

Effects of Fermented Red Ginseng Extracts on Hyperglycemia in Streptozotocin-induced Diabetic Rats

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Fermented red ginseng (FRG) was prepared by inoculating 0.1% *Lactobacillus fermentum* NUC-C1 and fermenting them at 40°C for 12 hours. The ginsenoside contents of FRG were increased compared with those of red ginseng (RG). Moreover, the levels of the ginsenosides Rg2, Rg3, and Rh2 in FRG increased significantly. In an oral glucose tolerance test (OGTT), blood glucose levels were lower in animals fed with RG and FRG extracts than in normal controls. In particular, FRG extracts in OGTT were superior to RG extracts. The antidiabetic effects of FRG in streptozotocin (STZ)-induced diabetic rats were investigated. Rats were divided into four groups: normal control, diabetes mellitus (DM), FRG administered at 100 mg/kg, and FRG administered at 200 mg/kg groups. FRG extracts were orally administered to each treatment group for 3 weeks, and blood glucose, insulin, and lipid levels of each group were determined. Orally administered FRG extracts significantly reduced blood glucose levels and increased plasma insulin levels in diabetic rats. Additionally, the activities of disaccharidases, including sucrase, lactase, and maltase, were decreased significantly in the FRG groups. FRG groups also had reduced triglyceride and total cholesterol levels, compared with the DM group. These results suggest that FRG may have antidiabetic effects in STZ-induced diabetic rats.

Keywords: Red ginseng, Fermentation, Antidiabetic effect, Streptozotocin

INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia, resulting from a lack of insulin secretion by the pancreas or low biological activity of the insulin secreted, and is classified into insulin-dependent (type 1) and -independent types (type 2) [1]. Recently, the World Health Organization reported that the incidence of diabetes was estimated to be 170,000,000 worldwide in the year 2000. However, this incidence is expected to rise to 360,000,000 by the year 2030. Moreover, the incidence of diabetes in Korea has rap-

idly increased, because of poor diet and obesity [2,3]. The treatment of diabetes depends on insulin injections, diet, and exercise. Insulin injection, the major therapy for type 1 diabetes, can produce several side effects. Thus, to ameliorate diabetes, many studies have searched for active ingredients found in herbs [4-6]. Ingredients from medicinal herbs, beans, ginseng, and red ginseng, and their extracts have been shown to be efficacious in decreasing hyperglycemia, and subsequently, in ameliorating diabetes [7-10]. Among the different herbs, ginseng is the most efficacious for immune

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stimulation, and the prevention of hyperlipidemia and diabetes [11-14]. Additionally, red ginseng, which is produced by steaming fresh ginseng, comprises modified saponin and amino acids, and sugar products. Thus, red ginseng is more efficacious for long-term storage [15-17]. The active ingredients in red ginseng are classified into saponin components (ginsenosides) and non-saponin components (the polyacetylene compounds, panaxatriol and panaxadiol, acidic polysaccharides, and amino acids), and these ingredients are responsible for immune stimulation, and the prevention of diabetes, cancer, fatigue, stress, and hyperlipidemia [18-22].

Recently, microbial methods have been introduced for the transformation of medicinal herbs, and active ingredients generated by microbial transformation have been investigated [23]. In particular, the pharmacological effects of a new saponin generated by red ginseng fermentation and mass production have been reported [24]. Fermentation of red ginseng by intestinal microorganisms transforms saponins, such as Rb1, Rb2, Rc, and Rd, into readily absorbed forms, such as compound K, which is active in cancer, diabetes, and immune stimulation [25]. These results demonstrated that fermentation of red ginseng and medicinal herbs with microorganisms, such as lactic acid bacteria, transforms pharmacological ingredients into low-molecular-weight active compounds with higher absorption [24]. Additionally, fermentation reduces the toxicity of specific components and can degrade pesticides [23].

Diabetes was induced by treating animals with alloxan or streptozotocin (STZ), both of which produce several side effects, including liver and kidney dysfunction, and bone marrow destruction [26]. Because STZ has a lower toxicity than alloxan, STZ is generally used in rat models of diabetes [27].

