INFLUENCE OF CHRONIC ADMINISTRATION OF KOREAN RED GINSENG ON SOME BIOCHEMICAL PARAMETERS RELATED TO AGING IN RAT

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To evaluate the effect of ginseng(*Panax ginseng* C.A. Meyer) on aging, we investigated the change in some biochemical parameters related to aging in rats administered with its water extract in drinking water(25 ㎎/㎏/day) continuously from 6 weeks of age to spontaneous death.

Rats did not show any discernible signs or the rejection symptoms by palatability of the solution. A long-term administration of ginseng extract did not cause any significant changes in gain of body and organs weight, food intake, and general properties of urine. However, ginseng caused to decrease the level of serum cholesterol, glucose, and TBARS and it attenuated effectively the age dependent decline of LDH activity. However, other biochemical parameters measured from blood were not significantly changed. The activities of antioxidant enzymes such as SOD, GPXase and catalase, and microsomal mixed function oxidase in the liver of ginseng administered rats were well maintained. In histopathological examination, ginseng treated rats also showed lesser degree of degenerative changes in spleen, pancreas, liver, and lung.

These results suggest that long-term period of administration of ginseng modulates lipid metabolism, enhances antioxidant capacity and retards the age-related deteriorations in several biochemical parameters. Such inclusive beneficial effects of ginseng seems to be resulted from normalizing effect by the harmony of various components rather than by a single component.

INTRODUCTION

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 (1, 2). This phenomenon is common to all living things since the aging process and death are universal. The last several decades' research 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 (3, 4).

Recently, with decline of the infectious diseases, such degenerative diseases which together account for the major cause of death have become a matter of foremost concern. Degenerative diseases have their main sites in one or a small number of tissue or organ, however, most are thought to be the result of the accumulation of cause extending over a long period and affecting the entire system. Therefore, for the remedy and prevention of the diseases, various treatment should be employed because these are different from others in pathogenesis causally. Many investigators have been exerting their effort to exterminate such diseases. However, despite of the impressive accomplishment of the modern pharmaceutical industry, a large number of these disease remain, for which treatment has limited benefit. In some case, although chemotherapy may temporarily suppress the condition of disease or remove individual symptom resulting from diseases, they never remedy the true nature of a disease nor will eliminate perfectly.

Natural medicines have been utilized for the natural healing of disease, and many of them have been known to enhance the spirit by their indirect action without any side effects. As such reasons, there is an increasing need for the development of natural medicines and health foods predictable pharmacological activity. A variety of such products have gained wide acceptance, especially, in oriental countries. Korean red ginseng, one of the best-known herbal medicines, has been used since AD 190. During the last century, two thousands of scientific research papers have been reported about its pharmacological efficacy and remarkable evidences on its efficacy have been accumulated. However, the question still remains, "what is the real efficacy of the ginseng?" In order to answer the question, the follows should be considered with our traditional wisdom in regard to use of natural products including ginseng.

Is ginseng a preventive medicine or a remedial one? This is very important question to understand its real efficacy and to use it accurately. According to an ancient literature, *Shin Nong Bon Cho Kyung*, ginseng belongs to the first-class of natural medicine which is defined as a drug taking the effect to enhance vitality and to extend the life span without toxicity. It has been considered as one of the most valuable herb and had been used in the Royal family. It is also interesting that ginseng is necessary for the prescription of most oriental medicines at present. These may indicate that ginseng has been used more preferably as a preventive medicine rather than as a curable one. If ginseng has a preventive effect against a certain disease, a proper taking time and a suitable dosage can be important factor for its best efficacy.

Nevertheless, recent scientists tend to prove only remedial effects. If ginseng is beneficial to the remedy of a disease, it

may have very potent pharmacological activity against pathogenesis or target organs and if so, it may have also effects on other tissues and biomolecules. However, investigators have little paid attention to other side behind their interesting biomarkers.

In treatment methods, natural medicines have utilized commonly with not solvent extract but water extract, therefore, the decoction being made from the traditional method might contain quietly different components from solvent extract. Therefore, the composition of components in the water extract may be a key for the efficacy. In the studies on components, many investigators have made every efforts to seek a certain active ingredient from ginseng. However, they did not provide an evidence that the real efficacy of ginseng was solely due to a certain single component.

In relation to this, we have to consider why ginseng is effective in some people but not in others and how the same products can be effective in several different disease with different pathogenesis. Most physicians of oriental medicine have insisted that natural medicines must be applied to each person differently according to their physical constitution since all peoples have a different physical constitution. In animal studies, however, it is impossible to consider this point.

All points of such issues imply that ginseng must be administered to organism with a traditional concept to manifest its real efficacy. Nevertheless, various pharmacological efficacies such as anti-tumors (5-7), anti-oxidants (8), anti-hypercholesteremia (9, 10), anti-fatigue (11), enhancement of immune function (12, 13), and alcohol detoxification (14, 15) were observed in animals and human. 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 possess life prolonging effect too.

On the basis of such research accomplishment and our traditional wisdom as reviewed above, we attempted this study to manifest the effect of long-term administration of the water extract of korean red ginseng on some biochemical parameters related to aging in rats.

