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Anti-Diabetic Effect of Red Ginseng-Chungkukjang with Green Laver or Sea Tangle

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Abstract

The hypoglycemic effects of red ginsgeng-chungkukjang plus seaweeds, green laver and sea tangle, in streptozotocin (STZ)-induced diabetic rats were investigated. Five groups of male Sprague-Dawley rats weighing 140±10 g (10 animals/group) were fed for four weeks with the following: nondiabetic control (NC group); STZ-induced diabetic (D group); diabetic rats fed 3% red ginseng (20%, w/w)-chungkukjang (D-RC group); diabetic rats fed RC containing 10% (w/w) green laver powder (D-RCG group); diabetic rats fed RC containing 10% (w/w) sea tangle powder (D-RCS group). Partially normalized body weight gain, FER, and blood glucose levels were observed in the D-RC, D-RCG and D-RCS groups as compared to the D group. In these three groups, serum levels of triglycerides, total cholesterol, and LDL-cholesterol were found to be lower than in the D group, whereas HDL-cholesterol levels increased. Serum insulin level in D was significantly lower than that of NC, although D-RC, D-RCG, and D-RCS almost recovered to the NC. Serum ALT activity was markedly increased in the D group, while the serum ALT levels in the D-RC, D-RCG, and D-RCS were almost the same as the NC group. Due to diabetes, hepatic xanthine oxidase (XO) activity was significantly increased and administration of red ginseng-chungkukjang or seaweeds resulted in decreased levels of the XO activity. Activity of hepatic antioxidant enzymes (superoxide dismutase and glutathione peroxidase) were significantly decreased in the D group, but the activity in the D-RC, D-RCG, and D-RCS groups were similar to that of the NC group. Results of the present study indicate that supplementation of red ginseng-chungkukjang with seaweed after the onset of diabetes ameliorated hyperglycemia via an increase in serum insulin.

Key words: diabetes, sea tangle, green laver, red ginseng, chungkukjang

INTRODUCTION

Diabetes is a chronic metabolic disease with serious complications, and its incidence in Korea has increased rapidly. In diabetic patients, the metabolism of carbohydrate, protein, and lipid due to the imbalance of hormones via excessive caloric intake, a lack of physical activity, and oxidative stress is abnormal and thus hyperglycemia and hyperlipidemia develop (1,2). In addition, hyperglycemia is an essential factor in the development and progression of diabetic complications such as neuropathy, nephropathy, cardiopathy and retinopathy (3-5). Generally, dietary management, exercise, and/or drug therapy are recommended in combination as treatment for diabetes. Unfortunately, therapeutic modes for the complete normalization of diabetes have not thus far been established. The primary objective of diabetes treatment is to maintain normal blood glucose levels, so the development of diabetic complications is prevent or alleviate (6,7).

Presently, the use of medicinal and dietary plants is increasing, largely because of the development of several successful healthy functional foods and chemotherapeutic drugs derived from natural products (8-10).

It is well known that red ginseng can improve diabetic hyperglycemia and hyperlipidemia (11-13). Additionally, chungkukjang may prevent or alleviate hyperglycemia, hyperlipidemia (14,15) etc. Recently, Shin et al. (16) reported that blood glucose levels in diabetic rats fed red-ginseng with chungkukjang powder were significantly lower than that of diabetic rats fed red ginseng or chungkukjang only.

Seaweed is widely used as food and as a seasoning in Korea. It is well documented that seaweeds such as green laver and sea tangle may regulate hyperglycemia (17-19), hyperlipidemia (18,19) and oxidative stress (20) etc. Furthermore, it is well accepted that dietary fibers of edible seaweeds may regulate hyperglycemia and hyperlipidemia due to inhibited absorption of glucose and

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lipid in the intestine (21-23).

However, no reports are available on the effect of red ginseng-chungkukjang with either green laver or sea tangle on diabetes. Therefore, this study was designed to evaluate the hypoglycemic effect of red ginseng-chungkukjang with either green laver or sea tangle powder for use as a healthy functional food. We observed improvements in the body weight gain, feed efficiency ratio, blood glucose, serum insulin, lipid profile, and ROS generating and scavenging enzyme activity in STZ-induced diabetic rats.