In this study, red ginseng was prepared from white ginseng, and was further fermented with *Lactobacillus fermentum* NUC-C1. The anti-diabetic effects were determined following the oral administration of fermented red ginseng in STZ-induced diabetic rats, and body weight, blood glucose level, and other serological indicators were examined.

MATERIALS AND METHODS

Samples

The fermented red ginseng (FRG) used in this study was produced at the Bio Research Institute of NUC Electronics Co., Ltd. (Daegu, Korea). Referred to as 'NUC fermented red ginseng extracts powder,' it was

prepared using the following procedure: 2 L of purified water was added to 300 g of 6-year-old white dried ginseng, purchased from Geumsan Insam Nong-hyup (Korea), and steamed for 24 hours. A further 4 L of distilled water was added, and the ginseng solution was steamed at 90°C for 48 hours to make red ginseng (RG) extracts. The RG extracts was then used to make FRG extracts by the addition of 0.1% *Lactobacillus fermentum* NUC-C1 (KCCM10929P) and 12 hours of fermentation at 40°C. RG and FRG extracts were both dried *in vacuo* (Eyela, Tokyo Rikakikai Co., Tokyo, Japan), then freeze-dried and pulverized, and finally stored at -20°C until needed for experiments.

Ginsenoside content analysis

After extraction of RG and FRG dried powders with 80% methanol, the products were dried *in vacuo* and dissolved in distilled water; then, the soluble constituents were removed by diethyl ether extraction. Water-saturated butanol was added to the remaining water layer, and crude saponin was prepared by concentrating the *n*-butanol layer. Crude saponin was again diluted with methanol, and then filtered and high-performance liquid chromatography (HPLC) analysis was performed using an X-Terra RP18 column (4.6×250 mM; Waters, Milford, MA, USA). For HPLC mobile phase analysis, acetonitrile and distilled water were combined in a ratio of 80:20, and the solution was used for elution. The flow rate was controlled at 1.0 mL/min, the sample infusion volume was 20 µL, the detection wavelength was 203 nm, and the column temperature at 25°C for the analysis.

Oral glucose tolerance test

Blood glucose levels of normal rats that fasted for at least 12 hours were determined; then, rats were orally administered RG or FRG extracts dissolved in distilled water at 100 mg/kg or 200 mg/kg, respectively. For the control group, an equal amount of normal saline was given. Subsequently, 40% glucose was orally administered to all groups at 1 g/kg, followed by blood collection from tail veins at 30, 60, 90, and 120 minutes post-glucose administration to observe changes in blood glucose levels.

Induction of diabetes in experimental animals

Sprague-Dawley rats (Orient Bio Inc., Seongnam, Korea) weighing 180±10 g were used. Cages were maintained at 23±2°C, with a humidity of 60±5%, and 12/12-h light/dark cycles. Rats were fed *ad libitum* with

solid rat food and water for 1 week to adjust them to the environment; then, the rats were used in the subsequent 3 weeks, with close adherence to the university's ethical guidelines for animal experiments.

The animals were divided into one normal control group (NC) and three diabetes induction groups. The diabetes induction groups were further divided into diabetes control (DM) and FRG groups (FRG administered at 100 mg/kg [FRG100] and FRG administered at 200 mg/kg [FRG200]). Six rats were maintained for 3 weeks in each group. In terms of feeding, the NC and DM groups were fed only with the normal feedstuff, whereas the FRG groups were orally administered 100 or 200 mg/kg FRG extracts dissolved in water, at 10 a.m. daily. The sample concentration was determined in preliminary experiments, and during the experiments, food and water were given *ad libitum*, and the room was maintained under 12/12-h light/dark conditions. Rats that had undergone a 1-week adjustment period for diabetes induction were fasted for at least 12 hours, and peritoneal injection of streptozotocin, diluted in 0.01 M citrate buffer, was given at 60 mg/kg. In the NC group, the same concentration of normal saline was used for the peritoneal injection. Blood collected from tail veins was used to confirm diabetes induction, and rats with fasting blood glucose levels above 300 mg/dL were used in experiments.