MATERIALS AND METHODS

Preparation of ginseng extract

The korean red ginseng, which was good grade ("Yang-Sam", 30 Ji), manufactured by Korea Tobacco and Ginseng Corporation, 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 (16). The extract was concentrated to a gel state whose solid content was about 50% under atmospheric pressure. This preparation contains commonly 26 kinds of saponins including panaxa-diols and triols.

Animals and their treatment

Male Sprague-Dawley rats were used. Animals were housed individually in a polycarbonate cages with 12 hrs light/dark cycle at 22± 1℃. Sixty-eight rats each had free access to water extract of ginseng (25 mg/kg 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 through their life or until they were sacrificed for biochemical assay. Diet from commercial source was used. Twenty-eight animals of them, 7 animals for each group, were used for the analysis of biochemical markers which were assayed at 3, 6, 12, and 24 months of age. The rest of the animals in each group were utilized for longevity study. All rats fed *ad libitum*. Food intake and the consumption of drinking water was regularly checked every morning.

Body and organ weights

The body weight was measured every week. Weight of organs such as brain, heart, lungs, spleen, kidneys, testis etc. was measured at 3, 6, 12, and 24 month of age, respectively.

Urinalysis

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

Blood biochemistry

Hematocrit value and plasma total proteins were determined by a capillary tube method and reflectometry, respectively. 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 Pharmaceutical Co. Ltd.). The content of serum TBA reactive substances(TABRS) was also determined (17).

Antioxidant capacity

Antioxidant capacity and microsomal detoxification enzymes were assayed in the liver of both groups. The tissue was homogenized in 4 volumes of 30 mM HEPES buffer (pH 7.4) containing 150 mM KCl, and cytosol and microsomal fractions were prepared from homogenates by a differential centrifugation. In cytosol, superoxide dismutase (SOD) (18), catalase (19), glutathione peroxidase (20), glutathione-S-transferase (21), total thiols and free thiols levels (22) were determined.

Microsomal detoxicification enzymes activity

Microsomal cytochrome P-450 (P-450) and cytochrome b5(b5) contents were measured by the method of Omura and Sato (23). NADPH P-450 reductase (P-450 reductase) and NADH b5 reductase (b5 reductase) were assayed by methods of Williams and Kamin (24) and Mihara and Sato (25), respectively. P-450 dependent ethoxycoumarin-O-deethylase (ECDE) and benzphetamine-N-demethylase (BPDM) activities were measured by methods of Greenlee and Foland (26), and Thomas *et al.* (27), respectively.

Histopathological examination

Autopsy was performed immediately after spontaneous death of the animals. Weight of the internal organs was measured and histopathological examination was carried out. In brief, tissue samples were fixed in 10% neutral buffered fromalin for 24~48 hrs and treated as in routine method. Five μm-thick paraffin sections were stained with hematoxylin-eosin and examined with a light microscope. If necessary, trichrome of Gomori stains were performed for collagen.

Statistical analysis

The results are expressed as mean± SD of five to seven rats per group. The data were analyzed by Student's t-test using T-Test software.

RESULTS

Longevity

Fig. 1. shows survival curve of rats. Mean life span of normal rats was 651± 99 days and maximum life span was 957 days. In the case of ginseng administered rats, mean and maximum life span was 647± 105 days and 820 days, respectively. The life span of rats was not extended by long-term period of administration with ginseng under the condition.

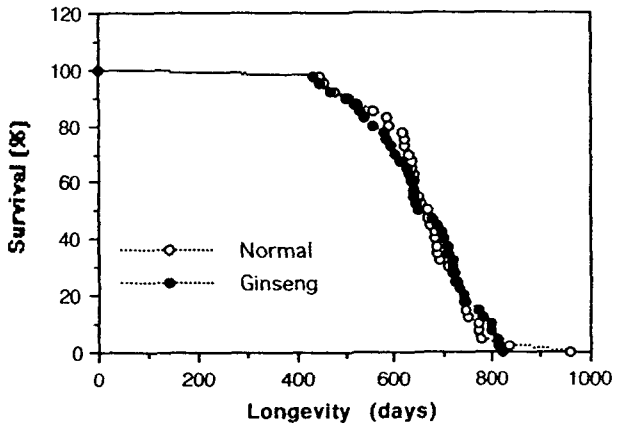


Fig. 1. Survival curve for rats

The changes in body weight and longevity

Adult rats in both groups consumed about 25 g of chow a day and they did not show a rejection symptom by palatability of the ginseng solution. Fig. 2. 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 in both groups slightly decreased before death.

