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Physiological Changes with Age by the Chronic Administration of Korean Red Ginseng in Spraque-Dawley Rats

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ABSTRACT : The present study was designed to elucidate the physiological changes with age by chronic administration of red ginseng. All rats were reared in the conventional system. Ginseng treated rats were continously supplied with ginseng water extracts together water from 6 weeks of age to the age 24 months. Rats did not show any discernible signs or the rejection symptoms by red ginseng water extracts. A long-term administration of red ginseng extracts did not cause any physiological changes in the gain of body and organs weight, food intake and general properties of urine. However, red ginseng caused to decrease the level of serum cholesterol, glucose and TBARS, and it attenuated effectively the age-dependent decline of LDH activity. Other biochemical parameters measured from blood and general properties of urine were not significantly changed. These results suggest that long-term administration of red ginseng to rat does not cause any clear physiological changes in appearance and urine, and it retards age-related deteriorations in some biochemical parameters such as LDL-cholesterol, glucose and LDH in serum.

Key words : red ginseng, physiological changes age, chronic administration, urine, blood

INTRODUCTION

The aging of the population is a world-wide problem. This problem is particularly evident in industrialized countries, but within a decade it will be a major problem in Korea. Aging is characterized to be the progressive functional deficit of a organism with time. This deterioration involves a loss in abilities of the self-regulating mechanism responsible for the maintenance of homeostasis, a decrease in adaptation, an increased susceptibility to disease and toxic effect of xenobiotics, and the increased probability of death (Ryff & Singer, 2005; Kenyon, 2005). This phenomenon is common to all living things since the aging process and death are universal. The last several decadesresearch in aging have provided abundant evidence that such deterioration resulted in a high incidence of chronic diseases including arteriosclerosis, cancer, diabetes, and neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease (Cameron & Demerath, 2003; Maier & Chan, 2002)

Natural medicines have been utilized for the natural healing of disease, and many of them have been enhanced the spirit by their indirect action without any side effects. Korean red ginseng, one of the best-known herbal medicines, has been used since AD 190. Two thousands of researches for red ginseng have been reported, various pharmacological efficacies such as anti-tumors (Shin *et al*, 2004), anti-hypercholesteremia (Kang *et al*, 1995), anti-fatigue (Reay *et al*, 2005), enhancement of immune function (Han *et al*, 2005), and detoxification effects (Lee *et al*, 2002) have been observed in animal and humans. These results suggest strongly that ginseng benefits to most degenerative diseases being issued recently. If such efficacies are true, we can easily expect that ginseng may modulate the aging process of organism and process life prolonging effect too. In treatment methods, natural medicines have utilized commonly with not solvent extracts but water extracts, the decoction being made from the traditional method might contain quietly different components, compared with solvent extracts.

On the basis of such research accomplishment and our traditional knowledge, we attempted this study to manifest the effect of long-term administration of the water extract of Korean red ginseng on some physiological parameters related to aging in rats.

MATERIALS AND METHODS

Preparation of ginseng extract

The Korean red ginseng which was good grade ("Yang-

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Sam", 30Ji), manufactured by KT&G central institute, was sliced up a 2 cm thickness and was extracted with hot water at twice for 2 hrs. Temperature of water was maintained at 70 ℃ to prevent saponins and other phenolic compounds from being destroyed by heat (Han, 1968), The extract was concentrated to a gel state whose solid content was about 50% under atmospheric pressure. The preparation contains commonly 26 kinds of saponins including panax-diols and triols.

Animals and treatment

Male Sprague-Dawley (SD) rats were used as an experimental animal. Animals were housed individually in a polycarbonate cages with 12 hrs light/dark cycle at 22±1 ℃. Thirty two rats each had free access to water extract of ginseng (25 ㎎/㎏ body weight per day) in drinking water from 6 weeks of age and the same number of rats were given only drinking water for normal group. Water was replaced everyday and ginseng supplement was continued until they were sacrificed for biochemical assay. Biochemical assays were carried out at 3, 6, 12 and 24 months of age. Diet from commercial source was used. All rats fed *ad libitum*. Food intake and the consumption of drinking water were regularly checked every morning.