MATERIALS AND METHODS

Materials

Green laver, sea tangle, red ginseng powder (100 mesh) which was made from six year old dried ginseng, and soybeans (Glycine max Enha) used to prepare chungkukjang were all purchased from the Agricultural Cooperatives located in Wando, Kumsan, and Kyungsan, Korea.

Preparation of sea tangle and green laver

The seaweeds were soaked in distilled water (2 times the mass of the seaweed) for 4～5 hours to drain all the salt from the seaweed. The seaweeds were then sufficiently dried using a warm air dryer (GR-101, Hanyoung Co., Ltd., Seoul, Korea) at 40°C and was then put into a drying oven (Han Young Co., Ltd., Seoul, Korea) at 150°C for 5 minutes. They were then ground into a powder (50 mesh).

Preparation of red ginseng-chungkukjang (RC), RC with green laver (RCG) and sea tangle (RCS)

Red ginseng-chungkukjang powder (RC) was prepared by the method of Shin et al. (16). RCG or RCS was prepared by blending the RC powder with green laver or sea tangle powder. Contents of red ginseng, sea tangle, or green laver powders contained in RC, RCS, or RCG were adjusted to 20%, 10%, and 10% of chungkukjang, respectively.

Animals and diet

Male Sprague-Dawley rats with a mean body weight of 140±10 g were purchased from Oriental Co., Ltd (Busan, Korea). The rats were fed a standard rodent pellet chow (Purina Co., Seoul, Korea) and acclimatized to their environment for 1 week before commencement of the experiments. Five groups of rats (10 rats per group) were fed for 4 weeks with the following; non-diabetic control (NC), STZ-induced diabetic control (D), diabetic rats fed diet supplemented with red ginseng-chungkukjang (D-RC), diabetic rats fed diet supplemented (RC) with green laver (D-RCG), diabetic rats fed diet supplemented RC with sea tangle (D-RCS) (Table 1). The rats were individually housed in stainless steel wire bottom cages in a room maintained at 20±2°C and 60±5% relative humidity. The room was exposed to alternating 12 hr periods of light and dark.

To confirm hyperglycemia, fasting blood (12 hr after feed withdrawal) was sampled from the tails, and blood glucose levels were determined using Smart Scan™ (Inc

Table 1. Composition of experimental diets (g/kg diet)

Ingredients	Groups[1)]				
	NC	D	D-RC	D-RCG	D-RCS
Casein	200	200	190	190	190
Corn starch	150	150	142.5	142.5	142.5
Sucrose	500	500	500	500	500
Cellulose	50	50	40	40	40
Corn oil	50	50	48	48	48
AIN mineral mix.[2)]	35	35	34.5	34.5	34.5
AIN vitamin mix.[3)]	10	10	10	10	10
DL-methionine	3	3	3	3	3
Choline bitartrate	2	2	2	2	2
Red ginseng-chungkukjang powder (RC)	–	–	30	–	–
RC with green laver (RCG)	–	–	–	30	–
RC with sea tangle (RCS)	–	–	–	–	30
Total	1,000	1,000	1,000	1,000	1,000

[1)]NC: normal control, D: streptozotocin-induced diabetic, D-RC: 3% red ginseng-chungkukjang powder diet, D-RCG: 3% red ginseng-chungkukjang powder with green laver diet, D-RCS: 3% red ginseng-chungkukjang powder with sea tangle diet.
[2)]AIN mineral mixture (g/kg): calcium lactate 620.0, sodium chloride 74.0, potassium phosphate di-basic 220.0, potassium sulfate 52.0, magnesium oxide 23.0, manganous carbonate 3.3, ferric citrate 6.0, zinc carbonate 1.0, cupric carbonate 0.2, potassium iodate 0.01, sodium selenite 0.01, chromium potassium sulfate 0.5, finely powdered to make 1,000 g.
[3)]AIN vitamin mixture (mg/kg): thiamin-HCl 600, riboflavin 600, pyridoxine-HCl 700, nicotinic acid 3,000, D-calcium pantothenate 1,600, folic acid 200, D-biotin 20, vitamin B12 2.5, vitamin A400,000 IU, vitamin D3 100,000 IU, vitamin E 7,500 IU, vitamin K 75, finely powdered to make 1,000 g.