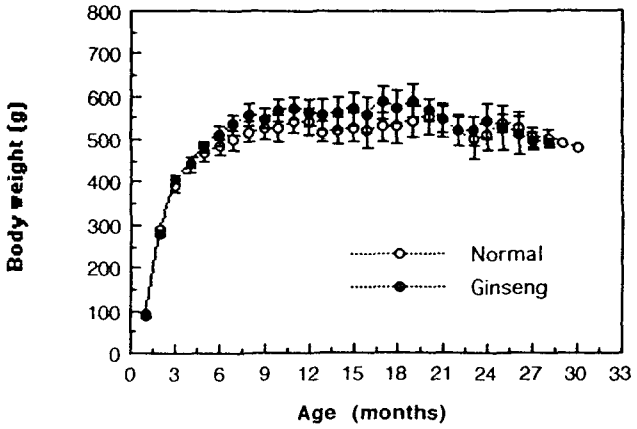


Fig. 2. Changes in body weight of rats

Urinalysis

Several biochemical properties of urine were measured periodically. As shown in Table 1, pH of urine from 3 month-old normal rats was 7.3± 0.6 and that of ginseng treated rats was 7.6± 0.3 and it in both groups was not changed with age. Specific gravity was not also changed, and other parameters such as occult blood, ketone bodies, white blood cells, glucose, and protein were not detected in both groups.

Table 1. The influences of ginseng administration on properties of urine from aging rats

	Normal rats (3months)	Age related change	
		Normal	Ginseng
pH	7.3± 0.6	NC	NC
Specific gravity	1.027± 0.003	NC	NC
Occult blood	≤ ±	NC	NC
Protein	≤ ±	NC	NC
Ketone bodies	≤ ±	NC	NC
Bilirubin	≤ ±	NC	NC
Glucose	ND	NC	NC
Urobilinogen	≤ ±	NC	NC
White blood cells	≤ ±	NC	NC

ND : Not detected
NC : Not changed

Organs weight

The data in Table 2. shows weight of each organ. There was no significant difference between two groups in the weight of all organs. However, weight of liver, kidney and testis were slightly high in old rats administered with ginseng extract.

Serum constituents

Hematocrit value was 44.0± 0.7% in 3 month - old normal rats and it was 46.2± 3.3% in 24 month - old ones. The content of serum total protein was also slightly increased with age, but there was no significant difference between two groups. In nor-

Table 2. The influence of aging and chronic administration of ginseng extract on organ weights in rats

		Age(months)			
		3	6	12	24
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± 0.2
	G	0.8± 0.2	0.7± 0.1	0.9± 0.2	0.9± 0.2
Hypophysis	N	0.01± 0.00	0.01± 0.00	0.01± 0.00	0.02± 0.00
	G	0.01± 0.00	0.01± 0.00	0.01± 0.00	0.01± 0.00
Adrenal glands	N	0.05± 0.01	0.05± 0.00	0.05± 0.01	0.06± 0.02
	G	0.06± 0.01	0.06± 0.01	0.04± 0.02	0.07± 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	2.1± 0.1
Kidney(Right)	N	1.4± 0.2	1.5± 0.2	1.8± 0.2	2.0± 0.2
	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
N : Normal rats
G : Ginseng administered rats

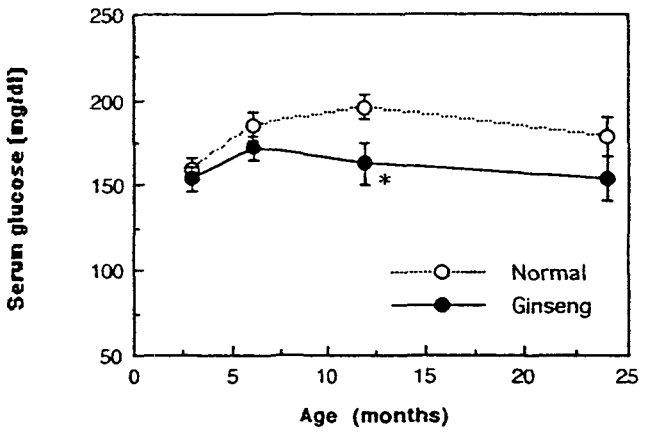


Fig. 3. The effect of age and chronic administration of ginseng extract on serum glucose in rats. * Significantly different from 12 month old normal rats ($p<0.05$).

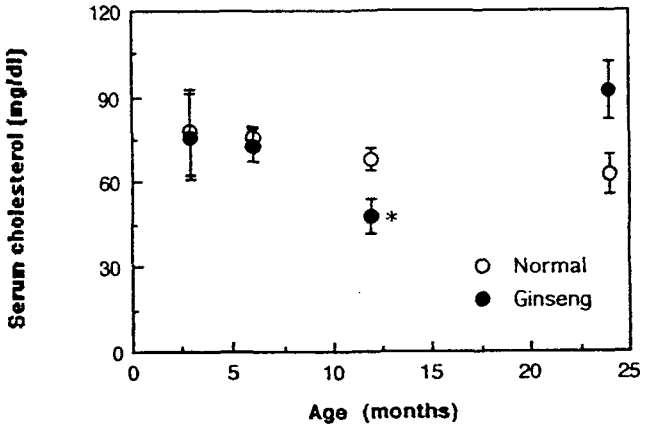


Fig. 4. Changes in the level of serum cholesterol of normal and ginseng administered rats. * Significantly different from 12 month old normal rats ($p<0.05$).

mal rats, the levels of serum albumin, total bilirubin, blood urea nitrogen, HDL - cholesterol, and TBA reactive substances were not significantly changed with age virtually, but the content of glucose was gradually increased until 12 months - old, thereafter, it remained consistently. Creatinine and triglyceride contents were slightly increased especially in 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. 3.($p<0.05$). Cholesterol content remarkably decreased by 25% of normal rats only in 12 month - old rats fed ginseng ($p<0.05$) (Fig. 4). Whereas, triglyceride rather increased by about 45% and other components measured were similar between two groups (Table 3). Interestingly, serum TBA reactive substances content was low in ginseng treated rats than in normal ones (Fig. 5).