Weight and feed intakes

The increase in body weight was measured at the same time each week for the 3-week period of the study. The feed intakes were recorded by measuring the remaining feedstuff every 3 days, and subtracting that amount from the feedstuff originally provided.

Blood glucose level and biochemical analysis

Changes in blood glucose levels during the feeding period were measured weekly using a blood glucose monitoring system (ACCU-CHEK Sensor; Roche Diagnostics GmbH, Mannheim, Germany), and blood that was collected from rat tail veins after fasting the rats for over 12 hours. At the end of the 3-week feeding period, the rats that were fasted for 12 hours were anesthetized and dissected. Blood was collected from peritoneal veins using heparin-treated syringes, and, after letting the blood samples stand for 30 minutes, they were centrifuged to separate the plasma. The liver, spleen, kidneys, pancreas, and small intestine were also removed, washed with phosphate-buffered saline, depleted of moisture, and then weighed. Separated plasma and tis-

ues were snap-frozen in liquid nitrogen, and kept at -70°C until analyzed. Analysis of the diabetic marker insulin was performed using an insulin kit (Rat Insulin ELISA; Mercodia, Uppsala, Sweden), and from the separated plasma, triglyceride levels, total cholesterol content, and high density lipoprotein (HDL) cholesterol content were measured using a triglyceride measuring kit, a total cholesterol content measuring kit (Asan Pharmaceutical, Whasung, Korea), and an HDL cholesterol measuring kit (Asan Pharmaceutical), respectively.

Small intestinal disaccharidase measurements

Mucosal samples obtained from the small intestines were thawed at room temperature and a four-fold greater amount of distilled water was added to them, followed by homogenization with a homogenizer. Based on Dahlqvist's methods [28], maltose, sucrose, and lactose were used as substrates, and activation of disaccharide hydrolytic enzymes, such as maltase, sucrase, and lactase, were quantified. Glucose that was produced from the enzymatic reactions was oxidized into gluconic acid and H_2O_2 by glucose oxidase, and then H_2O_2 reacted with peroxidase to form a colored product, which was measured. Activation of a disaccharide hydrolytic enzyme is represented as units/g protein (specific activity) after setting 1 unit as 1 μmole of glucose produced by the enzyme in 1 minute.

Statistical analysis

The means and standard deviations of the data were calculated. Evaluation of each group's significance was performed using the SAS ver. 8 (SAS Institute, Cary, NC, USA) at a 5% significance level, using Duncan's multiple range tests.

RESULTS AND DISCUSSION

Comparison of ginsenoside contents in RG and FRG

As shown in Table 1, FRG, for which *Lactobacillus fermentum* NUC-C1 was used in the fermentation process, contained more ginsenoside types than RG. Additionally, FRG had a significant increase in the ginsenosides Rg2, Rg3, and Rh2, with 95.11% Rg3. This result indicated that ginsenosides were degraded into non-glycosides, such as Rg3, by the fermentation [29]. In ginseng, diol-type saponins, such as ginsenoside Rb1, Rb2, Rc, Rd, Rg3, and Rh2, exhibit anti-diabetic activity [30], and ginsenoside Rh2 increases insulin secretion in STZ-induced diabetic rats to decrease the

Table 1. Ginsenoside contents of red ginseng (RG) and fermented red ginseng (FRG)

| Ginsenoside | Contents (mg%) | |
|-------------|----------------|-------------------|
| | RG | FRG ¹⁾ |
| Rb1 | - | 0.14 |
| Rb2 | - | 0.09 |
| Rb3 | - | 0.07 |
| Rc | - | 0.13 |
| Rd | 0.30 | 0.32 |
| Re | 1.86 | 0.01 |
| Rg1 | 1.45 | 0.01 |
| Rg2 | 1.62 | 12.6 |
| Rg3 | 23.62 | 95.11 |
| Rh1 | 26.02 | 16.41 |
| Rh2 | - | 2.57 |
| Compound-K | - | Trace |

