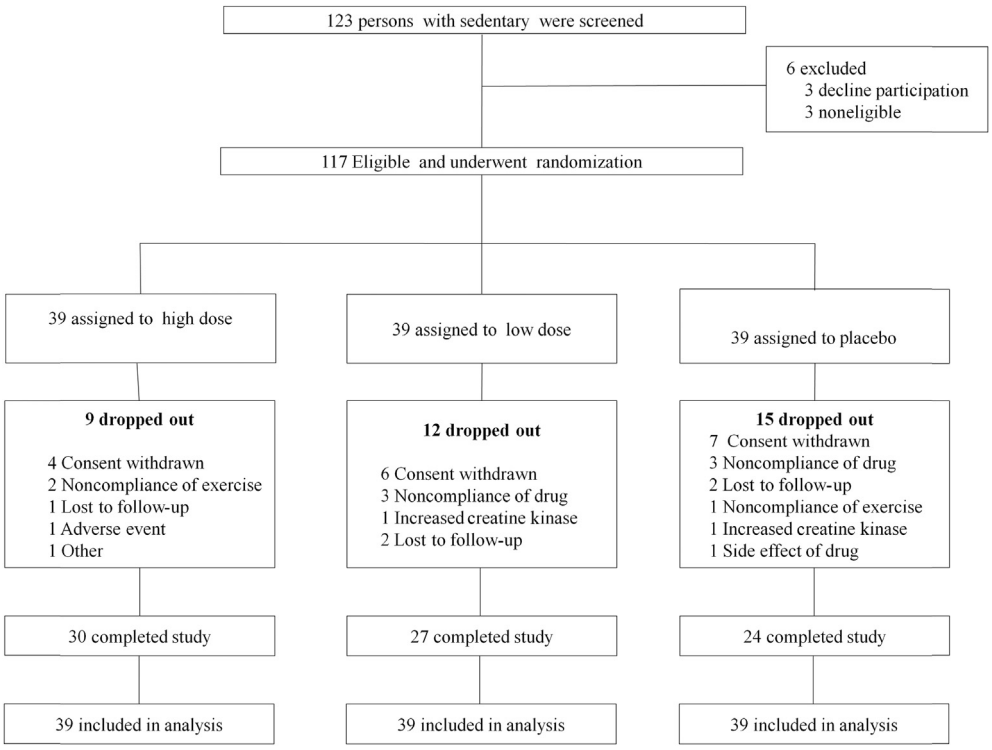

Fig. 1. Flow chart of the study process.

subtle, we also observed higher increase from baseline in AT of the high-dose group compared with the placebo group ($p = 0.038$; Table 2). However, there were no differences between the low-dose ginsenoside group and placebo group in VO_2max increase from baseline ($p = 0.254$) and AT increase from baseline (= 0.963). The same result was seen in comparison of the high dose and low-dose ginsenoside group. Both ITT set and PP set analysis showed no difference of change during exercise training in VO_2max, AT, and muscular strength among the three groups (Table 3).

Sixteen participants (13.6%) experienced adverse events during study period (Table 4). However, most of these adverse events were mild in intensity. Most common adverse events in three groups were upper respiratory infection and knee pain. Ginsenoside group showed allergic reaction. Others included diarrhea, increased blood creatine phosphokinase and polycystic ovaries. Among the adverse events, mild pruritus in the high-dose UG0712 group was regarded as a drug-related adverse event.

