



Subacute Oral Toxicity Study of Korean Red Ginseng Extract in Sprague-Dawley Rats

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Ginseng is a well-known traditional medicine used in Asian countries for several thousand years, and it is currently applied to medicine, cosmetics, and nutritional supplements due to its many healing and energy-giving properties. It is well demonstrated that ginsenosides, the main ingredient of ginseng, produce a variety of pharmacological and therapeutic effects on central nerve system (CNS) disorders, cardiovascular disease, endocrine secretions, aging, and immune function. Korean red ginseng extract is a dietary supplement containing ginsenoside Rb1 and ginsenoside Rg1 extracted from *Panax ginseng*. While the pharmacokinetics and bioavailability of the extract have been well established, its toxicological properties remain obscure. Thus, four-week oral toxicity studies in rats were conducted to investigate whether Korean red ginseng extract could have a potential toxicity to humans. The test article was administered once daily by oral gavage to four groups of male and female Sprague-Dawley (SD) rats at dose levels of 0, 500, 1,000, and 2,000 mg/kg/day for four weeks. Neither deaths nor clinical symptoms were observed in any group during the experiment. Furthermore, no abnormalities in body weight, food consumption, ophthalmology, urinalysis, hematology, serum biochemistry, gross findings, organ weights, or histopathology were revealed related to the administration of the test article in either sex of any dosed group. Therefore, a target organ was not determined in this study, and the no observed adverse effect level (NOAEL) of Korean red ginseng extract was established to be 2,000 mg/kg/day.

Key words: Korean red ginseng extract, *Panax ginseng*, Ginsenoside, Toxicity, Sprague-Dawley rats

INTRODUCTION

Ginseng is a well-known traditional medicine used in Asian countries for several thousand years, and it is currently applied to medicine, cosmetics, and nutritional supplements due to its many healing and energy-giving properties. In addition, it has been reported that five to six million people use ginseng regularly in the United States (1). It is well demonstrated that ginsenosides, the major ingredient of ginseng, produce a variety of pharmacological and therapeutic effects on central nerve system (CNS) disorders, cardiovascular disease,

endocrine secretions, aging, and immune function (2-6).

To date, more than 30 types of ginsenosides have been identified from ginseng (2,7). The top six major ginsenosides in quantity—Rg₁, Rc, Rd, Re, Rb₁, Rb₂, and Rb₀—make up over 70% of contents (8,9). In general, ginsenosides are classified into two groups; namely, the 20 (S)-protopanaxadiol group and the 20 (S)-protopanaxatriol group. Rb1 and Rg1 are the most abundant ginsenosides in ginseng and belong to the 20 (S)-protopanaxadiol and 20 (S)-protopanaxatriol groups, respectively (10). Rb1 has anti-inflammatory action, an obvious vasodilating effect, and a tranquilizing effect on the CNS, and it is known to have CNS-exciting, anti-fatigue, and hemolysis properties (11). Ginseng is a known adaptogen classified by herbalists, and its antioxidant activity increases the body's resistance to stress, trauma, anxiety, and fatigue (12). Furthermore, a population-based cohort study revealed that regular ingestion of ginseng at a dose of 1.3 g per day improved both overall and disease-free survival and enhanced the quality of life of Chinese female breast cancer survivors (13).

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Despite the worldwide consumption of red ginseng and its long history, its toxicological properties remain obscure due to differences in the composition of the various ginseng species and the manner of sample preparation, while its pharmacokinetics and bioavailability have been well established (14). In the present study, to assess its subacute oral toxicity, we administered Korean red ginseng extract, a dietary supplement mainly containing ginsenoside Rb1 and Rg1 extracted from *Panax ginseng*, to Sprague-Dawley (SD) rats for four weeks.

MATERIALS AND METHODS

Treatments and experimental animals. The test article, Korean red ginseng extract, was obtained from the Korea Ginseng Corp. (Daejeon, Korea). Korean red ginseng was extracted by cutting the root into 3~5-cm pieces and boiling it with 10 volumes of distilled water at 85°C for 8 hr. For concentrating, this process was repeated ten times, and the components of the ginsenosides in the Korean red ginseng extract are shown in Table 1. The test article was dissolved and suspended in distilled water (Daehan Pharm, Korea). Specific pathogen-free SD rats (CrI: CD, five weeks old) of both sexes were purchased from Orient Bio Ltd. (Gyeonggi-Do, Korea). The animals were randomly assigned to eight groups, each consisting of five males and five females. The four-week study was performed with five rats/sex/group dosed with Korean red ginseng extract or vehicle (distilled water) by daily oral administration using syringes with an oral zoned needle at doses of 0, 500, 1,000, and 2,000 mg/kg body weight (bw)/day, respectively, with a volume of 10 ml/kg bw.