2000, IFD/KR/HK/TW/OB/SMT; Lifescan, Milpitas, CA, USA) on the 3rd day after streptozotocin (Sigma-Aldrich Chemical Co., St. Louis, MO, USA) intramuscular injection (55 mg/kg body weight in 0.1 M citrate buffer, pH 4.3). The normal control rats received an isovolumetric dose of citrate buffer as a vehicle. Rats with blood glucose levels above 300 mg/dL were considered diabetic and used in the study. All rats were allowed free access to diets and drinking water. The experimental protocols were conducted in accordance with internationally accepted principles for laboratory animal use and care as found in KFDA guidelines.

Measurements of body weight, feed intake, and feed efficiency ratio

Body weight and feed intake were measured at the designated times once a week during the experimental period. The feed efficiency ratio (FER) was calculated by dividing total weight gain with total feed intake during the experimental period.

Preparation of biochemical samples

After 4 weeks on the experimental diets, rats were fasted for 12 hr, and blood was collected from the abdominal aorta under anesthesia with ether. The liver was exhaustively perfused with cold physiological saline solution through the portal vein and quickly removed. The liver was then homogenized with 4 volumes of 0.25 M sucrose, centrifuged at 1,000×*g* for 10 min and the supernatant recentrifuged at 10,000×*g* for 20 min. The pellet was resuspended with 0.25 M sucrose to use as mitochondrial fraction, and the supernatant was used as postmitochondrial fraction. The collected blood was centrifuged at 2,000×*g* for 10 min at room temperature and the serum was stored in a cryogenic freezer at -70°C.

Analysis of serum insulin level, lipid profiles, and alanine aminotransferase (ALT) activity

Serum insulin levels were evaluated by radioimmunoassay using an insulin IRMA kit (Biosource Co., San Diego, CA, USA). Triglyceride, total cholesterol, and HDL-cholesterol in serum were measured by using kit reagents (AM 157S-K, AM 202-K, AM 203-K, Asan Pharmaceutical Co., Korea). LDL-cholesterol was calculated by the method of Friedewald et al. (24). ALT activity was assayed by a commercial kit (Asan Pharmaceutical Co.) as described previously (25).

Analysis of hepatic xanthine oxidase (XO), superoxide dismutase (SOD), and glutathione peroxidase (GPX) activities

XO activity was measured by the method of Stirpe and Della (26) and the activity was expressed as uric acid nmol/min/mg protein. SOD activity was estimated by a method of Martin et al. (27). One unit of the activity represented the amount of enzyme that inhibits the rate of hematoxylin oxidation by 50%. GPX activity was measured by the method of Paglia and Valentine (28) and the activity was defined as the amount of NADPH oxidized/min/mg protein. Protein content was determined by the Lowry method (29) with bovine serum albumin as a standard.

Statistical analysis

The results were expressed as mean±standard deviation (SD) of 10 animals. Statistical comparisons of differences between the different groups were carried out by two-way ANOVA test followed by Duncan's multiple range test using SPSS statistical software package (Version 12.0, SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

Weight gains, feed and water intake and FER

After the induction of diabetes, animals were fed the experimental diets for 4 weeks, and the subsequent body weight gain, the amount of feed intake, and the FER were examined (Table 2). At the beginning of the experiment, the average body weights of the animals among the five groups were not significantly different (178.03 ~184.98 g). Final body weight, weight gain and FER were significantly lower in the diabetic groups than in the NC group; however, they were significantly higher in the red ginseng-chungkukjang supplemented diets

Table 2. Changes in weight again, feed intake, and FER in STZ-induced diabetic rats fed different experimental diets for 4 weeks

Groups[1)]	Initial body weight (g)	Final body weight (g)	Weight gain (g/week)	Food intake (g/week)	FER[3)]
NC	184.98±9.23[NS2)]	397.10±17.80[a4)]	53.03±5.88[a]	181.10±7.96[b]	0.29±0.04[a]
D	176.96±8.45	208.08±10.61[c]	7.78±2.54[c]	206.50±9.44[a]	0.04±0.01[c]
D-RC	178.98±6.98	242.70±16.18[b]	15.93±2.41[b]	209.36±8.92[a]	0.08±0.01[b]
D-RCG	181.37±10.86	260.89±25.72[b]	19.88±4.63[b]	208.20±7.80[a]	0.10±0.02[b]
D-RCS	178.03±8.90	233.49±26.17[bc]	13.85±2.45[b]	207.62±8.38[a]	0.07±0.01[b]