Table 1
Characteristics of the study population

Characteristic	High-dose ($n = 39$)	Low-dose ($n = 39$)	Placebo ($n = 39$)	$p^{1)}$
Age (yr)	41.05 ± 7.19	40.18 ± 8.54	40.92 ± 8.61	0.878
Female (%)	31 (79.49)	27 (69.23)	27 (69.23)	0.503
Education (%)				0.431
≤ 12 yr	14 (35.90)	9 (23.08)	13 (33.33)	
> 12 yr	25 (64.10)	30 (76.92)	26 (66.67)	
Smoking (%)				0.999
Current smoker	7 (17.95)	8 (20.51)	8 (20.51)	
Nonsmoker	30 (76.92)	29 (74.36)	29 (74.36)	
Ex-smoker	2 (5.13)	2 (5.13)	2 (5.13)	
Alcohol (%)				0.033
Yes	25 (64.10)	31 (79.49)	20 (51.28)	
No	14 (35.90)	8 (20.51)	19 (48.72)	
Coffee (cups/wk)	13.60 ± 10.50	14.79 ± 12.28	15.39 ± 8.87	0.799
Physical performance at entry				
VO_2max	28.64 ± 4.87	29.09 ± 4.74	30.42 ± 6.73	0.336
AT	19.28 ± 4.23	18.83 ± 3.46	20.03 ± 5.11	0.466
Muscular torque of knee (60°)				
Right extension	102.79 ± 29.46	110.15 ± 39.94	119.64 ± 47.07	0.173
Right flexion	56.62 ± 18.37	57.31 ± 21.63	64.79 ± 24.84	0.189
Lactic acid change after exercise	9.9 ± 13.5	11.0 ± 12.1	11.7 ± 15.4	0.870

AT, anaerobic threshold
[1)] The analysis of variance test was used for comparisons between groups in age, coffee consumption amount, aerobic exercise, and physical performance at entry. The Chi-square test used for education, smoking, and alcohol

4. Discussion

The major finding of this study is that ginsenoside supplementation had a better effect on increasing the VO_2 max compared to the placebo, during the 12-wk exercise training. This effect was observed only in the high-dose (500 mg) group. Our results support the hypothesis that a positive ergogenic effect is associated with ginseng supplementation in high-dosages.

Several researchers [16,26] have suggested the theory that significant improvement in physical performance by ginseng only occurs in the studies with high-dose ginseng, relatively longer study durations (> 8 wk), and large numbers of participants. This ergogenic effect of high-dose ginseng has been supported by the results of recent clinical trials by Liang et al [13] and Kim et al [27]. These studies provide evidence that the different effects of ginseng may be mediated by the dose. However, they did not compare physical performance according to the dose. The strength of our study is in the comparison of high-dose and low-dose ginseng supplementation to a placebo, respectively, in the same time period. Our study showed definite evidence of an ergogenic effect of ginseng, but the effective amount of ginsenoside complex used (UG0712 500 mg/d) was relatively lower than the that of previous studies (e.g., 3 g, 6 g). This might be due to the difference in the type of ginseng used. Ginseng used in previous studies were a standard

Table 2
The effect of the ginsenoside complex on changes in physical performance and serum lactic acid during 12−wk exercise training (ITT)[3)]

	Baseline	1st follow-up	2nd follow-up	3rd follow-up	p
VO_2max (mL/kg/min)					
High-dose ($n = 39$)	28.6 ± 4.9	30.8 ± 5.2	31.6 ± 5.00	33.7 ± 4.9	<0.001[1)]
Low-dose ($n = 39$)	29.1 ± 4.7	30.6 ± 5.1	32.0 ± 5.3	33.3 ± 6.0	0.005[1)]
Placebo ($n = 39$)	30.4 ± 6.7	31.3 ± 6.3	31.6 ± 6.6	32.8 ± 6.6	0.474[1)]
High-dose versus placebo					0.029[2)]
Low-dose versus placebo					0.254[2)]
Anaerobic threshold (mL/kg/min)					
High-dose ($n = 39$)	19.3 ± 4.2	19.9 ± 3.6	20.2 ± 2.9	20.9 ± 3.5	0.238[1)]
Low-dose ($n = 39$)	18.8 ± 3.5	19.0 ± 3.1	19.0 ± 3.5	19.0 ± 3.7	0.972[1)]
Placebo ($n = 39$)	20.0 ± 5.1	19.2 ± 4.0	19.3 ± 3.6	20.0 ± 4.9	0.366[1)]
High-dose versus placebo					0.038[2)]
Low-dose versus placebo					0.963[2)]
Muscular strength (Nm) at 60° during flexion of dominant knee					
High-dose ($n = 39$)	56.6 ± 18.4	61.5 ± 20.1	68.5 ± 22.5	69.4 ± 22.8	0.024[1)]
Low-dose ($n = 39$)	57.3 ± 21.6	63.4 ± 22.4	68.2 ± 24.5	71.2 ± 25.4	0.055[1)]
Placebo ($n = 39$)	64.8 ± 24.8	67.2 ± 23.6	72.4 ± 25.1	72.8 ± 24.5	0.393[1)]
High-dose versus placebo					0.319[2)]
Low-dose versus placebo					0.532[2)]
Change of lactic acid after exercise (mg/dL)					
High-dose ($n = 39$)	9.5 ± 12.9	11.7 ± 14.8	13.0 ± 17.2	11.2 ± 9.8	0.726[1)]
Low-dose ($n = 39$)	9.1 ± 14.1	11.5 ± 18.3	11.2 ± 17.9	9.9 ± 18.2	0.917[1)]
Placebo ($n = 39$)	12.4 ± 14.2	14.9 ± 15.1	15.9 ± 16.8	12.1 ± 14.3	0.615[1)]
High-dose versus placebo					0.827[2)]
Low-dose versus placebo					0.592[2)]

