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Safety and Tolerability of *Panax ginseng* Root Extract: A Randomized, Placebo-Controlled, Clinical Trial in Healthy Korean Volunteers

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Abstract

Objectives: *Panax ginseng* has been extensively used as an adaptogen and is among the top 10 selling herbal supplements in the United States over the past decade. However, there have been few reports about the toxicity of *P. ginseng* in human studies. Given the lack of toxicological studies in human, this study investigated whether *P. ginseng* administration causes any noticeable toxic effects in healthy volunteers.
Methods: This study was designed as a randomized, double-blind, placebo-controlled, and parallel group trial in healthy volunteers. The subjects were required to be healthy, free from any significant disease, as assessed at screening by physical examination, medical history, and laboratory (hematological and biochemical) tests. Eligible subjects received *P. ginseng* extract (1 g/day or 2 g/day) or placebo over a 4-week period.
Results: Although mild adverse events, such as dyspepsia, hot flash, insomnia, and constipation, were reported in both *P. ginseng* and placebo group, no serious untoward reactions were reported following *P. ginseng* administration. Nonsignificant changes were observed in hematological and biochemical tests.
Conclusions: *P. ginseng* administration for 4 weeks was shown to be safe, tolerable, and free of any untoward toxic effect in healthy male and female volunteers. Future results from ongoing multicenter collaborative efforts to evaluate short- and long-term effects of *P. ginseng* may contribute to our current understanding of safety and tolerability of this herbal product.

Introduction

Ginseng has been used medicinally for thousands of years in Korea, China, and Japan,[1] and it is widely used in Western herbal preparations as an adaptogen.[2,3] Ginseng has been among the top 10 selling herbal supplements in the United States over the past decade.[4] The term ginseng refers to the dried root of several species in the plant genus *Panax*, which belongs to the Araliaceae family. It comprises two commonly used ginseng species (i.e., *P. ginseng* C.A. Meyer (Asian ginseng) and *P. quinquefolius* L. (North American ginseng).[5]

P. ginseng (PG) contains triterpene glycosides as its major active compounds, commonly referred to as ginsenosides or saponins. Up to 40 distinct ginsenosides have been identified from PG.[3,6] Modern therapeutic studies claim a wide range of pharmaceutical activity of PG such as vitality, immune function, cancer, cardiovascular disease, cognitive and physical performance, and sexual function.[7–14]

PG is generally considered to be very safe and well tolerated in animals,[15–18] whereas there have been few reports about the toxicity of PG in human studies. In spite of the worldwide use of PG, there has been concern about the lack of clinical toxicology information of PG.[7] This study aimed to examine whether the 4-week administration of PG exhibits any noticeable toxic effect in healthy volunteers in a randomized controlled trial.

Materials and Methods

Study design and participants

This study was designed as a randomized, double-blind, placebo-controlled, and parallel group study in healthy Koreans at a single center (Oriental Hospital of Daejeon University). The subjects were required to be in satisfactory health, free from any significant cardiac, hepatic, renal,

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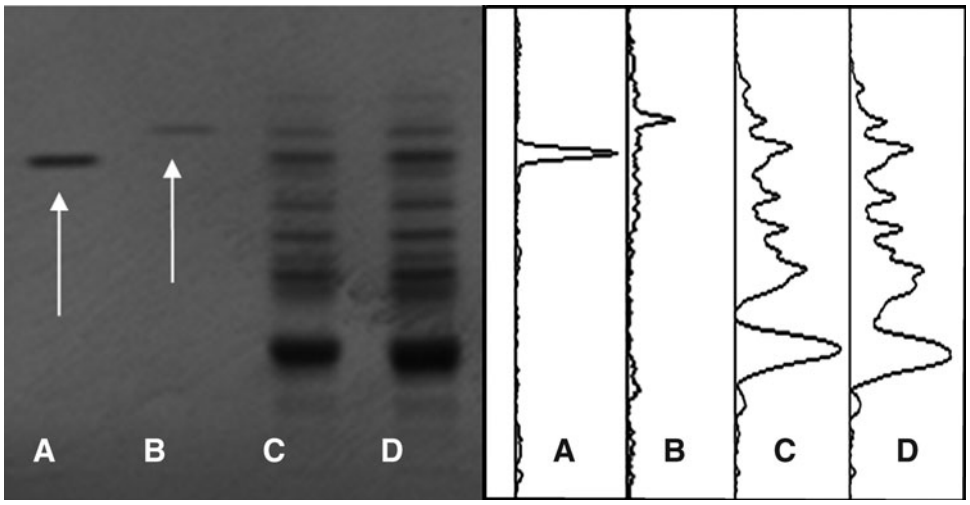