[1)]See Table 1 for abbreviations. [2)]Not significant. [3)]FER (food efficiency ratio)=total weight gain/ total food intake.
[4)]Values are means±SD of 10 rats. Values with different superscripts within the same column indicate significant differences ($p<0.05$).

groups (RC, RCG and RCS) than in the D group during the experimental periods. While, food intakes in all diabetic groups were significantly higher than that of the NC group, there was no significant difference among all diabetic groups. In diabetes, body weight decreases, because of the abnormal metabolism of glucose caused by the imbalance of hormones, and polyphagia and polyuria occur (1,2,30). Our results suggest that a diet with RC, RCG, or RCS has a positive effect on weight gain in diabetes.

Organ weight

Organ weights (as percent per body weight) after feeding of the experimental diets for 4 weeks to diabetic animals are shown in Table 3. Spleen weights in all experimental groups were similar. The weight percentages of liver, kidney, heart, and testis in all diabetes groups were significantly higher than that of NC group. On the other hand, liver weight in RC, RCS, and RCG group was significantly lower than that of D group. Especially, kidney weight in RCG group was significantly lower than that of **NC group**.

Generally, liver, kidney, heart and testis in rats with diabetes induced by STZ are enlarged because of abnormal glucose metabolism and the accumulation of lipid caused by reduced insulin formation and insulin resistance (31). The current results suggest that RC, RCG, and RCS may ameliorate the organ damage resulting from hyperglycemia as typically seen in liver. Furthermore, RCG may be more protective against organ damage than RC and RCS.

Levels of blood glucose and serum insulin

The changes in blood glucose levels during the 4 weeks after induction of diabetes and in the level of insulin at 4 weeks are shown in Table 4 and Table 5.

The levels of blood glucose in normal control group (NC) were 93.00～113.0 mg/dL. While blood glucose levels in the D group were markedly enhanced compared with the NC group during experimental periods, they decreased gradually from 528.01～512.04 to 243.56, 167.23, 208.63 mg/dL in the RC, RCG, or RCS group, respectively. Especially, fasting blood glucose levels in rats fed RCG or RGS diet after 4 weeks were significantly lower than those of D and RC groups (Table 4).

The level of serum insulin was significantly decreased in the D group. However, the decreased insulin levels following the injection of STZ was completely restored to the NC group level by supplementation of the diet with RC, RCG, or RCS (Table 5).

It is well known that red ginseng has hypoglycemic effects in diabetic animals (32) and ginsenoside Rb1 and Rb2 of red ginseng appears to have an anti-diabetic activity (33). Furthermore, it is reported that fermented red ginseng-chungkukjang may have more potent hypoglycemic effects and ability to normalize serum insulin levels compared to the red ginseng or chungkukjang only in diabetic animals (34). Moreover, hyperglycemia and

Table 3. Changes in relative organ weights in STZ-induced diabetic rats fed different experimental diet for 4 weeks (g/100 g BW)

Groups[1)]	Liver	Kidney	Heart	Spleen	Testis
NC	2.77±0.15[c2)]	0.65±0.03[c]	0.27±0.12[b]	0.18±0.02[NS3)]	0.76±0.10[b]
D	4.20±0.36[a]	1.44±0.09[a]	0.41±0.03[a]	0.18±0.02	1.59±0.03[a]
D-RC	3.68±0.15[b]	1.27±0.05[ab]	0.37±0.03[a]	0.19±0.02	1.54±0.11[a]
D-RCG	3.62±0.08[b]	1.14±0.11[b]	0.34±0.06[a]	0.18±0.02	1.28±0.21[a]
D-RCS	3.74±0.36[b]	1.28±0.14[ab]	0.36±0.04[a]	0.17±0.02	1.44±0.30[a]

[1)]See Table 1 for abbreviations.
[2)]Values are means±SD of 10 rats and values with different superscripts within the same column indicate significant differences ($p<0.05$).
[3)]NS: not significant.