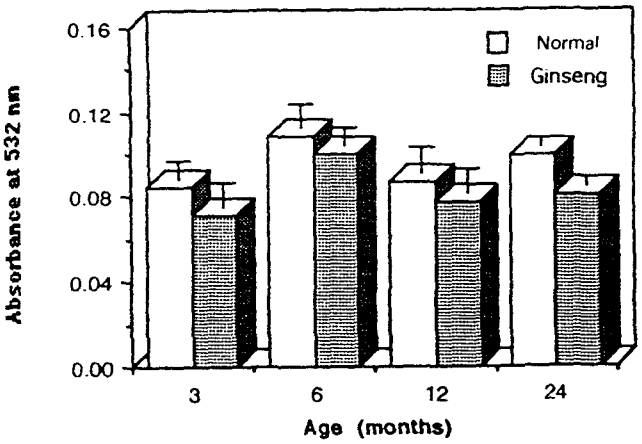


Fig. 5. Changes in the content of serum TBA reactive substances in normal and ginseng administered rats with age

Table 3. Influences of aging and chronic administration of ginseng on contents of serum constituents in rats

		Age(months)			
		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	79± 10	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
Creatinine[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

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. The data in Table 4. show the change in activities of such 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 treated 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 1162 units in 3 month - old to 560 units in 24 month - old. The decrease of LDH activity was, however, effectively attenuated by ginseng supplement as shown in Fig. 6.

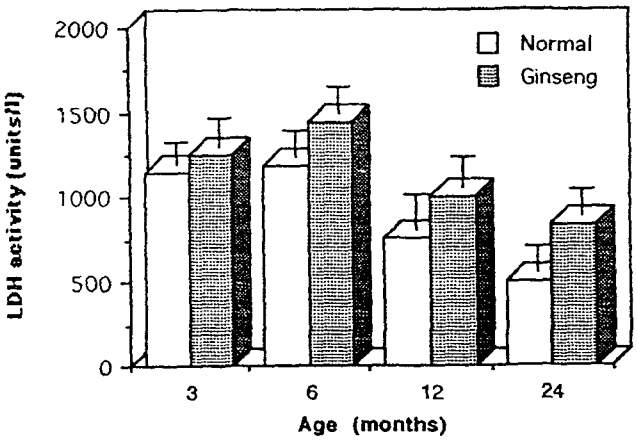


Fig. 6. Changes in LDH activity in serum of rats with age

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

		Age(months)			
		3	6	12	24
Alkaline phosphatase[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± 8
	G	18± 2	33± 11	22± 4	36± 4
Amylase[b]	N	761± 5	758± 14	760± 6	680± 22
	G	760± 5	750± 3	756± 6	734± 39

a : units/l
b : units/dl

Antioxidant capacity

Major antioxidant enzymes in the liver showed interesting results. The activities of SOD, catalase, and GPXase were decreased with age (Fig. 7). However, in the case of ginseng treated rats, these enzyme activities were well maintained during their life. Especially, catalase and GPXase activities were consistently higher than in normal rats. The levels of total - SH and glutathione reductase were not changed in both groups, but glutathione - S - transferase was gradually decreased with age (Table 5).