FIG. 1. High-performance thin-layer chromatography (TLC)–based fingerprint of *Panax ginseng* (PG). Two micrograms of ginsenoside Rg1 **(A)**, 10 μg of ginsenoside Rg3 **(B)**, 150 μg of PG **(C)**, and 300 μg of PG **(D)** were applied onto prewashed silica gel 60 F_{254} TLC plates, then separated with mobile phase (chloroform:ethyl acetate:methanol:water [17:46:25:12]). The migrated components were visualized under white light after derivatization with 10% sulfuric acid solution (left), and the densitograms were generated (right). The arrows appeared in the first lane was ginsenoside Rg1 and ginsenoside Rg3 in the second lane.

pulmonary, neurological, gastrointestinal, and hematological disease, as assessed at screening by physical examination, medical history, and laboratory (hematological and biochemical) tests. Volunteers between the ages of 18 and 60 years with a body–mass index of 16–31 kg/m^2 were eligible for participation. Eligible female volunteers enrolled in this study were not pregnant. All participants gave their written informed consent and were able to comprehend fully the protocol, including the nature and purpose of the study as well as the possible risks and side-effects. Subjects were not eligible if they met any of the following criteria applied at the time of screening (pre-study): clinical abnormalities (including abnormal hematological and biochemical tests), participation in other clinical trials simultaneously or within

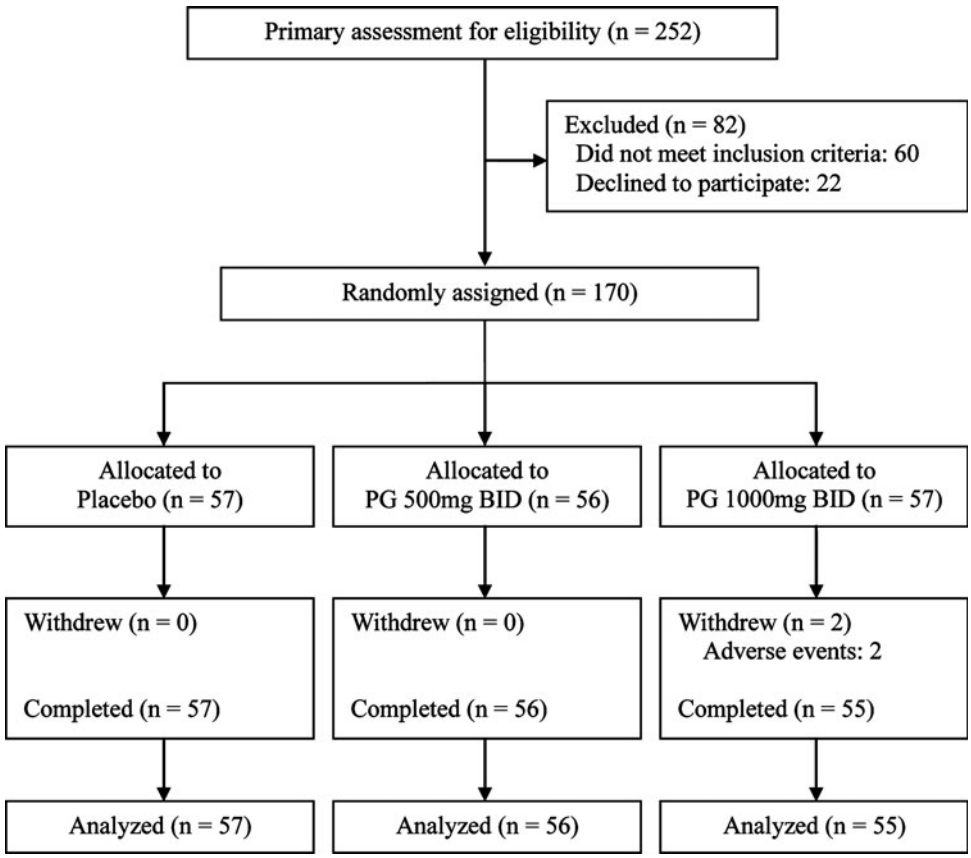

FIG. 2. Trial flow chart. Primary recruitment identified 252 volunteers. After excluding 60 ineligible persons and 22 subjects declined to participate in this trial, the authors randomly assigned 170 persons to groups as follows: placebo ($n=57$), *Panax ginseng* (PG) 500 mg twice a day (BID) ($n=56$), or PG 1000 mg BID ($n=57$).

