Antihypertensive effects of Korean wild simulated ginseng (Sanyangsam) extracts in spontaneously hypertensive rats

Jae-Nam Moon¹ · Jong-Kuk Kim² · Seul Lee¹ · Joong-Ho Kwon¹

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Abstract Ginseng possesses a wide spectrum of medicinal effects and has widely been used in traditional medicine for thousands of years. In this study, the antihypertensive effect of Korean wild simulated ginseng in spontaneously hypertensive rats was investigated. Three groups of hypertensive rats—a group without wild simulated ginseng treatment; another group treated with 100 mg of wild simulated ginseng extract/kg of body weight; and the other group treated with 200 mg of wild simulated ginseng extract/kg of body weight were tested over 8 weeks. The two wild simulated ginseng-treated groups showed significantly ($p < 0.05$) reduced systolic blood pressure at 4 and 6 weeks of wild simulated ginseng treatment. However, the wild simulated ginseng treatment did not adversely affect the food intake, serum electrolytes, osmolality, heart weight, heart rate, and the cross-section of the aorta as well as enzyme activities. The results suggested that Korean wild simulated ginseng is effectively used for reducing high systolic blood pressure in hypertensive patients without causing adverse health effects.

Keywords Antihypertensive effect · Spontaneously hypertensive rat · Systolic blood pressure · Korean wild simulated ginseng

Introduction

Ginseng (*Panax* spp.) is a popularly used herb in the traditional oriental medicine as it possesses a variety of pharmaceutical properties, such as tonic, immunomodulatory, antimutagenic, adaptogenic, and antiaging (Lee et al., 2005). The in vitro (Kimura et al., 1981) and in vivo (Kimura et al., 1999) studies and clinical trials (Vuksan et al., 2000) support the claim that the roots of *P. ginseng* and other species of ginseng such as *P. quinquefolius* possess antihyperglycemic. It has also been reported that ginseng cause hypoglycemic effect on diabetic mice producing a decreased blood glucose level (Park et al., 2012a). A considerable number of reports describe the efficacy of ginseng in alleviating stress and enhancing immune systems as well as contributing towards retaining desirable oxidative status to protect against some chronic diseases and aging (Fu and Ji, 2003; Kitts and Hu, 2000). Ginseng has become an important component of Eastern medication for over 4000 years and has been reported to prevent and cure diabetes and several different ailments (Park et al., 2012b).

Although the incidence of hypertension as a disease is low, a number of health problems like stroke, myocardial infarction, diabetes, and heart failure are associated with this problem. It may also lead to cardiac and vascular muscle hypertrophies and arterioscleroses (Alexander, 1995). It is one of the vital risk factors leading to the cardiovascular diseases (CVDs) (WHO, 2013) which affects about 20–40% of the total adults' population and

✉ Joong-Ho Kwon
jhkwon@knu.ac.kr

Jae-Nam Moon
mjn96@hanmail.net

Jong-Kuk Kim
kjk@knu.ac.kr

Seul Lee
duqtmf8749@hanmail.net

¹ School of Food Science and Biotechnology, Kyungpook National University, Daegu 41566, Korea

² Department of Food and Food-Service Industry, Kyungpook National University, Sangju 37224, Korea

the figure is ever increasing (Padwal et al., 2016; WHO, 2013). The use of complementary and alternative medicine (CAM) is remarkably high in CVD patients compared to the general population. Reports show that the use of herbal medicines is one of the frequently used types of CAM (Liwa et al., 2014; Sibbritt et al., 2015). Ginseng has been used for a number of health benefits, such as improving erectile dysfunction (Jang et al., 2008), cognitive function (Geng et al., 2010; Lee et al., 2009), menopausal symptoms (Kim et al., 2013), type 2 diabetes (Kim et al., 2011), and symptoms of cancer (Jin et al., 2016). Modulating vascular function by ginseng or individual ginsenosides has been widely studied. A hypotensive-component-enriched fraction from red ginseng with persimmon vinegar was evaluated for its effect to improve hypertension in rats (Lee et al., 2016).

A number of reports about health benefits of ginseng have been published, however, to the best of the authors' knowledge, the effect of Korean wild simulated ginseng on the spontaneously hypertensive rats has not been well documented. The objective of this study was to investigate the health effect of Korean wild simulated ginseng extract on spontaneously hypertensive rats.