Housing conditions. The animal room was maintained at a temperature of 23 ± 3°C, relative humidity of 50 ± 10%, air ventilation of 10 to 20 times/hr, and light intensity of 150 to 300 Lux with a 12 hr light/dark cycle. During the experiment period, the temperature and relative humidity of the animal room were automatically controlled, and the frequency of ventilation and light intensity were periodically monitored. Pelleted feed for experimental animals was purchased from PMI Nutrition International (LabDiet #5053, USA). The pellet chow was gamma-rayed and given ad libitum to animals. This study was reviewed and assessed by the Institutional Animal Care and Use Committee (IACUC) of the Korea Institute of Toxicology (KIT).

Clinical signs and mortality. During the treatment period, all animals were observed for clinical signs and mortality once a day.

Body weight and food consumption. All animals' body weights were measured at the initiation of treatment and then once a week until the day of necropsy. Food consumption per cage was measured once before dosing and once a week during the treatment period. A weighed amount of feed was supplied to each cage, and the remaining feed was measured the next day. The daily food consumption (g/rat/day) was calculated by the difference.

Ophthalmological examinations. The external eye examinations were conducted during the acclimation period. In the last week of dosing, the ocular fundi of all males and females in the vehicle control group and the Korean red ginseng extract-administrated groups were examined using a binocular indirect ophthalmoscope (GENESIS, Kyowa, Japan) after being treated with mydriatic eye drops (Mydrin-P, Santen Pharmaceutical Co, Japan).

Urinalysis. Before the day of necropsy, urinalysis was carried out on the urine collected from all animals, which had fasted for approximately 16 hrs in a metabolic cage. Analysis included volume (Vol), glucose (GLU), bilirubin (BIL), ketone body (KET), specific gravity (SG), occult blood (BLO), pH, protein (PRO), urobilinogen (URO), nitrite (NIT), and color (COL). Urine volume was measured by the naked eye using a mass cylinder. Microscopic examination was performed on the sediment. The remaining urinalysis items were analyzed using an automatic tester (CliniTek-500, Bayer) and a urine stick (Multistix 10 SG, Bayer).

Hematology. All animals were fasted overnight before blood sampling. Blood samples were drawn from the posterior vena cava of the animals under isoflurane anesthesia, and EDTA-2K was used as an anticoagulant. White blood cell count (WBC), red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets (PLT), neutrophils (NEU), lymphocytes (LYM), monocytes (MON), eosinophils (EOS), basophils (BAS), large unstained cells (LUC), and reticulocytes (RET) were measured by a hematological auto-analyzer (ADVIA120 Hematology System, Bayer, USA). Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured using a blood coagulation analyzer (ACL 9000 Plus, Instrumentation Laboratory, Italy) after rats were treated with 3.2% sodium citrate.

Serum biochemistry. A serum biochemical examination was performed on all the animals on which a hematology

Table 1. Ginsenoside components and contents of the Korean red ginseng used

Components	Rg1	Re	Rf	Rh1	Rg2s	Rb1	Rc	Rb2	Rd	Rg3s	Rg3r
Content (mg/g)	0.66	0.81	1.00	1.00	1.44	6.66	2.79	2.56	0.93	2.70	1.22

ogy examination had been done. Blood samples were collected from the posterior vena cava of all the animals and then placed at room temperature. Serum samples were obtained after centrifugation (3,000 rpm, 10 min). The following items were analyzed using a clinical chemistry auto-analyzer (200FR NEO, Toshiba Co., Japan): aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (CREA), glucose (GLU), total cholesterol (TCHO), albumin/globulin ratio (A/G), total protein (TP), albumin (ALB), creatine kinase (CK), triglycerides (TG), total bilirubin (TBIL), phospholipids (PL), gamma-glutamyl transferase (GGT), calcium (Ca), inorganic phosphorus (IP), chloride (Cl), sodium (Na), and potassium (K).