Table 1. Baseline Demographics

Characteristics	*Placebo* (n = *57*)	*PG 500 mg BID* (n = *56*)	*PG 1000 mg BID* (n = *57*)
Age (yr)			
Mean ± SD	40.8 ± 11.3	39.8 ± 9.3	41.3 ± 10.3
Range	18–60	19–59	19–60
Race, *n*			
White	0	0	0
Asian	57	56	57
Black	0	0	0
Mixed	0	0	0
Male gender			
n (%)	13 (22.8)	14 (25.0)	14 (24.6)
Weight, kg			
Mean ± SD	59.7 ± 10.7	58.7 ± 10.1	58.2 ± 10.1
Range	42.6–86.8	41.9–78.7	42.9–88.3
Height, kg			
Mean ± SD	161.4 ± 8.6	161.5 ± 7.0	162.3 ± 8.3
Range	147.0–185.0	148.0–179.0	146.0–184.0
BMI, kg/m^2			
Mean ± SD	22.8 ± 2.8	22.4 ± 2.7	22.1 ± 3.0
Range	18.3–29.1	17.0–28.7	16.1–30.3

One hundred and seventy (170) participants were randomly assigned to placebo, PG 500 BID, or PG 1000 BID.

PG, *Panax ginseng*; BID, twice a day; SD, standard deviation; BMI, body–mass index.

Table 2. Adverse Events

Subjects with adverse events, *n* (%) ($p = 0.895$)	*Placebo* (n = *57*)	*PG 500 mg BID* (n = *56*)	*PG 1000 mg BID* (n = *57*)
	18 (31.6)	19 (33.9)	17 (29.8)
Symptoms and signs, *n*	20	20	19
Dyspepsia, *n*	4[a]	4[a]	3
Hot flash, *n*	4	3	4
Insomnia, *n*	3	1[a]	2[a]
Constipation, *n*	1[b]	4	1
Low energy, *n*	1	2	2
Headache, *n*	2[a]	2	1
Skin disorders, *n*	2[b]	0	2[b]
Dizziness, *n*	1	1	1
Nausea, *n*	1	0	1[b]
Diarrhea, *n*	1	1	0
Abdominal pain, n	0	1	1
Epistaxis, *n*	0	1	0
Rapid heartbeat, *n*	0	0	1[a]
Committee results, overall Severity			
Mild, *n*/*N*(%)	20/20 (100.0)	20/20 (100.0)	19/19 (100.0)
Moderate, *n*	0	0	0
Severe, *n*	0	0	0

Panax ginseng (PG) was administered (500 mg twice a day [BID] or 1000 mg BID) for 4 weeks. During the study period, all the adverse events were documented. χ^2 statistics were used for calculating *p*-values.

[a]Events in same patient.

[b]Events in same patient.

the last 4 weeks, previous history of hypersensitivity to ginseng preparations, history of any acute/chronic diseases, history of drug dependence or chronic alcohol, history of chronic medication within the past 6 weeks, regular smokers who smoke more than 20 cigarettes weekly, and night workers.

Ethics aspects

This study was approved by the ethical committee of Daejeon University Hospital (authorization number: DJOMC-33-1) and was conducted in accordance with ethical standards for human experimentation established by the Declaration of Helsinki (1965) with subsequent revisions (Tokyo, 1975, Venice, 1983, Hong Kong, 1989, and Somerset, 1996), and current standards for Good Clinical Practice in clinical trials.

Preparation of ginseng extract and placebo

A 20% ethanol extract of 4-year-old PG root was prepared by Guryoung Pharmaceutical Company Ltd. (Cheorwon, Korea) according to over-the-counter Korean monographs. Lyophilized PG extract (13.2% [w/w]) was obtained. Placebo control material was carefully prepared to match the appearance, volume, weight, color, flavor, and taste of ginseng in a formulation of starch (99.68%, Daesang Co., Korea), artificial ginseng flavor (0.3%, Hanbit flavor & Fragrance Co, Korea), and caramel color (0.02%, Namyoung Food Co., Korea) in a capsule. The 100% PG extract, 50% PG extract with 50% placebo material, or 100% placebo material was contained in a soft capsule as 250 mg in each.

Fingerprinting using high-performance thin-layer chromatography

Gensenoside Rg1 (2 mg/mL), ginsenoside Rg3 (10 mg/mL), and PG (150, 300 mg/mL) were dissolved in 90% methanol, sonicated for 1 hour, and centrifuged for 15 minutes at 3000 rpm. The supernatant was applied onto prewashed silica gel 60 F_{254} thin-layer chromatography plates (20 × 10 cm; 0.2-mm thickness) (Merck, Darsttadt, Germany) using an automated applicator, Linomat IV (CAMAG, Mu cenz, Switzerland). The constituent ingredients of PG were separated with mobile phase (chloroform: ethyl acetate:methanol:water [17:46:25:12]) in automated multiple development AMD2 (CAMAG) and visualized by a Reprostar 3 mounted digital camera (CAMAG) under white light after derivatization with 10% sulfuric acid. Images were captured by Win CATS software. Densitograms were generated by the VideoScan software (Fig. 1).