¹⁾FRG fermented with *Lactobacillus fermentum* NUC-C1 at 40°C for 12 hours.

blood glucose concentration [31]. Thus, we hypothesized that the greater increase in these components in FRG compared with RG would enhance the anti-diabetic activity of FRG in this study. Furthermore, it has been reported that following fermentation of RG, the metabolized products of saponin are converted by intestinal bacteria into compound K, which is readily absorbed in the body. Compound K possesses anti-diabetic properties [25], and, in this study, it was detected in FRG in small quantities. Although, in comparison with RG, FRG had lower levels of the ginsenosides Re and Rg1, which exhibit anti-diabetic effects [32], FRG enhances anti-diabetic activities through its greater number of ginsenoside types and the level of their content, resulting in their complex effects.

Oral glucose tolerance in RG and FRG

Oral glucose tolerance tests of manufactured RG and FRG extracts demonstrated the highest blood glucose level at 30 minutes following glucose administration, with decreasing blood glucose levels thereafter (Fig. 1). Compared with the group that was administered glucose alone, without sample administration, the RG and FRG groups showed a significant reduction in blood glucose levels. Additionally, at 30 minutes following glucose administration, the 200 mg/kg RG and FRG groups had a greater drop in blood glucose levels than the 100 mg/kg groups. At 60 minutes post-glucose administration, the blood glucose levels in the FRG groups were reduced by more than in the RG groups;

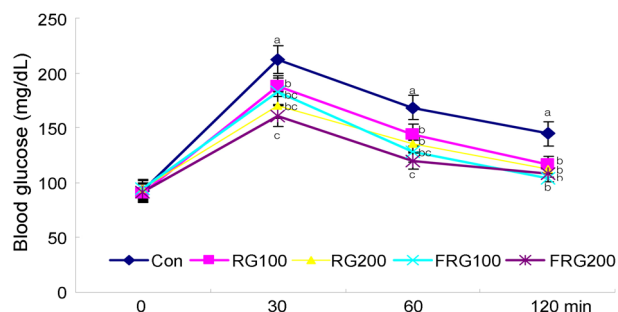


Fig. 1. Effects of red ginseng (RG) and fermented red ginseng (FRG) extracts in oral glucose tolerance tests (OGTT) in rats. In the OGTT, glucose levels were estimated following the oral administration of 1 g/kg D(+)-glucose at the indicated time points. con ($n=6$), normal control group; RG100 ($n=6$), the diabetic group fed with 100 mg/kg of RG extracts; RG200 ($n=6$), the diabetic group fed with 200 mg/kg of RG extracts; FRG100 ($n=6$), the diabetic group fed with 100 mg/kg of FRG extracts; FRG200 ($n=6$), the diabetic group fed with 200 mg/kg of FRG extracts. Mean values with different superscripts in the same column are significantly different ($p<0.05$).

the reduction was significant in the 200 mg/kg FRG group. At 120 minutes post-glucose administration, the blood glucose level was reduced to almost the level before fasting, regardless of the sample concentration used, and no significant difference between the samples was observed. In summary, as the concentration of RG and FRG in the samples increased, the blood glucose level decreased, and the degree of reduction was greater with FRG than RG. This may be because of the fermentation factors created by the *Lactobacillus* used in the process of RG fermentation, and their suppressive effects on rising blood glucose levels. Thus, in this study we demonstrated the effects of FRG in the improvement of glucose metabolism.