Body and organ weights

The body weight, and organs weight such as brain, heart, lungs, spleen, kidneys, testis etc. were measured at 3, 6, 12, 24 months of age, respectively.

Urinolysis

General properties of urine such as pH, specific gravity, protein, glucose, occult blood, ketone body, etc, were measured by using Clinitek 10 (Ames Miles)

Blood Biochemistry

Hematocrit value was determined by a capillary tube method. Blood was collected by cardiac puncture and serum was separated by centrifugation. Serum was divided into a small vials and stored at −70 ℃ until analysis. Levels of serum constituents such as glucose, cholesterol, HDL-cholesterol, triglyceride etc. and nonfunctional enzymes such as lactate dehydrogenase (LDH), glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT), and alkaline phosphatase were measured by using a kit reagents (A-san

Table 1. Age-related changes in body and organ weights of normal (N) and ginseng (G) administered rats.

Organs		Age(month)			
		3	6	12	24
Body weigts	N	296 ± 22	476 ± 43	594 ± 50	460 ± 86*
	G	289 ± 17	492 ± 43	636 ± 47	513 ± 62*
Brain	N	1.9 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	2.2 ± 0.1
	G	2.0 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	2.3 ± 0.1
Heart	N	1.0 ± 0.1	1.4 ± 0.2	1.6 ± 0.2	1.8 ± 0.6
	G	1.1 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.7 ± 0.1
Lung	N	1.6 ± 0.1	2.1 ± 0.2	2.4 ± 0.3	-
	G	1.6 ± 0.2	2.0 ± 0.4	2.2 ± 0.3	-
Liver	N	9.8 ± 1.1	15.9 ± 0.8	17.3 ± 2.2	12.0 ± 1.6*
	G	10.4 ± 1.7	15.3 ± 1.7	17.5 ± 2.2	14.1 ± 1.8
Spleen	N	0.6 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
	G	0.8 ± 0.2	0.7 ± 0.1	0.9 ± 0.2	0.9 ± 0.2
Hypophysis	N	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.002
	G	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.002
Adrenal glands	N	0.05 ± 0.01	0.05 ± 0.001	0.05 ± 0.01	0.06 ± 0.02
	G	0.06 ± 0.01	0.06 ± 0.01	0.04 ± 0.02	0.7 ± 0.01
Kidney (Left)	N	1.3 ± 0.2	1.5 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
	G	1.4 ± 0.1	1.6 ± 0.1	1.8 ± 0.2	2.0 ± 0.1
Kidney (Right)	N	1.4 ± 0.2	1.5 ± 0.2	1.8 ± 0.2	2.2 ± 0.1
	G	1.4 ± 0.2	1.7 ± 0.1	1.8 ± 0.2	2.2 ± 0.1
Testis (Left)	N	1.7 ± 0.1	1.8 ± 0.1	2.0 ± 0.1	1.8 ± 0.2
	G	1.8 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	1.8 ± 0.2
Testis (Right)	N	1.7 ± 0.1	1.7 ± 0.1	2.0 ± 0.1	1.8 ± 0.3
	G	1.7 ± 0.2	1.9 ± 0.1	2.0 ± 0.2	1.9 ± 0.2

Units : g
Male S.D. rats received drinking water with or without ginseng extracts (25 ㎎/㎏ body weight). Pneumonia was observed in lungs at the age of 24 months. Values are expressed as mean ± SD from 8 male SD rats.
* Significant different from 12 months old rats ($p < 0.05$).