Intervention

Eligible subjects were randomly assigned to receive PG extract 500 mg twice a day (PG 500 twice a day), PG extract 1000 mg twice a day (PG 1000 twice a day), or placebo for 4 weeks. A computer-generated randomization schedule was used to assign subjects to the study groups. PG was presented as 250-mg tablets, with placebo to match. All participants were administered four identical 250 mg capsules twice a day (9:00 AM and 9:00 PM) according to their allocation. No medication other than PG was allowed except under exceptional conditions only with the permission of the investigator. There was no restriction placed on normal and routine activity or diet during the study period. Venous whole blood was sampled at baseline, and at 4 weeks after randomization with all treatment regimens (PG 500

Table 3. Hematological Test Result of Male Subjects After 4 Weeks Administration of *Panax ginseng* (PG)

Variables	*Treatment*	*Placebo*	*PG 500 mg BID*	*PG 1000 mg BID*	*Reference range*
WBC ($10^2/\mu L$)	Before	61.4±14.6	67.6±17.1	58.7±14.7	45–110
	After	62.5±14.8	70.4±17.2	57.8±13.2	
Segmented (%)	Before	56.1±9.6	60.6±8.2	58.4±8.7	40–80
	After	56.6±10.2	63.2±6.9	58.6±9.3	
Monocyte (%)	Before	3.3±0.9	3.1±0.9	2.9±0.6	2–10
	After	2.6±0.8	2.6±0.7	2.9±1.1	
Lymphocyte (%)	Before	40.7±8.9	36.3±8.1	38.7±8.6	15–45
	After	40.8±10.2	34.2±6.8	38.5±8.4	
RBC ($10^4/\mu L$)	Before	491.2±35.0	488.4±37.3	487.7±54.8	450–650
	After	496.0±39.0	497.4±36.3	487.4±54.6	
Hemoglobin (g/dL)	Before	15.6±1.0	15.6±0.8	14.9±0.8	13–17
	After	15.5±0.8	15.8±0.8	14.6±1.1	
Hematocrit (%)	Before	45.2±2.6	45.5±2.1	43.6±2.4	38–52
	After	45.5±2.3	46.2±2.5	43.4±2.9	
ESR (mm/hr)	Before	5.8±5.4	3.1±1.9	4.6±3.7	0–10
	After	4.8±4.5	3.4±2.7	4.5±4.2	
Platelet ($10^4/\mu L$)	Before	24.3±3.9	22.1±3.1	23.9±5.1	15–45
	After	23.1±4.5	21.5±2.8	24.9±4.7	
MCV (fl)	Before	92.1±4.0	93.4±5.3	90.3±7.6	80–94
	After	92.1±4.9	93.2±5.6	89.8±8.1	
MCH (pg)	Before	31.9±1.3	32.0±1.8	30.8±3.0	26–33
	After	31.4±1.6	31.9±2.0	30.2±2.8	
MCHC (%)	Before	34.6±0.6	34.3±0.7	35.5±5.9	32–37
	After	34.1±0.3	34.2±0.4	33.6±0.8	
RDW (%)	Before	12.9±0.4	12.9±0.6	12.8±0.7	11.5–16.5
	After	12.7±0.5	12.4±0.5	12.8±0.8	

Data are expressed as mean±standard deviation.

BID, twice a day; WBC, white blood cells; RBC, red blood cells; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

Table 4. Hematological Test Result of Female Subjects After 4 Weeks Administration of *Panax ginseng* (PG)