Materials and methods

Plant material and extract preparation

Five-year-old wild simulated ginseng (*Panax ginseng*) grown in a farm of Andong, Korea was manually uprooted in September of 2016. The roots were carefully rinsed with tap water, allowed to dry under the shade, and ground using a commercial electric grinder (HIL-G-501; Hanil Co., Seoul, Korea). Fifty grams of the crushed root was extracted with 500 mL of sterile distilled water for 15 h in a Soxhlet apparatus. The extract was concentrated using a rotary evaporator (N-12; Eyela, Tokyo, Japan), vacuum dried (SFDSM 24L; Samwon Freezing Engineering Co., Busan, Korea), and stored at 4 °C for subsequent analyses.

Animals and diet

This study was conducted using 5-week-old male Wister Kyoto rats (WKR) (130 ± 10 g body weight) and 8-week-old male spontaneously hypertensive rats (SHR) (250 ± 10 g body weight) purchased from Orientbio Co. Ltd. (Seongnam, Korea). The rats were housed in polypropylene cages and were acclimatized to laboratory conditions (23 ± 2 °C, $50 \pm 10\%$ relative humidity and

12 h light–dark cycle) for 7 days before commencement of the experiment.

The rats were fed with a standard dry pellet diet and water ad libitum during the study period. This study was conducted as per the Institutional Animal Ethics Committee (IAEC) protocols. Also, all the necessary institutional and national rules and regulations for the care and use of laboratory animals were followed in the present study.

Experimental design

An equal number of rats were randomly distributed into 4 clusters containing 8 in each cluster, and named as WKR-control, a normal control without wild simulated ginseng treatment; SHR-control, hypertensive rats receiving no wild simulated ginseng treatment; SHR-G100, hypertensive rats receiving 100 mg of wild simulated ginseng extract/kg of body weight; and SHR-G200, hypertensive rats receiving 200 mg of wild simulated ginseng extract/kg of body weight. The control groups (WKR and SHR) were supplied with sterile distilled water, whereas the two treatment groups (SHR-G100 and SHR-G200) were administered with wild simulated ginseng extracts (100 mg/kg and 200 mg/kg body weight) using an Oral Zonde Needle (Namute, Sendai, Japan) for 8 weeks.

Body weight, food intake, and other biochemical parameters measurement

Body weight, as well as food intake were measured right before the onset of wild simulated ginseng treatments (0 weeks) and at every other week during the treatment. After completion of the 8-week long wild simulated ginseng treatment, the rats of each group were imposed with 12 h of fasting and then decapitated. The blood samples of the decapitated rats were kept into non-heparinised tubes (Fisher Scientific, Seoul, Korea) and centrifuged (Supra 22 K; Hanil Science Industrial Co., Incheon, Korea) at $1660 \times g$ for 15 min. The serum was analyzed to measure the biochemical parameters, including aminotransaminase (AST), alanine aminotransaminase (ALT), alkaline phosphatase (ALP), creatinine, blood urea nitrogen (BUN), urea acid, total cholesterol, total proteins, and albumin using an automatic analyzer (Hemagen Diagnostics Inc., Columbia, MD, USA).

Statistical analysis

Analysis of the data was carried out using a one-way analysis of variance and the significant differences among means were identified with Dunnett's multiple-range test at $p < 0.05$.

Results and discussion

Body weight

A gradual increase in the body weight of the four groups of rats from 0 to 8 weeks of treatment was observed (Table 1). Body weight was not significantly different ($p > 0.05$) between SHR-G100 and SHR-G200 groups until 8 weeks. A significantly ($p < 0.05$) high body weight was found in WKR-control followed by SHR-control rats until 6 weeks. At 8 weeks, the body weight of SHR-control (306.12 g) and wild simulated ginseng-treated (300.27–302.13 g) rats were not significantly different. This result suggested that the wild simulated ginseng extract could reduce body weight in hypertensive rats until a few weeks and after that period the body weight might be increased.

Ginseng inhibited gastric secretion (Suzuki et al., 1991), and this could reduce the absorption of carbohydrate by slowing down the food digestion which might also affect the body weight. Ginseng application also affected the state of mind, improved psychophysical behavior, and inhibited the body weight gain and fasting blood glucose level (Sotaniemi et al., 1995). Another report (Kang et al., 2006) also stated that ginseng treatment could reduce body weight gain in diabetic rats. Application of wild simulated ginseng may not play a role in increasing the body weight of rats (Cooper et al., 2007). The increased food and water consumptions but low weight gain in the ginseng-treated diabetic rats were probably because of the effect of ginseng extracts (von Wilmsdorff et al., 2010).