Table 4. Changes in blood glucose levels in STZ-induced diabetic rats for 4 weeks (mg/dL)

Groups[1)]	Time (weeks)				
	0	1	2	3	4
NC	113.05±9.78[b2)]	101.95±5.10[c]	98.23±4.87[c]	99.18±4.95[d]	93.12±4.65[d]
D	525.80±26.10[a]	464.34±23.20[a]	448.11±21.04[a]	435.30±32.75[a]	397.77±19.83[a]
D-RC	528.01±33.42[a]	426.04±27.28[ab]	400.44±19.95[b]	332.26±16.48[b]	243.56±22.15[b]
D-RCG	512.04±39.40[a]	402.78±32.05[b]	387.36±23.20[b]	280.17±23.78[c]	167.23±25.45[c]
D-RCS	517.36±40.05[a]	413.12±36.13[b]	394.13±25.54[b]	304.02±33.15[bc]	208.63±21.34[c]

[1)]See Table 1 for abbreviations.
[2)]Values are means±SD of 10 rats and values with different superscripts within the same column indicate significant differences ($p<0.05$).

Table 5. Serum insulin levels in STZ-induced diabetic rats fed different experimental diets for 4 weeks

Groups	NC	D	D-RC	D-RCG	D-RCS
Serum insulin (μIU/mL)	5.39±0.78[a]	3.01±0.31[b]	5.09±1.07[a]	5.68±0.90[a]	6.47±1.21[a]

[1)]See Table 1 for abbreviations.
[2)]Values are means±SD of 10 rats and values with different superscripts indicate significant differences ($p<0.05$).

mortality of diabetic rats were effectively prevented in diabetic animals treated with ethanol by red ginseng-chungkukjang (35). Additionally, it is well documented that dietary fiber may decrease hyperglycemia, hyperinsulinemia and plasma lipid profile in diabetic patients (36,37). Seaweed, a favorite food of Koreans, is a good source of dietary fiber and is reported to have a tendency to improve glucose tolerance and to lower plasma cholesterol levels in diabetic animals (38). Sea tangle and sea mustard have been shown to decrease blood glucose levels in STZ-induced diabetic rats (39,40).

This finding in RC group is in good accordance with previous reports (34,35). Furthermore, these results suggest that treatment with RCG, or RCS in diabetic rats may have more potent hypoglycemic effect compared to the RC group via delaying glucose absorption from the small intestine (41,42). Although the action mechanisms of the hypoglycemic effect and normalization of serum insulin by the seaweeds are unknown, these results indicate that co-administration of seaweed and RC may have a synergistic anti-diabetic activity.

Changes of serum lipid profile

The levels serum triglycerides (TG) levels, total cholesterol, HDL- and LDL-cholesterol after induction of diabetes are shown in Fig. 1. The levels of TG, total cholesterol and LDL-cholesterol in D group were significantly higher than those of the NC group, the level of HDL-cholesterol was significantly lower than that of NC. TG and LDL-cholesterol in animals fed RC, RCG, or RCS supplemented diet were normalized to levels similar to the NC group, total cholesterol except RCS group lower than that of D group. Additionally, HDL-cholesterol level in all experimental diet supplemented groups (RC, RCG, or RCS) tended to be higher than the D group, but not significantly.

It is well known that high levels of serum TG, total cholesterol, and LDL-cholesterol and low levels of HDL-cholesterol due to hyperglycemia may contribute to the development of cardiovascular disease in diabetes (43, 44). In addition, many studies report that constituents of red ginseng (11-13), chungkukjang (14,15) and seaweeds (18,19,21-23) may regulate hyperlipidemia. Therefore, the above results indicate that RC improved serum TG and LDL-cholesterol due to increased insulin secretion. Unlike blood glucose, the addition of green laver or sea tangle to RC resulted in no synergistic effect on serum lipid profiles.

Hepatic ROS generating and scavenging enzyme activities

The activities of hepatic xanthine oxidase (XO), an ROS generating enzyme, and superoxide dismutase (SOD) and glutathione peroxidase (GPX) in the experimental rats after induction of diabetes by STZ are shown in Fig. 2.