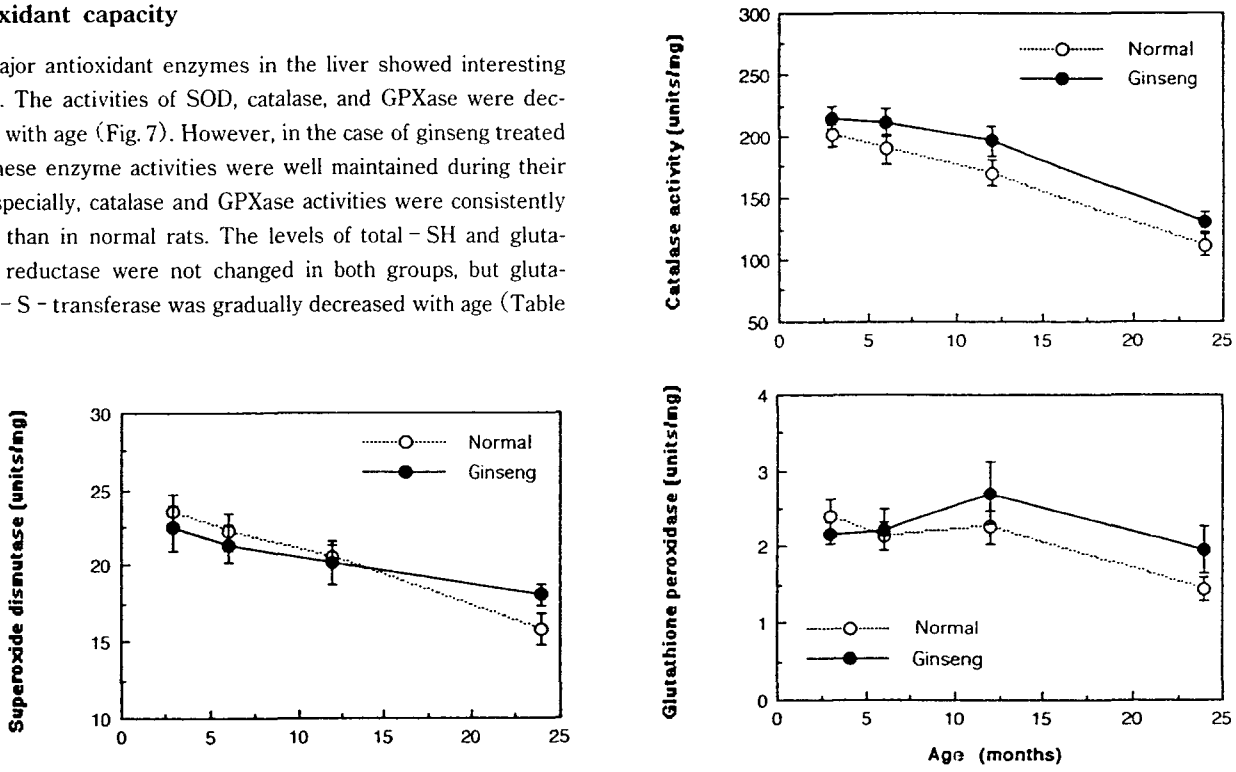


Fig. 7. The effect of age and chronic administration of ginseng extract on SOD, catalase and glutathione peroxidase in liver of rats

Table 5. Age - related change in the levels of total - SH, GSH reductase, and GSH - S - transferase in liver of normal and ginseng administered rats

		Age(months)			
		3	6	12	24
Total - SH[a]	N	15.0± 1.0	14.9± 1.6	15.2± 2.0	14.7± 0.9
	G	16.9± 1.2	16.1± 1.8	14.5± 2.4	15.0± 1.1
GSH reductase[b]	N	33.2± 4.2	26.1± 5.3	31.7± 6.8	25.1± 6.3
	G	32.7± 2.6	28.1± 4.2	24.4± 6.9	31.6± 4.1
GSH - S - transferase[c]	N	1.16± 0.02	1.01± 0.01	0.96± 0.07	0.44± 0.04
	G	1.15± 0.07	1.00± 0.11	1.06± 0.13	0.44± 0.05

a : μmoles/g of tissue
b : nmoles/mg of protein/min
c : μmoles/mg of protein/min

Detoxification enzymes

The levels of microsomal P-450, P-450 reductase, and b5 were progressively declined with age in normal rats, but the level of b5 reductase was not significantly changed as shown in Table 6. In ginseng-treated rats, P-450 content was remarkably increased in the liver of 3 month-old rats, however, it was returned to normal level at 6 months-old. Levels of P-450 reductase and b5 also showed a similar pattern as P-450. Interestingly, the activity of P-450 dependent BPDM was consistently higher in ginseng-treated rats than in normal ones.

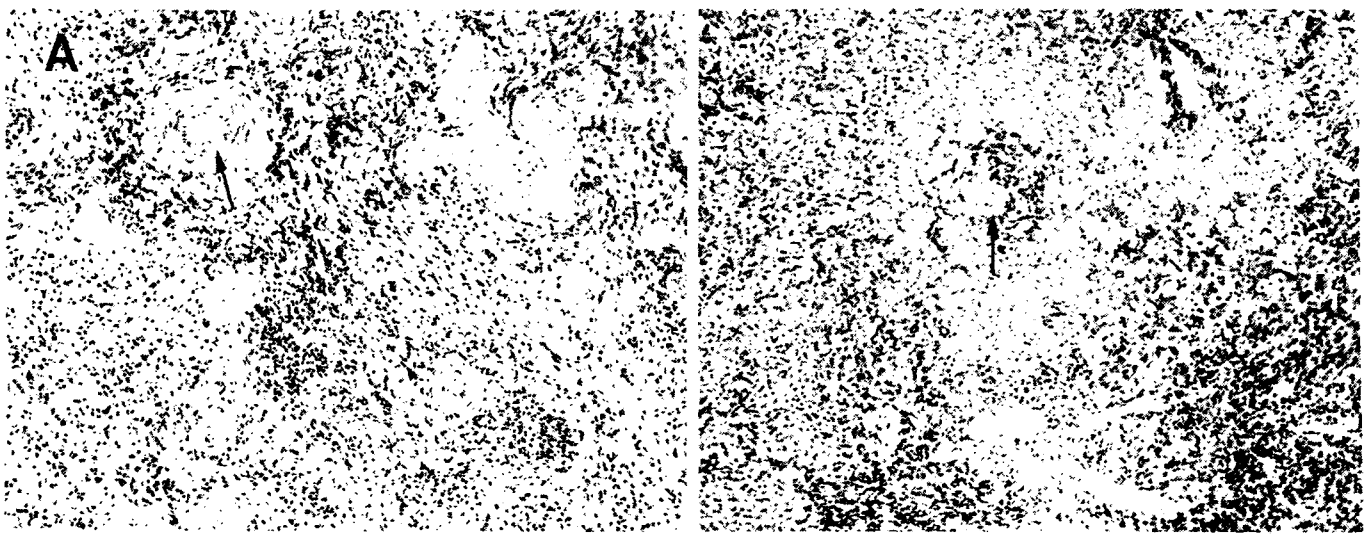
Table 6. Effects of aging and chronic administration of ginseng on liver microsomal cytochrome P-450 and its related enzymes in rats