Gross findings. All animals were fasted overnight and anaesthetized by isoflurane inhalation, followed by blood sampling. They were then sacrificed by exsanguination from the posterior vena cava and aorta prior to necropsy. Complete gross examinations were performed on all terminated animals.

Organ weights. When all animals were sacrificed, absolute organ weights were measured, and their relative organ weights (organ weight to fasted body weight ratios before necropsy) were calculated.

Histopathological examination. The tissues were fixed in neutral buffered 10% formalin and the testes and epididymides in Bouin's fixative. Using these fixed organs, the major organs in the vehicle control group and the high-dose group were embedded in paraffin, sectioned, stained with hematoxylin and eosin (H&E), and examined microscopically.

Statistical analysis. Data collected during the study was examined for variance homogeneity using Bartlett's test. When Bartlett's test indicated no significant deviations from variance homogeneity, the one-way ANOVA was performed at $\alpha = 0.05$. When significance was noted, a multiple comparison test (Dunnnett's test) was conducted to determine which pairs of group comparison were significantly different. In cases in which pairs of group homogeneity were observed, a non-parametric comparison test (Kruskal-Wallis test) was conducted. When a significant difference was observed in the Kruskal-Wallis test, Dunn's Rank Sum test was conducted to determine the specific pairs of group comparison. Statistical analyses were performed by using the Path/Tox System (Version 4.2.2, Xybion Co., USA). The level of significance was taken as $p < 0.05$.

RESULTS

Clinical signs and mortality. No clinical signs or mortality were observed in animals treated with Korean red ginseng

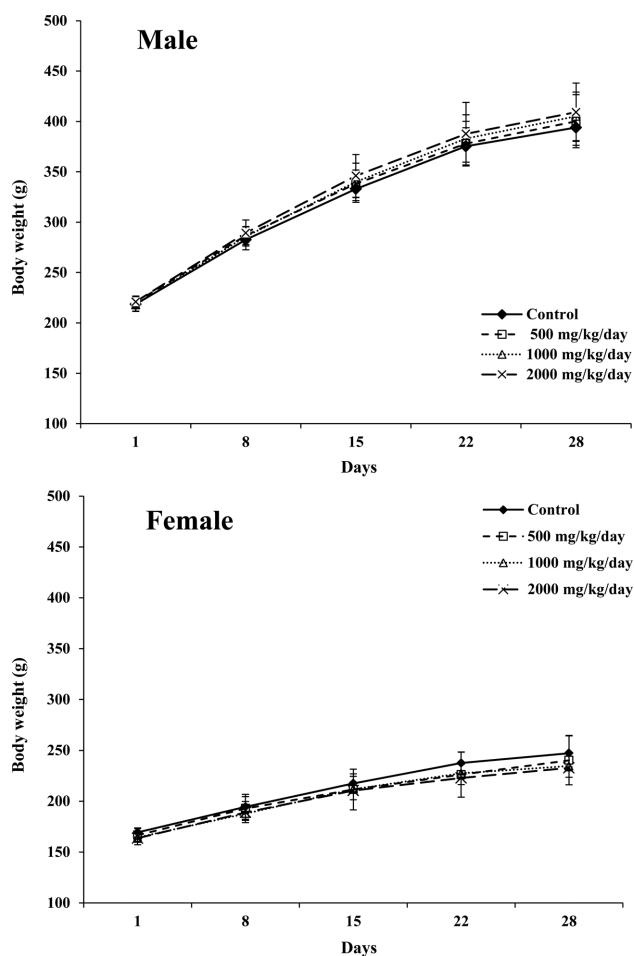


Fig. 1. Body weight changes of male and female SD rats orally administered with Korean red ginseng extract for 4 weeks.

extract at doses of 500, 1,000, and 2,000 mg/kg/day for four weeks (data not shown).

Body weight and food consumption. No significant differences in mean body weight or food consumption were observed in either sex treated with Korean red ginseng extract at various doses (500, 1,000, and 2,000 mg/kg/day) (Fig. 1 and Fig. 2).

Ophthalmologic examination. One case of corneal opacity was observed in the vehicle control group of males, but it was not related to the Korean red ginseng extract treatment.

Urinalysis. No effect related to Korean red ginseng extract treatment was observed in urinalysis of male or female rats (Table 2).