[1)] Repeated-measures measures analysis of variance was used for change over time
[2)] Repeated-measures analysis of covariance was used for determination of ginsenoside effect on performance change from the baseline at each visit: the covariate in the model was baseline level of each performance. Subgroup analysis was performed by Dunnett's multiple comparison
[3)] The last observation carried forward is used for missing data

Table 3
The effects of the ginsenoside complex on changes of physical performance during 12-wk exercise training (PP)

Treatment	Baseline	1st follow-up	2nd follow-up	3rd follow-up	p
VO_2max (mL/kg/min)					
High-dose ($n = 30$)	28.6 ± 5.1	31.5 ± 5.1	31.8 ± 4.6	34.5 ± 4.4	<0.001[1)]
Low-dose ($n = 27$)	28.0 ± 3.5	30.0 ± 4.3	32.0 ± 4.8	33.7 ± 5.8	<0.001[1)]
Placebo ($n = 24$)	29.2 ± 5.0	30.3 ± 4.2	30.5 ± 4.9	32.6 ± 5.1	0.104[1)]
High-dose versus placebo					0.048[2)]
Low-dose versus placebo					0.163[2)]
Anaerobic threshold (mL/kg/min)					
High-dose ($n = 30$)	19.3 ± 4.6	20.0 ± 3.9	20.3 ± 2.9	21.3 ± 3.6	0.238[1)]
Low-dose ($n = 27$)	18.4 ± 2.9	18.7 ± 2.3	18.6 ± 3.0	18.8 ± 3.0	0.972[1)]
Placebo ($n = 24$)	18.9 ± 3.6	18.1 ± 2.8	18.6 ± 2.9	19.9 ± 5.1	0.366[1)]
High-dose versus placebo					0.052[2)]
Low-dose versus placebo					0.957[2)]
Muscular strength (Nm) at 60° during flexion of dominant knee					
High-dose ($n = 30$)	56.6 ± 18.4	61.5 ± 20.1	68.5 ± 22.5	69.4 ± 22.8	0.018[1)]
Low-dose ($n = 27$)	57.3 ± 21.6	63.4 ± 22.4	68.2 ± 24.5	71.2 ± 25.4	0.004[1)]
Placebo ($n = 24$)	64.8 ± 24.8	67.2 ± 23.6	72.4 ± 25.1	72.8 ± 24.5	0.177[1)]
High-dose versus placebo					0.815[2)]
Low-dose versus placebo					0.963[2)]

[1)] Repeated-measures analysis of variance was used for change over time
[2)] Repeated-measures analysis of covariance was used for determination of ginsenoside effect on performance change from the baseline at each visit: the covariate in the model was baseline level of each performance. Subgroup analysis was done by Dunnett's multiple comparison

Table 4
The side effects of the U0712 group or placebo group during 12 wk of exercise