		Age(months)			
		3	6	12	24
Cytochrome P-450[a]	N	0.98± 0.08	0.90± 0.07	0.70± 0.11	0.56± 0.12
	G	1.26± 0.05	0.88± 0.07	0.79± 0.11	0.59± 0.04
P-450 reductase[b]	N	106± 55	93± 19	65± 18	37± 10
	G	112± 10	97± 20	62± 17	34± 5
Cytochrome b_5[a]	N	0.60± 0.01	0.50± 0.06	0.41± 0.02	0.40± 0.6
	G	0.77± 0.02	0.45± 0.03	0.46± 0.04	0.40± 0.02
b_5 reductase[c]	N	1.70± 0.05	3.52± 0.35	2.60± 0.33	2.67± 0.22
	G	2.26± 0.05	3.45± 0.24	2.87± 0.13	2.75± 0.21
ECDE[d]	N	40.5± 4.7	32.1± 4.8	30.2± 4.5	24.8± 9.9
	G	46.4± 4.9	35.4± 6.7	33.1± 2.9	30.0± 13.6
BPDM[e]	N	8.4± 0.7	7.8± 1.1	7.1± 1.1	5.7± 1.0
	G	8.8± 0.6	7.6± 1.0	8.5± 1.0	6.4± 0.7

a : nmoles/mg of protein
b : nmoles/mg of protein/min
c : μmoles/mg of protein/min
d : Ethoxycoumarin-O-deethylase(Arbitrary units)
e : Benzphetamine-N-demethylase(nmoles/mg of protein/min)

Autopsy and histopathological findings

At autopsy, there were no specific or characteristic findings including neoplastic lesions in the internal organs except lungs of the both of normal and the ginseng treated animals. Both of the lung showed relatively widespread tumor-like lesions. Pulmonary lesions with pneumonia were found in 70% of normal rats, while 22% of the ginseng treated rats did. Also the extent and the severity of the pulmonary lesion were small and moderate respectively in ginseng treated rats. Especially, they showed lesser degree of degenerative change in the parenchymal cells of the internal organs including spleen, pancreas, and liver (Fig. 8).