Hematology. In hematological examination, there were no statistically significant differences except that MCHC was decreased in females of the 2,000 mg/kg/day group. How-

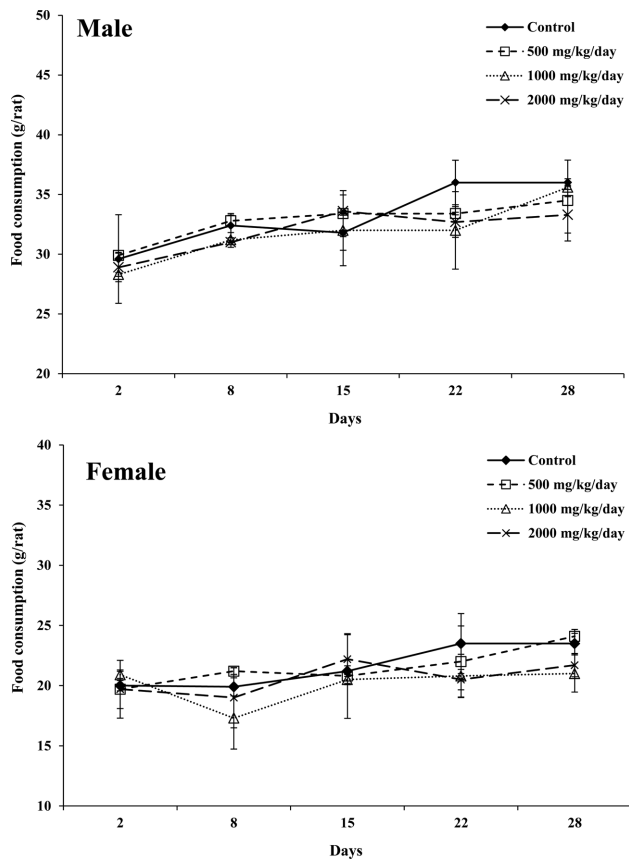


Fig. 2. Food consumption of male and female SD rats orally administered with Korean red ginseng extract for 4 weeks.

ever, the value was within the normal physiological range, and a decrease in MCHC was not observed in males (Table 3).

Serum biochemistry. In terms of serum biochemistry, the calcium level in males of the 1,000 mg/kg/day group was increased compared to those of the control group, but this increase was not observed in males of the 2,000 mg/kg/day group or in females treated with Korean red ginseng extract (Table 4).

Gross findings and organ weight. No treatment-related gross findings were observed at necropsy. Absolute and relative organ weights of the thyroid glands were increased in males of the 2,000 mg/kg/day group. The relative organ weight of the lung decreased in males at 500 mg/kg/day (data not shown). In females, there were no significant differences in absolute and relative organ weights between the control and treatment groups (data not shown).

Histopathological examination. Korean red ginseng extract did not induce treatment-related histopathological changes in brain, pituitary gland, adrenal glands, liver, spleen, kidneys, heart, thymus, lung, salivary gland (included submaxillary gland and sublingual gland), thyroid (included parathyroid), testes, epididymides, seminal vesicle, prostate, uterus (included cervix), or ovaries (Fig. 3).

DISCUSSION

Ginseng is an aromatic herb widely used in herbal medi-

Table 2. Urinalysis data of males and females SD rats orally administered with Korean red ginseng extract for 4 weeks

Sex	Males				Females			
Dose group (mg/kg/day)	Control	500	1000	2000	Control	500	1000	2000
No. of animal	5	5	5	5	5	5	5	5
Volume ^a	20 ± 6.3	20 ± 6.0	28 ± 8.8	21 ± 10.7	18 ± 6.8	10 ± 5.1	11 ± 5.9	11 ± 5.4
GLU	negative	5	5	5	5	5	5	5
BIL	negative	5	5	5	5	5	5	5
KET	negative	4	3	0	5	5	5	5
	Trace	1	2	4	0	0	0	0
	1+	0	0	1	1	0	0	0
SG ^a	1.018 ± 0.006	1.022 ± 0.003	1.016 ± 0.004	1.02 ± 0.008	1.021 ± 0.007	1.024 ± 0.004	1.024 ± 0.007	1.024 ± 0.002
BLO	negative	5	5	5	5	5	5	5
pH	6	0	0	0	0	3	2	0
	6.5	1	3	0	4	1	3	5
	7	4	2	5	2	1	0	0
PRO (mg/kg)	negative	1	0	1	0	4	2	3
	Trace	3	5	2	3	1	1	2
	1+	1	0	2	2	0	2	0
URO (EU/dl) ^a	0.2	0.2	0.2	0.2	0.2	0.36 ± 0.358	0.36 ± 0.358	0.2
NIT	negative	4	4	2	3	5	2	4
Color	straw	5	5	5	5	5	5	5

^aSpecific gravity : Each value represents mean ± S.D.