Variables	*Treatment*	*Placebo*	*PG 500 mg BID*	*PG 1000 mg BID*	*Reference range*
WBC ($10^2/\mu L$)	Before	52.2±12.3	55.0±14.9	53.9±14.4	45–110
	After	55.5±17.3	58.4±16.9	57.3±18.2	
Segmented (%)	Before	55.0±8.2	56.6±8.8	56.4±6.3	40–80
	After	56.7±9.8	58.6±7.9	57.6±9.6	
Monocyte (%)	Before	3.2±0.9	3.4±1.0	3.1±1.0	2–10
	After	3.1±1.0	2.9±0.7	3.1±1.0	
Lymphocyte (%)	Before	41.8±8.3	40.0±8.5	40.5±6.3	15–45
	After	40.2±9.5	38.5±7.7	39.3±9.3	
RBC ($10^4/\mu L$)	Before	419.9±32.8	428.0±27.7	429.5±29.3	400–600
	After	424.2±29.7	427.7±29.9	429.1±31.4	
Hemoglobin (g/dL)	Before	12.7±1.5	13.3±1.2	12.9±1.2	12–16
	After	12.7±1.5	13.1±1.1	12.8±1.4	
Hematocrit (%)	Before	37.8±3.6	39.1±2.9	38.4±3.1	36–46
	After	38.1±3.8	39.0±3.0	38.4±3.7	
ESR (mm/hr)	Before	14.9±8.5	12.0±7.4	14.4±8.1	0–20
	After	13.9±8.0	12.1±7.8	11.8±6.1	
Platelet ($10^4/\mu L$)	Before	23.9±6.2	23.7±5.0	23.8±5.7	15–45
	After	24.1±5.6	23.2±3.9	24.1±5.8	
MCV (fl)	Before	90.2±7.2	91.5±4.9	89.7±7.3	81–99
	After	90.0±7.3	91.4±4.8	89.5±7.2	
MCH (pg)	Before	30.3±3.1	31.1±2.1	30.2±3.0	26–33
	After	30.0±3.1	30.7±2.0	30.0±2.9	
MCHC (%)	Before	33.6±1.2	33.9±0.9	33.6±0.9	32–37
	After	33.2±1.2	33.5±0.9	33.4±0.9	
RDW (%)	Before	13.0±1.1	13.0±0.9	13.2±1.1	11.5–16.5
	After	12.9±1.1	12.7±0.9	12.9±1.0	

Data are expressed as mean±standard deviation.

BID, twice a day; WBC, white blood cells; RBC, red blood cells; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

Table 5. Biochemistry Test Result of Male Subjects After 4 Weeks Administration of *Panax ginseng* (PG)

Variables	*Treatment*	*Placebo BID*	*PG 500 mg BID*	*PG 1000 mg BID*	*Reference range*
Total protein (g/dL)	Before	7.6 ± 0.3	7.5 ± 0.4	7.5 ± 0.3	6.4–8.3
	After	7.6 ± 0.3	7.6 ± 0.4	7.7 ± 0.4	
Albumin (g/dL)	Before	4.7 ± 0.3	4.8 ± 0.2	4.7 ± 0.2	3.8–5.1
	After	4.7 ± 0.2	4.7 ± 0.2	4.7 ± 0.2	
A/G ratio	Before	1.6 ± 0.2	1.7 ± 0.1	1.7 ± 0.2	
	After	1.6 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	
T. bilirubin (mg/dL)	Before	1.1 ± 0.4	1.0 ± 0.2	0.9 ± 0.4	0.1–1.2
	After	1.1 ± 0.5	0.9 ± 0.3	1.0 ± 0.4	
AST (IU/L)	Before	24.4 ± 10.6	22.2 ± 5.5	21.8 ± 4.5	0–40
	After	22.9 ± 7.6	23.6 ± 6.1	21.2 ± 4.6	
ALT (IU/L)	Before	26.4 ± 19.3	21.4 ± 11.6	21.0 ± 9.1	0–40
	After	24.6 ± 12.7	21.5 ± 9.7	19.5 ± 6.4	
ALP (IU/L)	Before	65.9 ± 17.3	79.7 ± 21.1	61.5 ± 9.8	30–120
	After	68.8 ± 18.7	80.4 ± 21.4	63.4 ± 11.0	
r-GTP (IU/L)	Before	28.6 ± 14.1	24.6 ± 12.7	28.2 ± 17.7	0–64
	After	25.4 ± 11.2	24.1 ± 11.0	24.8 ± 11.8	
Cholesterol (mg/dL)	Before	209.4 ± 38.9	187.0 ± 42.5	201.9 ± 33.7	140–271
	After	206.8 ± 47.0	188.1 ± 25.3	199.6 ± 26.3	
Triglycerides (mg/dL)	Before	144.4 ± 111.4	130.4 ± 61.1	145.6 ± 82.5	130–220
	After	153.6 ± 96.4	138.0 ± 86.3	155.3 ± 59.3	
HDL-Chol (mg/dL)	Before	47.8 ± 11.0	48.5 ± 8.7	49.1 ± 7.3	42–88
	After	45.3 ± 10.5	49.3 ± 10.6	48.1 ± 7.1	
Glucose (mg%)	Before	91.1 ± 7.8	88.9 ± 9.3	91.6 ± 5.9	70–115
	After	96.6 ± 10.7	92.3 ± 10.0	96.5 ± 10.6	
Creatinine (mg/dL)	Before	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.4–1.5
	After	1.1 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	
BUN (mg/dL)	Before	13.7 ± 3.7	13.3 ± 2.8	13.7 ± 2.5	5–24
	After	12.6 ± 2.4	12.7 ± 3.6	12.9 ± 3.0	

Data are expressed as mean ± standard deviation.