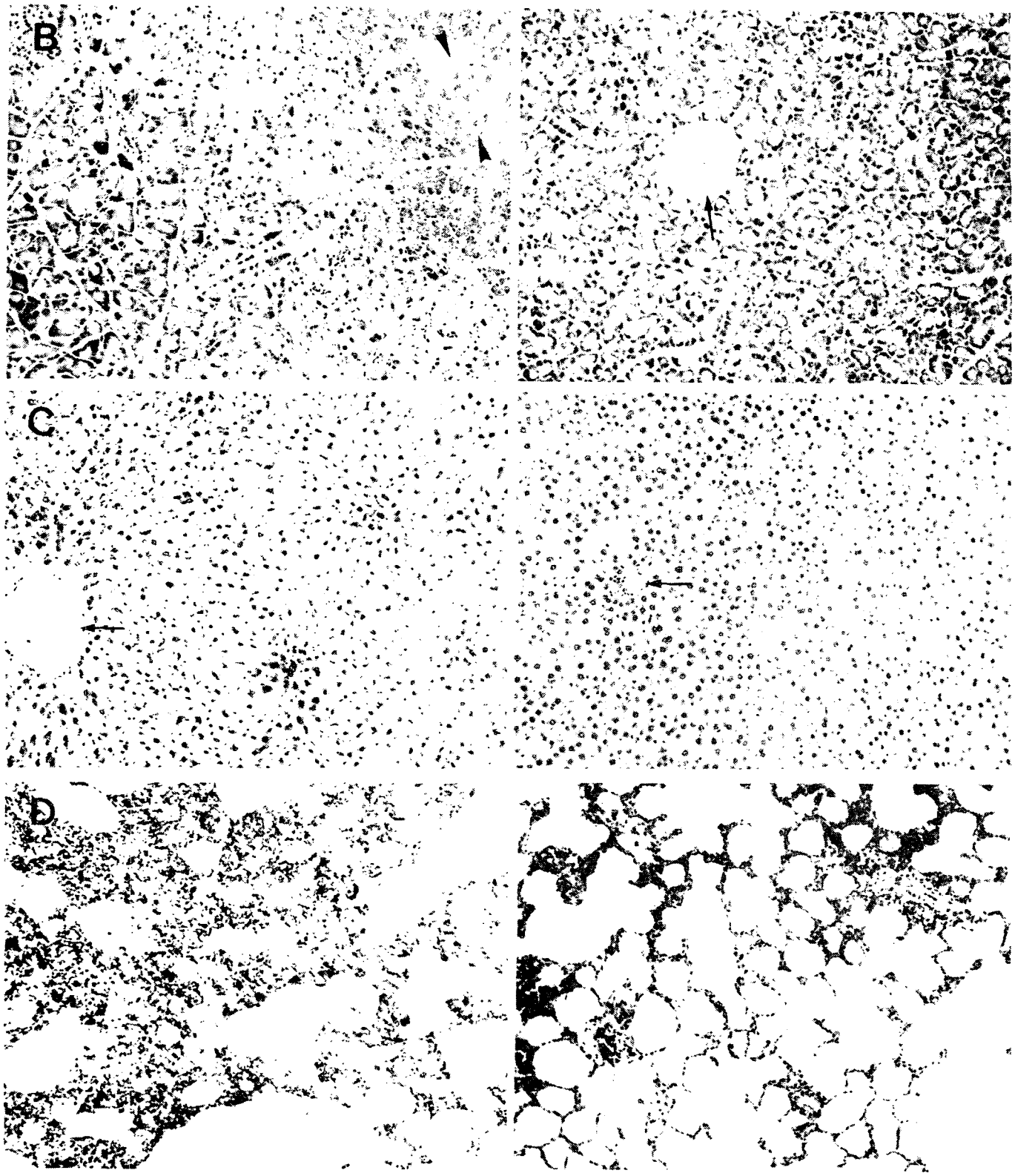


Fig. 8. Histopathological observation of the internal organs from dead rats. (A : Spleen of the ginseng treated (right) rat shows lesser of proliferation of fibrotic tissue around the splenic artery(arrows) than in the control (left). H - E, mag x117. B : Exocrine portion of pancreatic tissue of the control (left) shows degenerative changes (arrowheads) and septal widening. Pancreatic acinar cells also show ballooning. In contrast, exocrine portion of pancreatic tissue of the ginseng - treated(right) rat is relatively well preserved. Arrow indicates island of Langerhans. H - E, mag x117. C : Hepatic cells of the control are atrophic and degenerative (left). Those of the ginseng - treated rat(right) are relatively intact but show cellular infiltration in the sinusoids. Arrows indicate the central vein. H - E, mag x117. D : Airspaces are occupied by mixture of fluid, inflammatory cells, and blood cells in the lung parenchyme of the control(right). In contrast, airspaces are relatively well maintained with lesser severity of parenchymatous changes. H - E, mag x117.)

DISCUSSION

The present study demonstrated the effect of 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.

Once, it had been issued whether ginseng is a drug or a food. And people have been concerned with the safety of ginseng. Hong *et al.*(28) and others (29) reported that ginseng did not have genotoxic effect through the acute toxicity studies using animals and *Salmonella* mutagenesis test. We suggest here another important evidence on the safety of ginseng. Namely, rats were administred with ginseng chronically for their life, they did not exhibit any discernible symptom and change in gain of their body and organs weight compared to normal rats. Biochemical properties of urine and activities of serum enzymes were not also significantly changed except LDH. These data indicate that ginseng does not possess any toxicity and it is safe. The actual amounts of ginseng treated to the rat in this study correspond to 6 g of dry red ginseng powder per 60 kg body weight a day.

In general, the life span of rodents show large difference according to the strain and rearing conditions. Chronic administration of ginseng did not extend the life span of rats. The longevity of rats observed in this study was similar to the result of other investigators (30), but was somewhat short compared to that of Fisher 344 housed in SPF system (31). However, body weight of adult rats administered with ginseng was rather high. Ooura and Yokozawa (32) demonstrated that Wister rat fed with diet containing 0.1% and 1.0% of ginseng powder from 12 months old chronically caused to enhance body weight in the senescence period in female rats. These and our results indicate that body weight of rats increased from 7 months or thereabouts after administration of ginseng.

On the contrary, age - related change of serum components such as cholesterol, glucose and LDH were effectively modulated by ginseng supplement. Cho *et al.* (33) reported that ginseng has an effect to retard the age - related decline of LDH activity. The decrease of serum glucose is one of affirmative effects of ginseng. Yokozawa (34) reported that ginsenoside - Rb_2 reduced the level of blood glucose. But it is not clear yet whether the effect result from saponins such as Rb_2. The effect of ginseng on cholesterol metabolism have been reported by several investigators (9, 10). They used a large amount of saponin to elucidate its effect on cholesterol metabolism and found that saponins decrease cholesterol and triglyceride level but increase HDL - cholesterol. In our study, the level of cholesterol and HDL - cholesterol showed a similar tendency to result of others, but triglyceride exhibited a reverse pattern. These data clearly indicate that ginseng takes a reliable effect modulating the lipid metabolism.