Table 3. Hematological values of males and females SD rats orally administrated with Korean red ginseng extract for 4 weeks

Parameter	Dose group (mg/kg/day)			
	Control	500	1000	2000
<i>Males</i>				
WBC ($\times 10^9/L$)	13.56 \pm 1.023	12.18 \pm 3.687	11.28 \pm 1.786	12.10 \pm 2.788
RBC ($\times 10^{12}/L$)	8.54 \pm 0.221	8.79 \pm 0.285	8.49 \pm 0.303	8.55 \pm 0.262
HGB (g/dl)	16.2 \pm 0.60	16.1 \pm 0.53	15.9 \pm 0.46	16.2 \pm 0.52
HCT (%)	52.5 \pm 2.05	52.5 \pm 1.19	52.8 \pm 1.78	53.3 \pm 1.39
MCV (fl)	61.4 \pm 1.23	59.8 \pm 1.05	62.2 \pm 2.27	62.3 \pm 1.29
MCH (pg)	18.9 \pm 0.39	18.3 \pm 0.54	18.8 \pm 0.52	19.0 \pm 0.57
MCHC (g/dl)	30.8 \pm 0.11	30.7 \pm 0.46	30.2 \pm 0.75	30.5 \pm 0.35
PLT ($\times 10^9/L$)	1363 \pm 175.6	1307 \pm 104.5	1307 \pm 89.5	1268 \pm 116.3
RET (%)	2.3 \pm 0.26	2.3 \pm 0.27	2.6 \pm 0.40	2.6 \pm 0.37
NEU (%)	10.5 \pm 3.22	9.5 \pm 2.29	12.1 \pm 6.42	11.0 \pm 4.91
LYM (%)	84.2 \pm 3.86	85.9 \pm 2.33	82.0 \pm 6.55	83.5 \pm 4.88
EOS (%)	0.7 \pm 0.24	0.8 \pm 0.25	0.7 \pm 0.20	0.8 \pm 0.23
MON (%)	2.7 \pm 1.25	2.1 \pm 0.56	3.4 \pm 1.23	2.7 \pm 1.03
BAS (%)	0.8 \pm 0.22	0.8 \pm 0.21	0.8 \pm 0.11	1.0 \pm 0.30
LUC (%)	1.0 \pm 0.31	0.8 \pm 0.10	1.1 \pm 0.25	1.0 \pm 0.26
PT (sec)	15.7 \pm 0.43	16.2 \pm 0.21	15.5 \pm 0.64	15.6 \pm 0.47
APTT (sec)	16.6 \pm 1.37	16.7 \pm 0.73	15.5 \pm 2.26	15.4 \pm 1.38
<i>Females</i>				
WBC ($\times 10^9/L$)	8.66 \pm 2.061	7.39 \pm 1.420	7.36 \pm 1.979	7.29 \pm 1.314
RBC ($\times 10^{12}/L$)	8.64 \pm 0.360	8.60 \pm 0.530	8.57 \pm 0.291	8.73 \pm 0.237
HGB (g/dl)	16.0 \pm 0.50	15.9 \pm 0.89	15.8 \pm 0.58	16.1 \pm 0.70
HCT (%)	50.6 \pm 1.43	50.5 \pm 2.80	49.9 \pm 1.41	51.9 \pm 2.13
MCV (fl)	58.5 \pm 1.33	58.8 \pm 1.69	58.2 \pm 0.61	59.4 \pm 1.38
MCH (pg)	18.5 \pm 0.26	18.5 \pm 0.60	18.5 \pm 0.33	18.5 \pm 0.41
MCHC (g/dl)	31.6 \pm 0.28	31.5 \pm 0.15	31.7 \pm 0.46	31.1 \pm 0.23*
PLT ($\times 10^9/L$)	1447 \pm 168.2	1430 \pm 147.9	1379 \pm 136.3	1327 \pm 108.0
RET (%)	2.2 \pm 0.49	2.1 \pm 0.51	2.2 \pm 0.45	2.1 \pm 0.62
NEU (%)	9.6 \pm 1.56	13.6 \pm 8.12	14.0 \pm 7.68	12.1 \pm 5.22
LYM (%)	85.1 \pm 0.76	81.2 \pm 8.17	80.9 \pm 8.81	82.7 \pm 5.57
EOS (%)	1.1 \pm 0.40	1.1 \pm 0.30	1.0 \pm 0.49	1.1 \pm 0.45
MON (%)	2.3 \pm 0.98	2.1 \pm 0.61	1.9 \pm 0.88	1.9 \pm 0.50
BAS (%)	0.9 \pm 0.21	1.0 \pm 0.19	0.9 \pm 0.31	1.0 \pm 0.11
LUC (%)	1.1 \pm 0.31	1.1 \pm 0.28	1.2 \pm 0.58	1.2 \pm 0.45
PT (sec)	17.2 \pm 0.55	16.8 \pm 0.11	16.4 \pm 0.76	17.1 \pm 0.77
APTT (sec)	12.7 \pm 0.90	14.2 \pm 0.99	14.6 \pm 0.51	13.3 \pm 2.02