A/G, albumin to globulin ratio; T. bilirubin, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; r-GTP, gamma-glutamyl transpeptidase; HDL-Chol, high-density lipoprotein cholesterol; BUN, blood urea nitrogen.

twice a day, PG 1000 twice a day, placebo). All participants fasted overnight and were alcohol- and caffeine-free for 12 hours prior to, and during, assessment days. To test the intactness of the blind at the end of the study, participants were asked to guess which treatment (PG 500 twice a day, PG 1000 twice a day, placebo) they received. Compliance was confirmed at the 2nd and 4th week by checking each subject's medication intake and the number of remaining capsules.

Assessment of adverse events

All subjects were monitored for adverse events (including adverse drug reactions and illnesses with onset during the study). All of the adverse events were forwarded in a blinded fashion to the primary investigator to be rated as mild, moderate, severe and undesirable, life threatening or disabling, or death-related based on criteria suggested by the National Institutes of Health.[19] The primary investigator was alerted of potentially serious adverse events immediately so that appropriate steps could be taken, including notification of appropriate regulatory bodies. If an adverse event was still ongoing at the end of the study (week 4), suitable medical support was provided.

Laboratory tests

Safety laboratory tests (including hematology, chemistry, and urinalysis) were performed in laboratories at Oriental Hospital of Daejeon University at baseline and after 4-week treatment using standardized procedures.

Hematology tests include white blood cells, segmented cells, monocytes, lymphocytes, red blood cells, hemoglobin, hematocrit, erythrocyte sedimentation rate, platelet, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell distribution width.

Chemistry tests include total protein, albumin, albumin/globulin ratio, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, cholesterol, triglycerides, HDL-cholesterol, glucose, blood urea nitrogen and creatinine.

Urinalysis includes glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, and leukocytes.

Statistical methods

Means and standard deviations were reported for continuous scaled variables and number and percentages for categorical variables. The baseline characteristics were compared between the intervention groups using χ^2 tests for categorical and dichotomous variables and one-way analysis of variance, followed by Duncan's multirange analyses for continuous variables. Pre- and post-treatment data were compared by *t*-test. Differences at the level of $p < 0.05$ were regarded as statistically significant. This study was designed

Table 6. Biochemistry Test Result of Female Subjects After 4 Weeks Administration of *Panax ginseng* (PG)

Variables	*Treatment*	*Placebo BID*	*PG 500 mg BID*	*PG 1000 mg BID*	*Reference range*
Total protein (g/dL)	Before	7.6±0.4	7.5±0.3	7.5±0.3	6.4–8 3
	After	7.6±0.4	7.6±0.4	7.6±0.3	
Albumin (g/dL)	Before	4.6±0.2	4.5±0.2	4.6±0.2	3.8–5.1
	After	4.5±0.2	4.5±0.2	4.5±0.2	
A/G ratio	Before	1.5±0.2	1.5±0.2	1.6±0.2	
	After	1.5±0.2	1.5±0.2	1.5±0.1	
T. bilirubin (mg/dL)	Before	0.8±0.3	0.8±0.3	0.7±0.2	0.1–1.2
	After	0.8±0.3	0.8±0.2	0.8±0.3	
AST (IU/L)	Before	19.8±3.2	21.7±6.1	20.8±5.4	0–40
	After	20.9±8.0	21.6±6.4	20.7±4.7	
ALT (IU/L)	Before	14.8±6.8	17.5±8.0	16.3±8.3	0–40
	After	16.3±10.2	17.7±9.0	16.2±5.8	
ALP (IU/L)	Before	57.5±12.7	59.1±14.3	59.8±19.9	30–120
	After	57.4±14.2	59.1±15.8	59.4±19.7	
r-GTP (IU/L)	Before	15.1±6.7	16.7±7.8	15.5±6.1	0–64
	After	14.3±5.0	17.5±14.9	15.1±5.8	
Cholesterol (mg/dL)	Before	189.2±31.0	195.9±31.3	197.9±41.8	140–271
	After	188.0±25.5	194.1±29.5	200.8±47.0	
Triglycerides (mg/dL)	Before	103.0±68.1	108.0±65.2	96.6±64.3	130–220
	After	112.0±70.3	117.3±77.4	107.6±64.3	
HDL-Chol (mg/dL)	Before	55.5±11.4	53.8±11.4	55.4±10.6	42–88
	After	54.0±11.1	53.6±11.0	54.9±10.2	
Glucose (mg%)	Before	86.9±7.6	86.5±7.4	87.2±9.2	70–115
	After	89.3±8.1	88.8±7.3	89.4±9.3	
Creatinine (mg/dL)	Before	0.7±0.1	0.7±0.1	0.7±0.1	0.4–1.5
	After	0.8±0.1	0.8±0.1	0.8±0.1	
BUN (mg/dL)	Before	12.5±3.3	12.5±2.7	12.6±3.0	5–24
	After	12.4±3.2	11.4±2.4	12.8±3.4	