Table 2. Age-related changes of urine properties in normal and ginseng administered rats

	3months		24months	
	Normal	Ginseng	Normal	Ginseng
pH	7.3 ± 0.6	7.6 ± 0.3	7.4 ± 0.5	7.5 ± 0.4
specific gravity	1.027 ± 0.003	1.024 ± 0.003	1.030 ± 0.007	1.027 ± 0.005

Male S.D. rats received drinking water with or without ginseng extracts (25 mg/kg body weight). Values are expressed as mean ± SD from 8 male SD rats.

Table 3. Age-related changes in serum constituents content in normal(N) and ginseng(G) administered rats.

Constituents		Age(month)			
		3	6	12	24
HDL-cholesterol (a)	N	11 ± 4	13 ± 3	13 ± 3	19 ± 3*
	G	14 ± 2	15 ± 1	13 ± 2	30 ± 7*#
Triglyceride (a)	N	77 ± 18	83 ± 13	99 ± 17	49 ± 7*
	G	79 ± 15	99 ± 12	116 ± 13	59 ± 6*
Albumin (b)	N	3.3 ± 0.2	3.1 ± 0.6	3.3 ± 0.5	3.1 ± 0.2
	G	3.4 ± 0.1	3.5 ± 0.2	3.3 ± 0.3	3.0 ± 0.3
Uric acid (b)	N	0.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	2.4 ± 1.4
	G	0.9 ± 0.2	2.3 ± 1.0	1.5 ± 0.5	2.1 ± 0.8
Creatine (b)	N	0.50 ± 0.06	0.62 ± 0.03	0.68 ± 0.04	0.43 ± 0.04*
	G	0.48 ± 0.03	0.63 ± 0.03	0.52 ± 0.05	0.54 ± 0.02
BUN (a)	N	23 ± 3	20 ± 2	18 ± 1	20 ± 3
	G	18 ± 2	21 ± 2	22 ± 3	17 ± 1

(a) : mg/dl (b): g/dl
BUN : Blood urea nitrogen
Male S.D. rats received drinking water with or without ginseng extracts(25 mg/kg body weight). Values are expressed as mean±SD from 8 male S.D. rats.
* Significant different from 12 months old rats($p<0.01$).
# Significant different from normal 24 months old rats ($p<0.05$).

Pharmaceutical Co. Ltd.) The content of serum TBA reactive substance (TBARS) was also determined (Yu *et al*, 1990).

Statistical analysis

Data are expressed as mean standard deviation (SD). Data differences in the normal (N) and ginseng-administered rats (G) were determined using analysis of variance(Statview version 4.0 ;.Abacus Concepts, Inc., Berkeley, CA). If the differences between two groups were statistically significant ($p < 0.05$). Fisher's protected least significant difference test or Scheffe's F test was used to distinguish between pairs of groups.

RESULTS

Body and organ weights

Adult rats in both groups consumed about 25 g of a chow a day and they did not show a rejection symptom by palatability of the ginseng solution. Table 1 shows the change in body weight of rats with age. There was no significant difference in body weight gain between two groups. However, ginseng-treated rats were slightly higher than normal ones at the age of maturity. Body weight of rats was slightly decreased at the age of 24 months in both groups. The weight of all organs was not also changed between two groups. However, weight of liver, kidney and testis showed a slightly high trend in old rats administered with ginseng extracts. We could not measure the correct lung weight in both two groups because pneumonia was observed in lungs at the age of 24 months.

Urinalysis

Several biochemical properties of urine were measured periodically. As shown in Table 2, pH of urine at 3 month-old in normal rats and ginseng-treated rats were 7.3±0.6 and 7.6±0.3, respectively, and it was not changed with age in both group. Specific gravity was not also changed, and other parameters such as occult blood, ketone bodies, white blood cells and protein were not detected in both groups.