Side effects (%)	High-dose group ($n = 39$)	Low-dose group ($n = 39$)	Placebo ($n = 39$)
	5 (12.8)	4 (10.3)	7 (17.9)
Upper respiratory infection	2	1	3
Knee pain or headache	1	1	3
Skin disease or allergic reaction of skin	1	1	0
Others[1)]	1	1	3

[1)] Other = diarrhea, increased blood creatine phosphokinase, and polycystic ovaries

root extract (e.g., 0.35% ginsenoside in Korean white ginseng extract or 4% in G115) [28] but UG0712 is a new standardized complex with a higher concentration of ginsenoside (10.01%). The amount of ginsenoside is important for the ergogenic effect.

In this study, aerobic capacity (VO_2max and AT) was significantly increased by ginseng supplementation during exercise training. Aerobic capacity has been the most important variable to prove the ergogenic effect of ginseng in previous studies. Gross et al [29] evaluated the effect of a ginseng extract (G115) on VO_2max for 94 patients with moderately severe COPD. The patients received a placebo or 200 mg of G115 daily over a 3-month study period. VO_2max increased by 38% after 3 mo of ginseng supplementation. Pipat and Kanyarat [6] also reported a significant increase in VO_2max after 8 wk

of ginseng extract intake. These findings might be explained by the actions of ginseng, such as stabilizing blood pressure, influencing platelet aggregation [5,30], and improving pulmonary function [29]. A recent study proposed that Rg3 can improve mitochondrial antioxidant capacity and regulate mitochondrial dynamic remodeling [31]. All the mechanisms of ginseng are regarded to be associated with an enhancement of aerobic capacity, especially VO_2max or oxygen uptake. Thus, these measurements might be an important indicator for the ergogenic effect of ginseng.

There are minimal studies investigating the effect of ginseng on muscular strength, although studies investigating the effect of ginseng on muscular regeneration after damage have found mixed results [32,33]. We did not observe any difference in changes of muscular strength or serum lactic acid between the ginseng groups and placebo group during exercise training.

It is worth noting that our study showed an additional aerobic ergogenic effect of ginseng through exercise training. Pipat and Kanyarat [6] reported exercise induced effects of ginseng, but found no clear synergistic action on physical performance variables when both ginseng administration and exercise training were combined. On the contrary, our study results indicate an additional ergogenic effect of ginseng when combined with exercise training.

The strengths of this study include its well-designed clinical trial with an ample duration, different doses of ginseng, and relatively large number of participants, which is recommended by Bucci [16]. By this design, we could confirm that the ergogenic effect of ginseng is effected by the dose. Furthermore, the participants in this study were sedentary healthy people. In previous research, the ginseng effects were usually focused on athletes. Our finding, the improvement of aerobic capacity by ginseng for sedentary people, is more representative of the general population. This larger effect on sedentary participants could be supported by Gross et al's study [29] or by Oliynyk and Oh's review [26]. Gross et al [29] showed ginseng's effect on COPD patients. Oliynyk and Oh [26] suggested that the enhancement of physical capacity by ginseng is more prominent in participants with a relatively poor physical condition.

There are important limitations of this study that should be considered. First, dropout rate of all participants was high (30.8%) and the placebo group had the highest dropout rate (38.5%). Participant withdrawal was the most common reason for dropouts from this study. Clinical trials with exercise intervention often suffer from high dropout rates that could mislead the results. However, we did not find remarkable differences in the reasons of drop out including compliance of exercise or drug ingestion between placebo group and UG0712 group and the results between the ITT and PP set analysis were consistently persisted. Based on these reasons, we can ascertain that the high dropout rate did not indicate any bias. Second, all participants were designated to conduct exercise training. Since this is critical to the study design, we could not conclude the ergogenic effect of ginseng without exercise. So, this study does not assure that UG0712 has a similar effect on VO_2max by only ginseng intake and further study is necessary to confirm the independent effect of UG0712. Third, this study adopted indirect measurement for VO_2max. It is well-known that direct measurement is the best way to evaluate cardiopulmonary function. However direct measurement of VO_2max was based on maximal exercise tests posing a potential hazard for the participants without clear medical condition. Additionally, a previous study showed that there is no difference between direct measurement and indirect prediction of VO_2max [25], thus VO_2max prediction used in this study is regarded as an accurate alternative method.