Antioxidant activity of ginseng has been also extensively studied (8, 16, 35). Most investigations 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 enhances 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 as a sensitive marker of oxidative stress *in vivo*. In our study, it is difficult to expect that a certain component has contributed to the reduction of free radical damage, becasue the major components of water extract are mostly saponins and polysaccharides and the amount of anitoxidant components is rare. Therefore, such an increase of antioxidant capacity by ginseng is considered to be due not to direct action by a certatin single component but to indirect action. Another evidence was provided from antioxidant enzymes in liver. The activities of SOD, catalase and GPXase, which are responsible for scavenging oxygen free radicals, showed a similar age - trend in both groups, however, these activities were well maintained at the senescence stage of ginseng treated rats. This is the first report showing that the activities of antioxidant enzymes are well preserved in elderly rats when ginseng extract was administered chronically.

The change in these enzyme activities gave us a very important meaning in connection with *in vivo* free radical metabolism. If these enzymes were remarkably enhanced, it may indicate that ginseng caused to increase oxygen free radicals generation *in vivo*, furthermore, it implies its negative effects. Therefore our data suggest that ginseng does not stimulate the generation of oxygen free radicals *in vivo*. Although these enzyme acticvities were constantly higher in ginseng treated rats than in normal ones during their life, there was no significant difference between two groups. Especially, catalase and GPXase complement each other with respect to intercellular location. Namely, catalase scavenges more effectively at high concentration of hydrogen peroxide whereas GPXase scavenges at low (36). GPXase catalyze preferably large molecular hydroperoxides such as lipid hydroperoxides formed through the free radical attack on polyunsaturated fatty acids in membranes whereas catalase is suitable for scavenging low molecular hydroperoxides such as hydrogen peroxide (37). In ginseng treated rats, GPXase activity showed best preservation among three antioxidant enzymes. On the basis of these, the increase of GPXase activity might be more contributed to eliminate the toxic lipid hydroperoxides. This seems to be closely related to the decrease of TBA reactive substances.

Liver microsomal detoxification enzyme system is one of physiological functions declined with age (38 - 40). The effect of ginseng on this enzyme system was also demonstrated in acute intoxicated animals by several investigators (41, 42). To evaluate the effect of some components on the detoxification system, special attentions must be paid because not only the system recognized the component as a xenobiotic and catalyzes the biotransformation reaction but also it can be received damage by toxic metabolites (43). Most drugs and xenobiotics are metabolized to more polar compounds by microsomal mixed function

oxidase in liver and then excreted via urine. Microsomal P - 450, key enzyme of microsomal mixed function oxidase, was induced in liver of 3 month - old ginseng treated rats, and its level was returned to normal value thereafter as shown in Table 5. This suggest that the water extract contains some components inducing P - 450 isozyme. Lee *et al.* (41) also found that ginseng saponins induce P - 450, epoxide hydrolase and some conjugation enzymes, but do not induce arylhydrocarbon hydroxylase which is a specific monooxygenase for CYP IA1.

In this study, a low activity of ECDE which is another specific monooxygenase for CYP IA1 has also confirmed it. But the activity of BPDM specific for CYP IIB1 was consistently high in ginseng treated rats. These results indicate that ginseng contains some components inducing CYP IIB1 isozyme. Ginsenosides isolated from ginseng act as an inhibitor or activator toward microsomal P - 450 dependent monooxygenases, however, they exhibited diverse effects according to their kinds and P - 450 isozymes. Namely, binding of most ginsenosides with P - 450s showed type I spectral change, however, ginsenoside Rf exhibited type I spectral characteristic with PB - inducible P - 450 and type II with MC - inducible one (our unpublished data). These imply that the effect of ginseng on detoxification system reveal differently depend on the fractions used although saponins modulate mixed function oxidase activity. However, all of these were observed only when used at high concentration of saponins. Therefore, modulation of microsomal mixed function oxidase system observed in old rats in this study might be due to other mechanism such as stimulation of endocrine system by a certain components of ginseng.

Autopsy data also provided a valuable evidence for the evaluation of ginseng efficacy. Pulmonary lesions with pneumonia was found in large numbers in both groups, However, which is a common phenomenon appearing in rats reared in conventional barrier facilities (32). However, other neoplastic diseases were not found. Interestingly, ginseng treated rats showed lesser degree of mass formation with pneumonia, and degenerative change in spleen, pancreas and liver. These suggest that long - term period of administration of ginseng have a protective effect on degenerative or neoplastic lesions.

In present study, ginseng efficacy observed in rats could be summarized as follows : ginseng modulates especially lipid metabolism and enhances the detoxicification ability and antioxidant capacity *in vivo*. It also retards the age - related deteriorations of several biochemical parameters and inhibits the incidence of degenerative diseases.

What is the mechanism manifesting all of these positive effects ? The data indicate that ginseng has some preventive effect against degenerative changes of the organism rather than a curative effect. Such efficacy seems to be resulted from the normalizing effect by the harmony of various components rather than by a single component. Such effects reveal more obviously when it is supplemented chronically. From results of current studies including ours, it is likely that long term administration of ginseng may be beneficial to prevention against degenerative changes to a certain extent in aging, and it should be extended the life span if organism would take suitable amount of ginseng in a proper time in their life.

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