Data are expressed as mean±standard deviation.
A/G, albumin to globulin ratio; T. bilirubin, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; r-GTP, gamma-glutamyl transpeptidase; HDL-Chol, high-density lipoprotein cholesterol; BUN, blood urea nitrogen.

Table 7. Urinalysis Result of Male Subjects After 4 Weeks Administration of *Panax ginseng* (PG)

Variables	*Treatment*	*Placebo*	*PG 500 mg BID*	*PG 1000 mg BID*	*Reference range*
Specific gravity	Before	1.0±0.0	1.0±0.0	1.0±0.0	1.003–1.030
	After	1.0±0.0	1.0±0.0	1.0±0.0	
pH	Before	6.2±1.0	6.0±1.3	6.3±1.5	5.0–7.0
	After	5.8±0.8	6.0±1.1	6.0±1.3	
Albumin (%)	Before	0	0	0	
	After	0	0	0	
Leukocytes (%)	Before	0	12.5	0	
	After	0	12.5	0	
Nitrite (%)	Before	0	0	0	
	After	0	0	0	
Glucose (%)	Before	0	0	0	
	After	0	0	0	
Urobilinogen (%)	Before	0	0	0	
	After	0	0	0	
Ketone (%)	Before	0	0	0	
	After	0	0	0	
Bilirubin (%)	Before	0	0	0	
	After	0	0	0	
Blood (%)	Before	0	0	0	
	After	0	12.5	0	

Data are expressed as percentages of dipstick positive except specific gravity and pH.
BID, twice a day.

Table 8. Urinalysis Result of Female Subjects After 4 Weeks Administration of *Panax ginseng* (PG)

Variables	*Treatment*	*Placebo*	*PG 500 mg BID*	*PG 1000 mg BID*	*Reference range*
Specific gravity	Before	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.003–1.030
	After	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	
pH	Before	5.9 ± 1.0	5.8 ± 1.4	6.1 ± 1.0	5.0–7.0
	After	5.9 ± 0.8	6.0 ± 1.1	5.9 ± 0.9	
Albumin (%)	Before	0	0	0	
	After	0	0	0	
Leukocytes (%)	Before	20.8	38.1	21.7	
	After	45.8	33.3	21.7	
Nitrite (%)	Before	0	0	0	
	After	0	0	0	
Glucose (%)	Before	0	0	0	
	After	0	0	0	
Urobilinogen (%)	Before	0	0	0	
	After	0	0	0	
Ketone (%)	Before	8.3	0	0	
	After	4.2	0	0	
Bilirubin (%)	Before	0	0	0	
	After	0	4.8	0	
Blood (%)	Before	12.5	19	4.3	
	After	33.3	28.6	17.4	

Data are expressed as percentages of dipstick positive except specific gravity and pH.

to have 90% statistical power at a 5% significance level to detect differences between treatments. Data processing and analysis were performed with SPSS for Windows, version 13 (SPSS Japan, Tokyo, Japan).

Results

Subject disposition and demographic characteristics

Recruitment identified 252 volunteers. Participants were of Asian (Korean) background. After excluding 60 ineligible persons, 192 subjects were screened; 22 declined to participate after receiving the study information. After 22 subjects were excluded, 170 persons (41 males and 129 females; age range, 18–60 years; body–mass index 16.1–30.3 kg/m^2) were randomly assigned to PG 500 twice a day ($n = 56$), PG 1000 twice a day ($n = 57$) or placebo ($n = 57$) (Fig. 2). Baseline demographics characteristics among study groups are shown in Table 1.

Adverse effects

There were no deaths or serious adverse events in any of the study groups (Table 2). The four most frequently reported adverse events were dyspepsia, hot flash, insomnia, and constipation.