Serum constituents

Hematocrit value was 44.0±0.7% in normal 3 month-old rats and it was 46.2±3.3% in 24 month-old ones. Table 3 shows the change of serum constituents in rats with age by ginseng treatment. In normal rats, the levels of serum albumin, total bilirubin, blood urea nitrogen and HDL-cholesterol

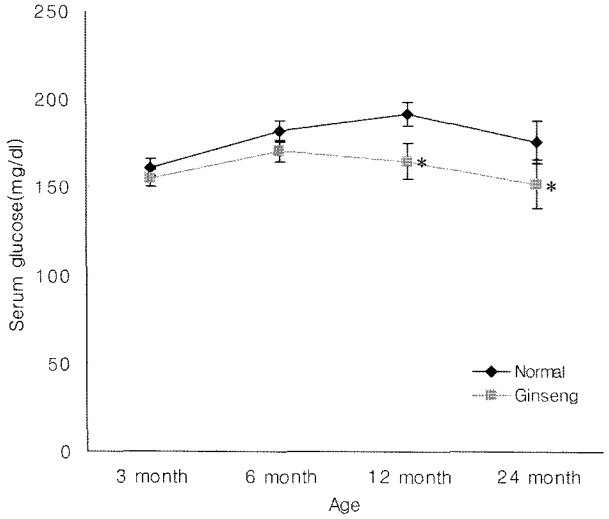

Fig. 1. Age-related changes in the serum glucose of normal and ginseng administered rats.
Male S.D. rats received drinking water with or without ginseng extracts(25 ㎎/㎏ body weight). Values are expressed as mean±SD from 8 male SD rats.
* Significant different from from normal rats at the same age ($p < 0.05$).

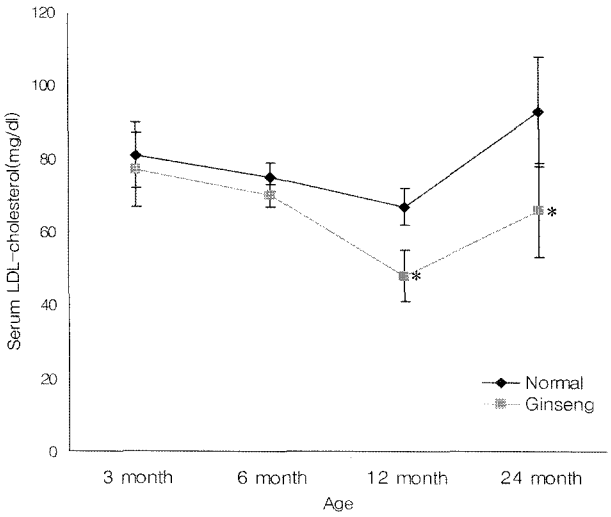

Fig. 2. Age-related changes in the level of serum LDL-cholesterol of normal and ginseng administered rats.
Male S.D. rats received drinking water with or without ginseng extracts(25 ㎎/㎏ body weight). Values are expressed as mean±SD from 8 male SD rats
* Significantly different from normal rats at the same age ($p < 0.05$).

were not significantly changed with age virtually, but the content of glucose was gradually increased until 12 month-old, thereafter, it remained consistently (Fig.1). Creatine and triglyceride contents were slightly increased, especially, in

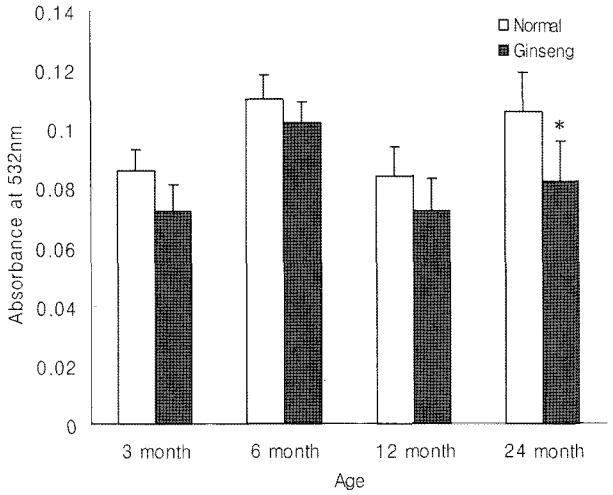

Fig. 3. Age-related changes in the content of serum TBA reactive substances of normal and ginseng administered rats.
Male S.D. rats received drinking water with or without ginseng extracts (25 ㎎/㎏ body weight). Values are expressed as mean±SD from 8 male SD rats
* Significantly different from 24 month old normal rats ($p < 0.05$).