In conclusion, our results showed that high doses of ginseng supplementation could enhance aerobic capacity during exercise training.

Conflicts of interest

None of the authors had any conflicts of interest with regard to the research described in this article. The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Acknowledgments

We acknowledge CRO LSK Global PS, who provided the SAS program for statistical analysis. The authors' responsibilities were as follows. ESL, YJY: actively involved in the planning of the research described herein and in writing the manuscript; JHL, YJY, and ESL: collected the data; YSY and ESL: planned and supervised the analysis. All authors contributed to and reviewed the final publication.

This study was supported by the Grant from Plant Diversity Research Center of Frontier Research Program in Ministry of Education, Science and Technology (#PF0321204-00). UG0712 and placebo was provided by UNIGEN. The funding organizations had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, and approval of the manuscript.

References

[1] Scholey A, Ossoukhova A, Owen L, Ibarra A, Pipingas A, He K, Roller M, Stough C. Effects of American ginseng (*Panax quinquefolius*) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study. Psychopharmacology (Berl) 2010;212:345–56.

[2] Helms S. Cancer prevention and therapeutics: *Panax ginseng*. Altern Med Rev 2004;9:259–74.

[3] Kim S, Shin BC, Lee MS, Lee H, Ernst E. Red ginseng for type 2 diabetes mellitus: a systematic review of randomized controlled trials. Chin J Integr Med 2011;17:937–44.

[4] Rhee MY, Kim YS, Bae JH, Nah DY, Kim YK, Lee MM, Kim HY. Effect of Korean Red Ginseng on arterial stiffness in subjects with hypertension. J Altern Complement Med 2011;17:45–9.

[5] Bahrke MS, Morgan WP, Stegner A. Is ginseng an ergogenic aid? Int J Sport Nutr Exerc Metab 2009;19:298–322.

[6] Pipat C, Kanyarat R. Effects of standardized ginseng extract and exercise training on aerobic and anaerobic exercise capacities in humans. J Ginseng Res 1995;19:93–100.

[7] Bardia A, Nisly NL, Zimmerman MB, Gryzlak BM, Wallace RB. Use of herbs among adults based on evidence-based indications: findings from the National Health Interview Survey. Mayo Clin Proc 2007;82:561–6.

[8] Cabral de Oliveira AC, Perez AC, Prieto JG, Duarte ID, Alvarez AI. Protection of *Panax ginseng* in injured muscles after eccentric exercise. J Ethnopharmacol 2005;97(2):211–4.

[9] Pannacci M, Lucini V, Colleoni F, Martucci C, Grosso S, Sacerdote P, Scaglione F. *Panax ginseng* C.A. Mayer G115 modulates pro-inflammatory cytokine production in mice throughout the increase of macrophage toll-like receptor 4 expression during physical stress. Brain Behav Immun 2006;20:546–51.

[10] Allen JD, McLung J, Nelson AG, Welsch M. Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance. J Am Coll Nutr 1998;17:462–6.

[11] Engels HJ, Fahlman MM, Wirth JC. Effects of ginseng on secretory IgA, performance, and recovery from interval exercise. Med Sci Sports Exerc 2003;35:690–6.

[12] Kulaputana O, Thanakomsirichot S, Anomasiri W. Ginseng supplementation does not change lactate threshold and physical performances in physically active Thai men. J Med Assoc Thai 2007;90:1172–9.

[13] Liang MT, Podolka TD, Chuang WJ. *Panax notoginseng* supplementation enhances physical performance during endurance exercise. J Strength Cond Res 2005;19:108–14.

[14] Pieralisi G, Ripari P, Vecchiet L. Effects of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements on physical performance during exercise. Clin Ther 1991;13:373–82.