Food intake

The application of wild simulated ginseng extract did not cause a significant difference in food intake in different groups of rats until 8 weeks (Table 2).

Ginseng application increased the consumption of food and water as well as the amount of urine in diabetic rats (Kang et al., 2006). Similar results of significantly increased food and water consumptions in ginseng

administered rats were also observed in another study (Cooper et al., 2007). Result of the present study was not in agreement with that of the previous reports which might be due to a difference in the research animal as non-diabetic rats were used in the present study.

Systolic blood pressure

The systolic blood pressure of wild simulated ginseng-treated SHR was significantly ($p < 0.05$) low at 4 and 6 weeks compared to the hypotensive groups (Table 3). The two groups of wild simulated ginseng-treated rats (SHR-G100 and SHR-G200) did not vary significantly for systolic blood pressure until 8 weeks.

The effect of ginseng in reducing the systolic blood pressure may vary with the age of rats and/or duration of the ginseng administration. An earlier report also showed that administration of Korea ginseng to the SHR significantly ($p < 0.05$) reduced systolic blood pressure compared to the control group for 1–2 months (Joo et al., 2008). Ginsenoside Rg3-enriched red ginseng has also been found to have a vital role in reducing blood pressure (Stavro et al., 2002). Total saponins and Rg3 have been found to play roles in vascular smooth muscles (Kim et al., 1999). A report showed that an 8–9% reduction in blood pressure may cause for a 21% reduction in heart attacks and a 37% reduction in stroke (Hur et al., 2010). The reduction in systolic blood pressure of wild simulated ginseng-administered rats found in the present study showed that wild simulated ginseng could be a potential source to reduce the systolic blood pressure.

Serum electrolytes and osmolarity

The serum electrolyte measured as the concentration of Na, K, and Cl as well as the osmolarity level were not significantly affected by the wild simulated ginseng extract (Table 4).

Electrolyte imbalances can be fatal if not corrected promptly (Crawford, 2014). K is associated with cellular metabolism, regulating protein synthesis as well as glucose

Table 1 Body weight (g) of normal and hypertensive rats with and without Korean wild simulated ginseng treatment for 8 weeks

Sample ¹	Period (week)				
	0	2	4	6	8
WKR-control	276.31 ± 3.12a ²	295.12 ± 2.31a	308.06 ± 3.11a	314.02 ± 3.12a	321.08 ± 4.02a
SHR-control	258.07 ± 2.02b	281.31 ± 3.69b	296.29 ± 2.32b	300.07 ± 2.60b	306.12 ± 3.51b
SHR-G100	241.30 ± 5.00b	265.21 ± 4.02c	287.30 ± 5.00c	290.37 ± 3.14c	302.13 ± 4.00b
SHR-G200	250.29 ± 4.39b	269.24 ± 5.10c	286.07 ± 4.18c	289.36 ± 3.12c	300.27 ± 3.22b

¹Samples are defined in the experimental design section (“Materials and methods” section)

²Mean values ± SD followed by different letters within a column indicate significant differences at $p < 0.05$ based on Dunnett’s multiple-range test ($n = 8$)

Table 2 Food intake of normal and hypertensive rats with or without Korean wild simulated ginseng treatment for 8 weeks

Sample ¹	Period (week)				
	0	2	4	6	8
WKR-control	8.51 ± 0.57a ²	8.94 ± 0.61a	9.55 ± 0.82a	9.93 ± 0.72a	11.21 ± 0.90a
SHR-control	8.06 ± 0.45a	8.76 ± 0.57a	9.38 ± 0.77a	9.74 ± 0.93a	10.08 ± 0.92a
SHR-G100	8.33 ± 0.42a	9.12 ± 0.75a	9.39 ± 0.86a	10.11 ± 1.01a	10.45 ± 0.95a
SHR-G200	8.25 ± 0.63a	8.79 ± 0.78a	9.43 ± 0.80a	9.69 ± 1.02a	10.19 ± 0.91a

¹Samples are defined in the experimental design section (“[Materials and methods](#)” section)

²Mean values ± SD followed by different letters within a column indicate significant differences at $p < 0.05$ based on Dunnett’s multiple-range test ($n = 8$)

Table 3 Changes in systolic blood pressure of normal and hypertensive rats with or without Korean wild simulated ginseng treatment for 8 weeks