adult rats. In the rats supplemented with ginseng extract, interestingly, glucose level was constantly lower than normal ones, and maintained as young rats as shown in Fig. 1. LDL-cholesterol content in 12 and 24 month-old rats fed ginseng remarkably was decreased compared with normal rats as shown in Fig. 2 ($p < 0.05$). But, other constituents in serum measured did not a significant difference at the same age between two groups (Table 3). Interestingly, serum TBA reactive substance content in 24 month-old was lower tendency in ginseng supplemented rats than in normal ones ($p < 0.05$) (Fig. 3).

Serum enzymes

The change of nonfunctional enzymes activities in serum has been utilized as an index of cellular damage since the increased activity reflects the leakage of intracellular enzymes. Table 4 shows the change in activities of serum enzymes in the rats with age. GPT and GOT were slightly increased only in 24 month-old in both groups, but GPT activity was consistently lower in ginseng supplemented rats than normal ones. Alkaline phosphatase, amylase, and urease activities were also not changed with age in both groups. The activity of LDH in normal rats was remarkably decreased from 1,162 units in 3 month-old to 524 units in 24 month-old. The decrease of LDH activity in old age was, however, effectively attenuated by ginseng supplementation as shown in Fig. 4 ($p < 0.05$).

Table 4. Age-related changes in serum enzymes activities of normal(N) and ginseng (G) administered rats.

Enzymes		Age(months)			
		3	6	12	24
Alakline posphatase (a)	N	32 ± 5	24 ± 3	23 ± 7	27 ± 6
	G	30 ± 3	28 ± 2	20 ± 2	29 ± 6
GOT (a)	N	55 ± 9	47 ± 4	45 ± 7	66 ± 13*
	G	54 ± 5	55 ± 6	54 ± 10	60 ± 15
GPT (a)	N	17 ± 4	37 ± 5	28 ± 5	43 ± 4*
	G	18 ± 2	33 ± 11	22 ± 4	36 ± 4*#
Amylase a	N	761 ± 5	760 ± 6	760 ± 6	680 ± 22*
	G	760 ± 5	750 ± 3	756 ± 6	734 ± 39#

(a) : units/l
GOT : Glutamate-oxaloacetate transminase, GPT : Glutamate-pyruvate transminase
Male S.D. rats received drinking water with or without ginseng extracts (25 mg/kg body weight). Values are expressed as mean±SD from 8 male SD rats.
* Significant different from 12 months old rats ($p<0.01$).
# Significant different from 24 months old normal rats ($p<0.05$)

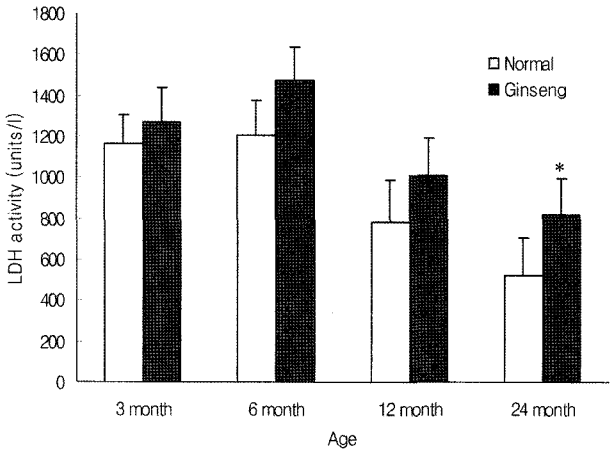

Fig. 4. Age-related changes in the serum LDH activity of normal and ginseng administered rats.
Male S.D. rtas received drinking water with or without ginseng extracts (25 mg/kg body weight). Values are expressed as mean±SD from 8 male SD rats
* Significantly different from 24 month old normal rats ($p < 0.05$).