Values are means \pm S.D.

*: Significant different in comparing with control ($p < 0.05$).

cine, dietary supplements, and cosmetics. Despite its long history of usage and widespread consumption, the adverse effects of ginseng are not understood well. The present study was performed to evaluate the potential toxicity of Korean red ginseng in SD rats by repeated oral dosing. The study revealed that there was no adverse effect of the test article when administrated at dose levels of 500, 1,000, and 2,000 mg/kg/day for four weeks.

No clinical signs or mortalities of toxicity were observed in either of the control or the test article administrated groups. Furthermore, test article administration induced no significant changes in body weight or food consumption up to 2,000 mg/kg/day. Even though food consumption in females

of the 2,000 mg/kg/day group was slightly decreased, there was no consistent effect on body weight and food consumption. Therefore, slight decreases in food consumption in females of the 2,000 mg/kg/day group were considered no toxicological significance. In urinalysis, some items such as KET, PRO, and NIT varied but were not presented in a dose-dependent manner or were not significantly different between the control group and the test article administrated groups, indicating that these differences were not related with the test article. Regarding hematological analysis, MCHC in females of the 2,000 mg/kg/day group was significantly decreased compared to that of the control group, but it was a very slight decrease compared with the control group.

Table 4. Biochemical serum values of males and females SD rats orally administered with Korean red ginseng extract for 4 weeks