Sample ¹	Period (week)				
	0	2	4	6	8
WKR-control	130.21 ± 13.78b ²	126.54 ± 11.23b	130.27 ± 8.51c	140.12 ± 12.56c	131.82 ± 13.45b
SHR-control	170.80 ± 12.11a	171.15 ± 12.08a	181.24 ± 18.34a	182.35 ± 15.15a	178.21 ± 14.36a
SHR-G100	171.72 ± 11.28a	169.68 ± 8.33a	163.24 ± 16.69b	168.16 ± 12.37b	167.97 ± 13.25a
SHR-G200	172.19 ± 8.75a	168.72 ± 13.45a	152.73 ± 14.41b	160.74 ± 9.46b	168.59 ± 16.64a

¹Samples are defined in the experimental design section (“[Materials and methods](#)” section)

²Mean values ± SD followed by different letters within the same column indicate significant differences at $p < 0.05$ based on Dunnett’s multiple-range test ($n = 8$)

Table 4 Changes in serum electrolytes and osmolality of normal and hypertensive rats with or without Korean wild simulated ginseng treatment for 8 weeks

	Sample ¹			
	WKR-control	SHR-control	SHR-G100	SHR-G200
Na (mmol/L)	138.34 ± 8.26a ²	145.72 ± 11.28a	144.21 ± 10.45a	143.17 ± 12.85a
K (mmol/L)	4.93 ± 0.47a	4.51 ± 0.46a	4.62 ± 0.41a	4.49 ± 0.68a
Cl (mmol/L)	102.45 ± 8.37b	120.28 ± 7.29a	118.25 ± 12.56ab	114.81 ± 13.43ab
Osmolality (mOsmol/L)	103.27 ± 10.23a	107.34 ± 10.41a	110.42 ± 10.95a	104.24 ± 11.51a

¹Samples are defined in the experimental design section (“[Materials and methods](#)” section)

²Mean values ± SD followed by different letters within the same row indicate significant differences at $p < 0.05$ based on Dunnett’s multiple-range test ($n = 8$)

use and storage. K concentration also influences the pH balance in the body based on its capacity to react to and exchange with H^+ . An acidic condition favors for intracellular movement of H^+ , causing K^+ to move out of the cells in order to keep electrical neutrality of the cells (Crawford and Harris, 2011). Increased blood osmolality is an indicator of water deficit. When antidiuretic hormone secretion is inhibited, kidneys produce a higher amount of water to keep normal osmolality. The water is ejected through kidneys to reduce the extracellular fluid volume (Morton and Fontaine, 2013). Results of the present study showed that the wild simulated ginseng extract did not

cause any significant effect in serum electrolyte concentration and osmolality.

Heart weight, heart rate, and cross-section aorta

Application of the wild simulated ginseng extract did not cause substantial variation in the heart weight, heart rate, and cross-section of the aorta (Table 5). It was also observed that the heart weight, heart rate, and cross-section of the aorta were within the normal ranges despite the administration of different amounts of wild simulated ginseng extracts.

Table 5 Changes in heart weight, heart rate, and cross-section aorta of normal and hypertensive rats with or without Korean wild simulated ginseng treatment for 8 weeks

	Sample ¹			
	WKR-control	SHR-control	SHR-G100	SHR-G200
Heart weight (mg)	104.24 ± 9.35a	119.54 ± 13.46a	117.17 ± 12.43a	112.57 ± 12.81a
Heart rate (beat/min)	327.41 ± 36.89a	342.73 ± 46.71a	355.36 ± 35.82a	341.28 ± 39.83a
Cross-section of aorta (mm)	0.58 ± 0.04b	0.73 ± 0.06a	0.71 ± 0.06a	0.70 ± 0.07a

¹Samples are defined in the experimental design section (“Materials and methods” section)

²Mean values ± SD followed by different letters within the same row indicate significant differences at $p < 0.05$ based on Dunnett’s multiple-range test ($n = 8$)

The results of heart weight found in the present study were similar to a previous study of Korean red ginseng oil in rats (Seo et al., 2017). Heart rates also showed similar results with that of a previous report (Lee et al., 2016).

Enzyme activity

The AST, ALT, and ALP activities; liver-specific enzymes detected in plasma were measured in the rats of all four groups at the end of 8 weeks; were not markedly different (Table 6). The AST and ALT values of SHR-G100 (86.92 and 47.16 unit/mL) were higher than those of SHR-G200 (84.18 and 38.73 unit/mL).