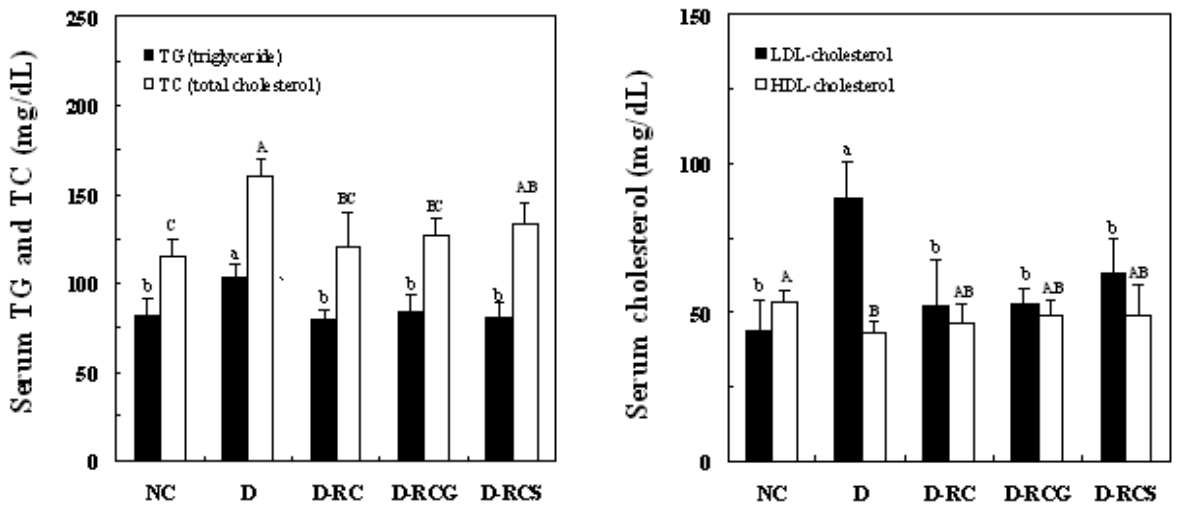

Fig. 1. Changes of serum TG, total cholesterol, HDL- and LDL-cholesterol in STZ-induced diabetic animals. Abbreviations for groups: See Table 1. Values are means±SD of 10 rats. Different letters above the bar indicate significant differences between groups by multiple comparison test ($p<0.05$).

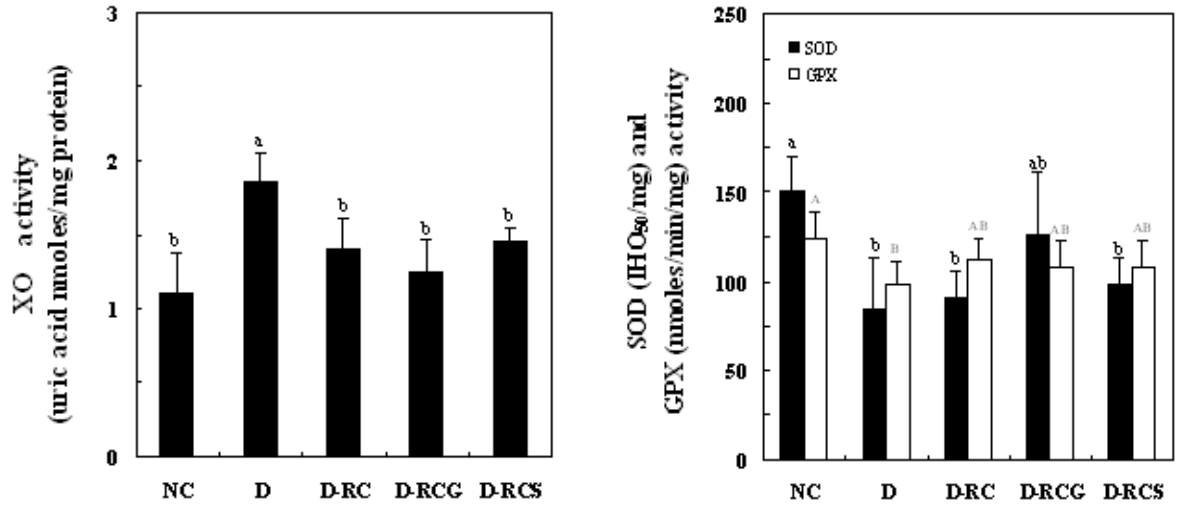

Fig. 2. Changes in hepatic xanthine oxidase (XO), superoxide dismutase (SOD) and glutathione peroxidase (GPX) activities in STZ-induced diabetic animals. Abbreviations for groups: See Table 1. Values are means±SD of 10 rats. Different letters above the bar indicate significant differences between groups by multiple comparison test ($p<0.05$).