[15] Choi J, Kim TH, Choi TY, Lee MS. Ginseng for health care: a systematic review of randomized controlled trials in Korean literature. PLoS One 2013;8:e59978.

[16] Bucci LR. Selected herbals and human exercise performance. Am J Clin Nutr 2000;72(2 Suppl). 624S–36S.

[17] Engels HJ, Wirth JC. No ergogenic effects of ginseng (*Panax ginseng* C.A. Meyer) during graded maximal aerobic exercise. J Am Diet Assoc 1997;97:1110–5.

[18] Tang W, Zhang Y, Gao J, Ding X, Gao S. The anti-fatigue effect of 20(R)-ginsenoside Rg3 in mice by intranasally administration. Biol Pharm Bull 2008;31:2024–7.
[19] Xu Y, Zhang P, Wang C, Shan Y, Wang D, Qian F, Sun M, Zhu C. Effect of ginsenoside Rg3 on tyrosine hydroxylase and related mechanisms in the forced swimming-induced fatigue rats. J Ethnopharmacol 2013;150:138–47.
[20] Jovanovski E, Bateman EA, Bhardwaj J, Fairgrieve C, Mucalo I, Jenkins AL, Vuksan V. Effect of Rg3-enriched Korean red ginseng (*Panax ginseng*) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial. J Am Soc Hypertens 2014;8:537–41.
[21] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA 2000;284:3043–5.
[22] Kim JY, Ri Y, Do SG, Lee YC, Park SJ. Evaluation of the genotoxicity of ginseng leaf extract UG0712. Lab Anim Res 2014;30:104–11.
[23] Shin WH, Ri Y, Do SG, Lee YC, Park SJ. 13-week subchronic toxicity study of a novel ginsenoside composition from ginseng leaves in rats. Lab Anim Res 2014;30:112–22.
[24] Chai H, Do S, Kim J, Kim D, Sung S, Lee Y, Woo SS, Kang JK. UG0712, A novel ginsenoside composition enhances the endurance exercise capacity and fatigue recovery. Lab Anim Res 2009;25:207–12.
[25] Marsh CE. Evaluation of the American College of Sports Medicine submaximal treadmill running test for predicting VO_2max. J Strength Cond Res 2012;26:548–54.
[26] Oliynyk S, Oh S. Actoprotective effect of ginseng: improving mental and physical performance. J Ginseng Res 2013;37:144–66.
[27] Kim SH, Park KS, Chang MJ, Sung JH. Effects of *Panax ginseng* extract on exercise-induced oxidative stress. J Sports Med Phys Fitness 2005;45:178–82.
[28] Reay JL, Scholey AB, Kennedy DO. *Panax ginseng* (G115) improves aspects of working memory performance and subjective ratings of calmness in healthy young adults. Hum Psychopharmacol 2010;25:462–71.
[29] Gross D, Shenkman Z, Bleiberg B, Dayan M, Gittelson M, Efrat R. Ginseng improves pulmonary functions and exercise capacity in patients with COPD. Monaldi Arch Chest Dis 2002;57:242–6.
[30] Zhou Q, Jiang L, Xu C, Luo D, Zeng C, Liu P, Yue M, Liu Y, Hu X, Hu H. Ginsenoside Rg1 inhibits platelet activation and arterial thrombosis. Thromb Res 2014;133:57–65.
[31] Sun M, Huang C, Wang C, Zheng J, Zhang P, Xu Y, Chen H, Shen W. Ginsenoside Rg3 improves cardiac mitochondrial population quality: mimetic exercise training. Biochem Biophys Res Commun 2013;441:169–74.
[32] Pumpa KL, Fallon KE, Bensoussan A, Papalia S. The effects of *Panax notoginseng* on delayed onset muscle soreness and muscle damage in well-trained males: a double blind randomised controlled trial. Complement Ther Med 2013;21:131–40.
[33] Jung HL, Kwak HE, Kim SS, Kim YC, Lee CD, Byurn HK, Kang HY. Effects of *Panax ginseng* supplementation on muscle damage and inflammation after uphill treadmill running in humans. Am J Chin Med 2011;39:441–50.