The activities of AST, ALT, and ALP enzymes are good indicators of knowing the toxic effects of any external substances administered. There were no remarkable variations in the AST, ALT, or ALP levels of the ginseng treated rats, indicating that the ginseng did not alter the liver functions of SHR (Seo et al., 2017). Moreover, concentrations of these enzymes are the indicators of

abnormality in organs, cellular damage, cell leakage, and loss of cell membrane integrity in different organs, including liver, kidney, and heart (Kim et al., 2011; Ramesh et al., 2012; Yokozawa et al., 2007).

Serum biochemical analysis

There were no significant changes in glucose, BUN, uric acid, cholesterol, T-protein, albumin, and A/G ratio; however, the concentration of creatinine was significantly reduced in SHR-G200 (0.48 mg/dL) compared with the SHR-control (0.59 mg/dL) (Table 6).

The concentrations of creatinine and BUN are the good indicators of kidney damage related to the dysfunctions of glomerular filtration and renal tubule. There was no significant difference in the creatinine and BUN levels between the WKR-control and the wild simulated ginseng-treated SHR, which suggested that the wild simulated ginseng did not have a toxic effect on renal functions (Seo et al., 2017). The insignificant variation in albumin levels

Table 6 Enzyme activity and serum biochemical analysis of normal and hypertensive rats with or without Korean wild simulated ginseng treatment for 8 weeks

	Sample ¹			
	WKR-control	SHR-control	SHR-G100	SHR-G200
AST (unit/mL)	79.27 ± 10.56a ²	83.65 ± 12.13a	86.92 ± 14.73a	84.18 ± 13.52a
ALT (unit/mL)	34.53 ± 5.82a	37.52 ± 6.35a	47.16 ± 7.85a	38.73 ± 6.51a
ALP (unit/mL)	112.45 ± 9.64a	117.16 ± 10.11a	113.54 ± 12.71a	115.24 ± 13.48a
Glucose (mg/dL)	145.24 ± 11.37a	151.28 ± 12.37a	147.26 ± 15.98a	153.52 ± 16.56a
Creatinine (mg/dL)	0.53 ± 0.05ab	0.59 ± 0.05a	0.51 ± 0.06ab	0.48 ± 0.06b
BUN (mg/dL)	16.47 ± 1.25a	18.34 ± 1.26a	16.25 ± 1.41a	15.28 ± 2.14a
Uric acid (mg/dL)	1.07 ± 0.07a	0.99 ± 0.07a	0.96 ± 0.12a	0.93 ± 0.15a
Cholesterol (mg/dL)	75.31 ± 6.84a	78.25 ± 7.29a	77.20 ± 6.37a	79.61 ± 8.54a
T-protein (g/dL)	6.48 ± 0.43a	6.50 ± 0.49a	6.63 ± 0.38a	6.55 ± 0.41a
Albumin (g/dL)	3.56 ± 0.21a	3.47 ± 0.22a	3.55 ± 0.21a	3.58 ± 0.19a
A/G ratio	1.63 ± 0.12a	1.58 ± 0.13a	1.61 ± 0.11a	1.65 ± 0.12a

AST aminotransaminase, ALT alanine aminotransaminase, ALP alkaline phosphatase, BUN blood urea nitrogen, T-protein total proteins, A/G ratio albumin/globulin ratio

¹Samples are defined in the experimental design section (“Materials and methods” section)

²Mean values ± SD followed by different letters within the same column indicate significant differences at $p < 0.05$ based on Dunnett’s multiple-range test ($n = 8$)

between the control and the wild simulated ginseng-treated groups indicated that the wild simulated ginseng extract was not toxic to the rats (Lee et al., 2012). The results of the levels of glucose and cholesterol found in the present study were different from that of a previous study (Vuksan et al., 2000), which reported that ginseng treatment considerably reduced the blood glucose and cholesterol levels. The discrepancy in levels of glucose and cholesterol might be due to species variation of ginseng as the previous study was conducted with *P. quinquefolius* L.

In conclusion, the effect of two different concentrations (100 and 200 mg of the wild simulated ginseng extract/kg of body weight) of Korean wild simulated ginseng was investigated in spontaneously hypertensive rats. The systolic blood pressure of the wild simulated ginseng-treated rats was significantly reduced at 4 and 6 weeks compared to the SHR-control. However, applications of the wild simulated ginseng did not adversely affect food consumption, serum electrolytes and osmolarity, heart weight, heart rate, a cross-section of the aorta, and enzyme activities. The results of this study indicated that Korean wild simulated ginseng could be useful in controlling high systolic blood pressure in spontaneously hypertensive rats without causing adverse health effects.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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