Parameter	Dose group (mg/kg/day)			
	Control	500	1000	2000
<i>Males</i>				
GLU (mg/dl)	119.6 ± 9.02	109.6 ± 18.09	135.0 ± 26.54	123.6 ± 29.18
BUN (mg/dl)	13.6 ± 0.58	12.0 ± 1.10	12.7 ± 1.36	11.9 ± 2.27
CREA (mg/dl)	0.52 ± 0.058	0.56 ± 0.100	0.57 ± 0.053	0.48 ± 0.089
TP (g/dl)	6.72 ± 0.232	6.80 ± 0.441	6.71 ± 0.145	6.58 ± 0.294
ALB (g/dl)	4.24 ± 0.108	4.26 ± 1.181	4.23 ± 0.077	4.20 ± 0.121
A/G (ratio)	1.72 ± 0.089	1.69 ± 0.134	1.71 ± 0.039	1.77 ± 0.089
TCHO (mg/dl)	59.4 ± 16.01	53.8 ± 4.97	69.4 ± 17.62	62.8 ± 1.79
TG (mg/dl)	35.4 ± 8.94	39.3 ± 10.45	54.4 ± 23.60	44.2 ± 19.63
PL (md/dl)	99 ± 20.2	88 ± 6.9	109 ± 16.7	98 ± 3.7
AST (IU/L)	118.6 ± 18.02	126.7 ± 32.16	113.2 ± 7.86	128.5 ± 18.93
ALT (IU/L)	40.9 ± 7.68	35.3 ± 3.10	35.4 ± 5.96	37.3 ± 4.28
TBIL (mg/dl)	0.097 ± 0.0136	0.095 ± 0.0066	0.096 ± 0.0111	0.086 ± 0.0059
ALP (IU/L)	461.0 ± 24.05	556.8 ± 118.93	488.4 ± 87.78	592.0 ± 71.55
CK (IU/L)	624 ± 124.3	746 ± 413.8	512 ± 49.9	720 ± 258.8
Ca (mg/dl)	11.29 ± 0.358	11.1 ± 0.438	11.89 ± 0.121*	11.33 ± 0.194
IP (mg/dl)	10.91 ± 0.327	9.99 ± 0.432	10.96 ± 0.857	10.47 ± 0.610
Na (mmol/L)	146 ± 0.8	146 ± 2.1	148 ± 1.7	148 ± 2.2
K (mmol/L)	8.98 ± 0.449	7.41 ± 0.913	8.56 ± 0.909	7.99 ± 1.490
Cl (mmol/L)	104 ± 1.3	104 ± 2.2	105 ± 1.1	106 ± 0.5
GGT (IU/L)	0.22 ± 0.381	0.04 ± 0.098	0.28 ± 0.400	0.24 ± 0.358
<i>Females</i>				
GLU (mg/dl)	92.1 ± 21.50	112.7 ± 26.76	92.4 ± 37.31	108.5 ± 38.94
BUN (mg/dl)	18.4 ± 1.98	16.4 ± 1.34	17.1 ± 3.26	16.1 ± 3.86
CREA (mg/dl)	0.55 ± 0.064	0.57 ± 0.111	0.60 ± 0.109	0.61 ± 0.086
TP (g/dl)	6.65 ± 0.205	6.81 ± 0.357	6.83 ± 0.301	6.72 ± 0.195
ALB (g/dl)	4.41 ± 0.057	4.41 ± 0.112	4.47 ± 0.112	4.37 ± 0.151
A/G (ratio)	1.98 ± 0.152	1.86 ± 0.211	1.91 ± 0.113	1.86 ± 0.126
TCHO (mg/dl)	61.2 ± 12.52	59.8 ± 15.07	60.0 ± 14.82	59.4 ± 5.03
TG (mg/dl)	30.2 ± 9.15	25.2 ± 6.02	23.2 ± 4.92	23.3 ± 2.34
PL (md/dl)	114 ± 18.7	116 ± 25.1	113 ± 26.3	111 ± 8.5
AST (IU/L)	120.5 ± 16.71	123.3 ± 12.31	131.4 ± 16.30	138.1 ± 30.50
ALT (IU/L)	28.5 ± 3.34	29.4 ± 5.66	28.5 ± 2.12	28.8 ± 3.55
TBIL (mg/dl)	0.093 ± 0.0120	0.094 ± 0.0131	0.101 ± 0.0195	0.093 ± 0.0084
ALP (IU/L)	354.5 ± 58.61	364.5 ± 82.68	310.3 ± 47.58	304.7 ± 36.52
CK (IU/L)	808 ± 257.3	636 ± 85.8	905 ± 117.1	900 ± 233.9
Ca (mg/dl)	10.97 ± 0.346	11.08 ± 0.291	11.12 ± 0.471	11.03 ± 0.258
IP (mg/dl)	9.97 ± 0.782	9.51 ± 0.979	9.72 ± 0.770	9.46 ± 0.895
Na (mmol/L)	145 ± 0.9	145 ± 0.9	145 ± 1.9	145 ± 1.3
K (mmol/L)	8.79 ± 0.866	8.08 ± 0.969	8.29 ± 0.752	8.48 ± 1.456
Cl (mmol/L)	106 ± 0.8	107 ± 2.3	107 ± 1.0	107 ± 1.1
GGT (IU/L)	0.72 ± 0.322	1.15 ± 0.323	0.68 ± 0.508	0.75 ± 0.320

Values are means ± S.D.

*: Significant different in comparing with control ($p < 0.05$).

Besides, MCV and MCH were within the normal range, indicating that these fluctuations are considered to be of no toxicological significance. In terms of serum biochemistry, the calcium level in male rats of the 1,000 mg/kg/day group was increased compared to that of the control group, but this occurred without dose response, indicating that the difference was not deemed to be test article administration related. Although there was no statistically significance, serum

TG levels were decreased in females treated with Korean red ginseng extract. The changes might be associated with slightly decreased food consumption in females because fat and carbohydrates in diet could affect serum TG levels (15,16). However, the slight changes were not seen in males or dose-dependent manner and there were no correlated histopathological findings; therefore, they are considered irrelevant to the test article treatment. An increase in absolute