DDISCUSSIONS

The present study demonstrated the effect of red ginseng on age-related changes in rats. We applied ginseng with traditional concept in the preparation of the extract and treatment method and obtained meaningful results predictable its efficacy. During the last decade, the benefits and safety of herbal and other natural products (dietary supplements) have led to growing concerns because a growing number of Americans are using herbal products for preventive and therapeutic purposes (Kelly *et al,* 2005; Marcus & Snodgrass, 2005; Kitts & Hu, 2000). Aphale *et al* (2005) reported that ginseng did not reveal any toxicity by doing subacute toxicity study in rats with 90 days oral administration. However, Coon & Emst (2002) explained that ginseng monopreparations are rarely associated with adverse effects and drug interactions. Combination products containing ginseng as one of several constituents have been associated with serious adverse events and even fatalities. Our results furnish on new meaningful information about the safety of ginseng. Namely, when traditional ginseng water extracts were administered to rats chronically for their life, they did not exhibit any discernible symptom compared to normal rats. There was no significant difference in body weight and organ weights from 3 months to 24 months between two groups. Biochemical properties of urine were not also significantly changed in young and old rats. The actual amounts of ginseng treated to the rats in this study correspond to 1.5 g of dry red ginseng powder per 60 kg body weight a day. These data indicates that ginseng water extracts is safe by long-term treatment.

On the contrary, age-related change of serum components such as cholesterol, glucose and LDH were effectively modulated by ginseng supplementation. Kang *et al* (2002) reported that ginseng has an effect to retard the decline of serum LDH activity by induced by the treatment of doxorubicin intraperitoneally. Some researchers have reported that some ginseng fractions stimulated insulin release, especially glucose-induced insulin release from pancreatic islets and thereby lowered the blood glucose level (Reay *et al*, 2005; Dey *et al*, 2003; Waki *et al*, 1982). Yokozawa & Oura (1990) have explained these results that ginsenoside-Rb2 of ginseng components might play a key role to reduce the level of blood glucose. But it is not clear yet whether the effect result from saponins such as Rb2. The effect of ginseng on cholesterol metabolism have

been reported by several investigators (Rho *et al*, 2005; Kim & Park, 2003). They used a largeamount of saponin to elucidate its effect on cholesterol metabolism, and found that saponin was decreased cholesterol and triglyceride level, but, it was increased HDL-cholesterol. In our study, the level of LDL-cholesterol and HDL-cholesterol showed a similar tendency to result of others (Rho *et al*, 2005; Kim & Park, 2003), but, triglyceride exhibited a reverse pattern. These data clearly indicate that ginseng take a reliable effect modulating the lipid metabolism.

Antioxidant effect of ginseng has been also extensively studied (Ryu *et al*, 2005; Yokozawa *et al*, 2004; Shao *et al*, 2004). Most investigators have focused on a direct action by some antioxidant components such as fat-soluble fractions including polyphenols. However, we demonstrated that long-term administration with the water extract of ginseng may enhance antioxidant capacity *in vivo*. This effect was more prominent in old rats. The low level of TBA reactive substances in ginseng treated rats provided clear evidence toward its antioxidant effect. Since TBA reactive substances in serum reflect the status of oxidative stress of whole body, it is used a sensitive marker of oxidative stress *in vivo*. In our study, it is difficult to expect whether a certain component has contributed to the reduction of free radical damage, because the major component of ginseng water extracts are mostly saponins and polysaccharides, and because the amount of antioxidant components of them is relatively rare. Therefore, an increase of antioxidant capacity by ginseng is considered to be due not to direct action by a certain single component, but to indirect action. Further research is needed to find out the mechanism.

On the basis of our results, it is concluded that ginseng water extracts is no any clear physiological changes by long-term treatment, and it retards age-related changes in some biochemical parameters such as cholesterol, glucose and LDH in serum.

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