Nineteen (19; 33.9%) subjects in the PG 500 mg twice a day group showed adverse events such as low energy, insomnia, hot flash, headache, dizziness, abdominal pain, dyspepsia, diarrhea, constipation, and epistaxis. Seventeen (17; 29.8%) participants in the PG 100 mg twice a day group reported adverse events (low energy, insomnia, hot flash, headache, dizziness, abdominal pain, nausea, dyspepsia, constipation, rapid heartbeat, and skin disorders). Eighteen (18; 31.6%) subjects in the placebo group reported adverse events (low energy, insomnia, hot flash, headache, dizziness, nausea, dyspepsia, constipation, and skin disorders). The difference in the number of subjects with adverse events among each of the three treatment arms was nonsignificant ($p = 0.895$).

Numbers of total adverse events were similar in each group (20 in PG 500 mg twice a day, 19 in PG 1000 mg twice a day and 20 in placebo). Of the 59 adverse events, the masked primary investigator rated all events as mild (i.e., self-resolving). The scheduled interim and final data safety and monitoring committee reviews recommended no changes to the study.

In total, 168 of 170 participants completed the intervention with good compliance. Discontinuation for adverse events occurred in 2 female subjects in the PG 1000 mg twice a day group. One (1) subject (age 54 years; weight 44.8 kg) experienced rapid heartbeat and insomnia from days 2 to 5, while a second subject (age 38 years; weight 61.9 kg) experienced rash and nausea from days 3 to 7. Even though their adverse events were rated to be mild, the participants wanted to discontinue this study protocol. Their adverse events resolved spontaneously after discontinuation of PG.

Laboratory tests results

The hematological and biochemical test results were within the normal range both at baseline and after 4 weeks of PG administration, and there were no statistical differences ($p > 0.05$) between clinical laboratory tests performed at screening (prestudy), and at final assessment (poststudy), and across three treatment arms (Tables 3–6).

The urinalysis results are summarized in Tables 7 and 8. Even though leukocytes, blood, and ketones in females were related, the safety committee decided those were not directly related with this study and were negligible. In addition, there were no signs of toxicity.

Discussion

In the present study, PG administration did not significantly alter the hematological and biochemical test results in 170 healthy volunteers. The results showed that 170 healthy volunteers administered PG over a 4-week interval did not show

any serious adverse reactions. Adverse events reported by volunteers were mainly mild in severity and included dyspepsia, hot flashes, insomnia, constipation, and so on. Most of the adverse events reported were all transient, resolving without any clinical sequelae. This is in accordance with a recent systematic review.[7] This report provides scientific results concerning the safety and tolerability of PG in healthy volunteers.

There is a limitation that needs to be acknowledged and addressed regarding the present study. Subjects who had a previous history of hypersensitivity to ginseng preparations were excluded. Therefore, possible adverse events from ginseng might have been missed.

PG is a long-standing medication used largely for reducing physical, chemical, and biologic stress, while increasing general vitality and immune function, including physical and mental capacity.[20–26]

In general, ginseng has a good safety record. The root of PG appeared nontoxic to rats, dogs, and humans.[16] In mice, a lethal oral dose of purified ginseng was determined to be higher than 5 g/kg, the highest dose that can be orally given to a mouse and considered good practice at the maximal dose volumes without violating animal welfare standards.[27] In a 2-year human study, 14 of a total of 133 subjects were reported to experience side-effects attributed to long-term exposure of ginseng when consumed at levels up to 15 g/day.[28] Despite its broad clinical use, there have been few toxicological studies performed in humans.

It is well known that the most common side-effects of PG resulting from its overdose are nervousness and excitability. These side-effects usually decrease after the first few days. In inappropriate uses, the most common side-effects are the inability to sleep and high blood pressure.

Other side-effects include mastalgia,[29] Stevens-Johnson syndrome,[30] psychiatric conditions,[31] cerebral arteritis,[32] agranulocytosis,[33] eye symptoms,[34] hypertension,[35] and pneumonitis.[36] PG may lower blood glucose levels.[37] In some cases, active substances of herbs can interact with other herbs' active substances, supplements, or medications. Interactions between ginseng and warfarin, phenelzine, or alcohol have been reported.[38–42]

For these reasons, herbs should be taken with care, under supervision of a practitioner knowledgeable in the field of botanical medicine.

Conclusions

In summary, PG was shown in the present study to be safe, tolerable, and free of any untoward toxic effect in healthy male and female volunteers, when administered during a 4-week period. Although minor side-effects were reported, the physical, hematological, and biochemical parameters measured were within normal limits. Future results from ongoing multicenter collaborative efforts to evaluate short- and long-term effects of PG may contribute to current understanding of safety and tolerability of this herbal product.

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