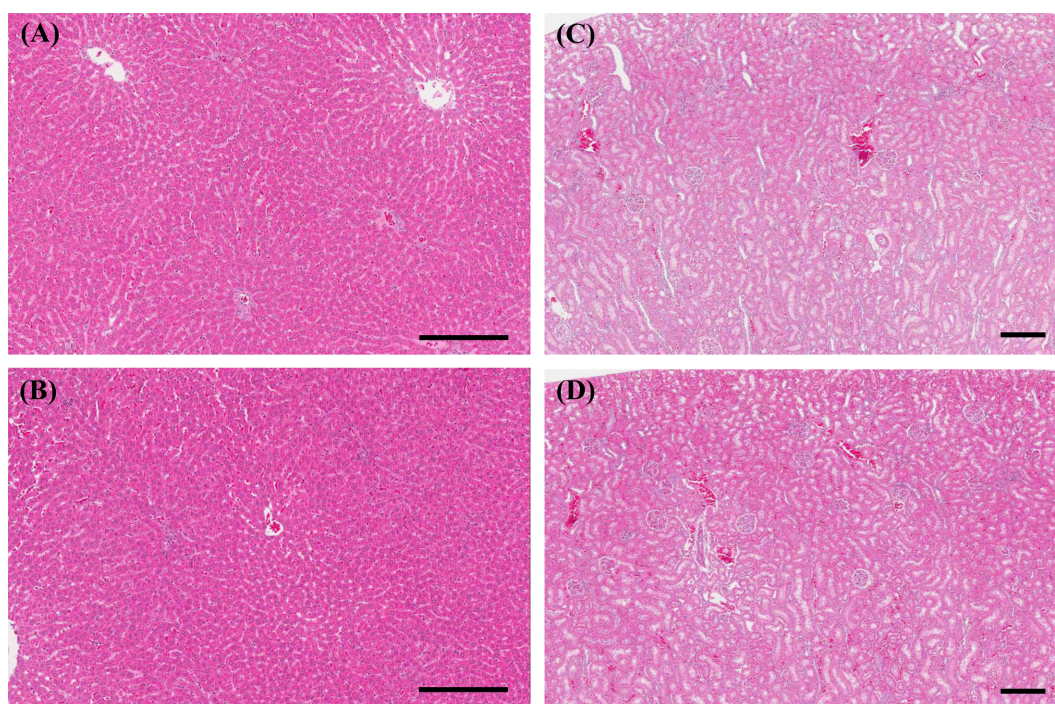


Fig. 3. Histopathology of the liver (A) and (B) and kidneys (C) and (D) of male rats administrated Korean red ginseng extract for 4 weeks. Panel A and C: 0 mg/kg/day group; Panel B and D : 2,000 mg/kg/day. HE staining. Scale bar: 250 µm.

and relative organ weights of the thyroid gland was observed in males of the 2,000 mg/kg/day group. However, as there was no corresponded finding in microscopic observation, it was not considered toxicologically significant.

Siegel reported adverse effects due to overexposure to ginseng and coined the phrase “ginseng abuse syndrome” (17). The clinical presentation of ginseng abuse syndrome includes hypertension, gastrointestinal disturbances, insomnia, nervousness, confusion, and depression (4). However, we did not observe any clinical symptoms in Korean red ginseng extract administrated male and female rats related to ginseng abuse syndrome. The present study corresponds with subchronic toxicity studies in which male and female SD rats fed diets containing ginseng extract with 0, 1.5, 5 and 15 mg/kg/day for 13 weeks developed no histopathological changes (18). Furthermore, in another study, no toxic effect was detected in rats following ingestion of ginseng extract at dose levels of 105 to 210 mg/kg/day for 25 weeks (19). However, the dose level used these studies was considered low, we tested approximately ten times higher level (2,000 mg/kg/day) of ginseng extract and showed no toxicity in the present study. In a chronic study in mice, consuming *Panax ginseng* increased behavioral responses to mild stress, but there were no significant differences in mean weights or survival ratios (20). Additionally, no evidence of toxicity was shown in male and female beagle dogs administrated ginseng extract for three months (21). These studies consistently suggest the safety of ginseng

administration and correspond with the present study.

In conclusion, there was no observation of toxicity in this four-week repeated oral dose toxicity study of Korean red ginseng extract in rats. In this study, the no observed adverse effect level (NOAEL) was considered to be 2,000 mg/kg/day in both sexes of rats.

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