Whereas the activity of hepatic XO in D was markedly higher than that of NC, all experimental diet feeding group (RC, RCG, or RCS) it was restored to levels near that of NC (Fig. 2). On the other hand, the activity of hepatic SOD and GPX in D was markedly lower than that of NC. After treatment with the experimental diets, SOD activity in the RCG was slightly higher than that of D group. Additionally, decreased GPX activity due to diabetes was slightly increased in all experimental diet groups, but the differences were not significant (RC, RCG, or RCS) (Fig. 2).

Xanthine oxidase is a non-specific enzyme involved in the metabolism of purine, pyrimidine, aldehydes and heterocyclic compounds; *in vivo*, it oxidizes primarily hypoxanthine via xanthine into uric acid. It has been reported that XO activity of diabetic rats is increased in liver and plasma (45). Generally, with low XO activity there is a decrease in the generation of ROS such as superoxide, hydroxyl radical, and hydrogen peroxide (45,46). On the other hand, SOD and GPX are widely considered to be two major intracellular antioxidant enzymes in mammals (47,48). Because SOD catalyses the conversion of superoxide anion into hydrogen peroxide which is a substrate of GPX, these enzymes are perceived to function consecutively with similar roles in coping with oxidative stress (48,49).

Therefore, these results suggest that RC, RCG, or RCS may inhibit the XO activity, an ROS generator, and increase the activities of the ROS scavengers, SOD and GPX. There did not appear to be any synergistic effect of RC with the seaweeds in the inhibition of XO activity or induction of SOD and GPX activity.

Serum ALT activity

Fig. 3 shows the activity of serum ALT of STZ-induced diabetic rats fed experimental diets for 4 weeks. Although the activity of serum ALT in D group was markedly higher than that of NC, all experimental diet groups (RC, RCG, or RCS) had activities similar to the NC group. It is well known that activity of serum ALT is biomarker for hepatic damage (50). Therefore, these results suggest that the experimental diets help counteract the damage to hepatic tissue by STZ induced hyperglycemia.

Considering the above results, although the exact mechanism of the anti-hyperglycemic effects of the red

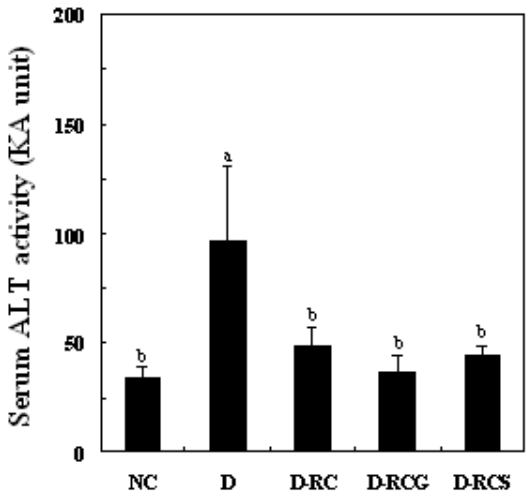

Fig. 3. Changes in serum alanine aminotransferase (ALT) activities in STZ-induced diabetic animals. Abbreviations for groups: See Table 1. Values are means±SD of 10 rats. Different letters above the bar indicate significant differences between groups by multiple comparison test ($p<0.05$).

ginseng-chungkukjang with either green laver or sea tangle are known, the red ginseng-chungkukjang with either green laver or sea tangle may have hypoglycemic and hypolipidemic effects due to increased insulin levels.

In conclusion, our study provides experimental evidence that the mixture of red ginseng-chungkukjang with either green laver or sea tangle powder may regulate hyperglycemia and hyperlipidemia via an increase in insulin. However, further study is needed to confirm these effects in humans.

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