Changes in body and organ weights

Changes in body weight of the rats with STZ-induced diabetes are shown in Fig. 2 after feeding for 3 weeks plus orally administered FRG extracts. In contrast to the steady increase in body weight in the NC group over time, the DM group had decreasing body weights, because of STZ. Although the body weight of the FRG extracts-administered group decreased more than the normal group, it was still significantly higher, compared with the body weight of the DM group. However, no significant difference in weight between groups receiving different FRG concentrations was observed. STZ administration causes β -cell destruction within the pancreas, leading to type 1 diabetes mellitus, and consequently insulin production deficiency and a decline in insulin action. Insufficiency in energy production from glucose metabolism affects growth and develop-

ment [27]. Insulin is involved in protein metabolism and stimulates the influx of amino acids into skeletal muscles to increase protein synthesis activity. In animals with induced diabetes, the decline in such actions of insulin leads to the decline in cellular glucose utilization and a starvation state [33]. This is why all the diabetic groups had greater weight reductions than the normal group. Moreover, the average daily dietary consumption of all the experimental groups was significantly higher than the NC group (Table 2), which was attributed to diabetic symptoms (i.e., polyphagia, polyuria, and polydipsia). When the feed intakes of the DM group (40.0 ± 1.5 g/day/rat) was compared with that of the NC group (24.6 ± 0.5 g/day/rat), that of the DM group increased significantly, by more than two-fold. Conversely, in the 200 mg/kg FRG group, feed intakes decreased significantly compared with the DM group. In this study, the weight of the DM group decreased continuously, despite high dietary consumption, and this may be because of regressive changes in body metabolism pathways caused by diabetes. However, in terms of changes in organ weight/body weight (Table 2), the weight of the pancreas and kidneys in the DM group increased

more than that in the NC group, while in the FRG group, the weight of the pancreas and kidneys seemed to decrease overall, but with no significant difference compared with the DM group. The spleen weight was not significantly different between the groups.

Changes in blood glucose concentration

Changes in blood glucose levels are shown in Fig. 3. Blood glucose levels increased significantly in the DM group, compared with the NC group, and although no difference between the DM and FRG groups before sample administration was observed, the FRG groups showed significantly reduced blood glucose levels from 1 week after sample administration, compared with the DM group. Blood glucose levels decreased more significantly with increasing duration of the feeding period, and at 2 and 3 weeks after sample administration, the 100 mg/kg FRG group had a more significant reduction in blood glucose levels, compared with the 200 mg/kg FRG group. The DM group had a greater increase in blood glucose levels compared with the NC group, because of the side effects of peritoneal injection of STZ, which include pancreatic β -cell destruction and inhibition of insulin secretion. However, because FRG decreases the blood glucose level, the FRG may have effects in the control of blood glucose levels. Moreover, when 100-200 mg/kg FRG was administered to the normal group, the blood glucose levels of each group did not differ significantly (data not shown). Thus, FRG had little influence on changes in the blood glucose level in normal animals.

Studies have demonstrated that STZ-induced rats fed with a diet containing tissue cultured ginseng powder decreased blood glucose levels [34], and red ginseng lowered the blood glucose level in hyperglucosemia induced by STZ [35]. This study also demonstrated blood glucose-lowering effects of FRG in rats with STZ-induced diabetes. Importantly, the 100 mg/kg FRG group

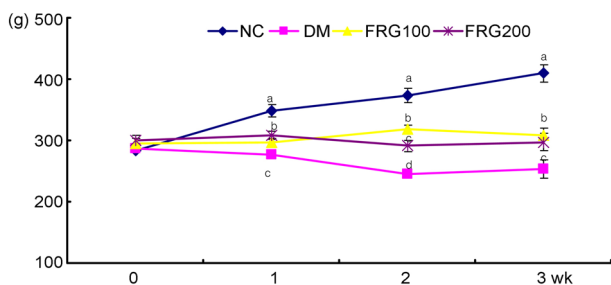


Fig. 2. Effects of fermented red ginseng (FRG) extracts on body weight in streptozotocin-induced diabetic rats. NC ($n=6$), normal control group; DM ($n=6$), diabetic mellitus group; FRG100 ($n=6$), diabetic group fed with 100 mg/kg of FRG extracts; FRG200 ($n=6$), diabetic group fed with 200 mg/kg of FRG extracts. Mean values with different superscripts in the same column are significantly different ($p < 0.05$).

Table 2. Effects of fermented red ginseng (FRG) extracts on feed intakes and organ weight in streptozotocin (STZ)-induced diabetic rats for 3 weeks

| | Feed intakes (g/day) | Organ weight (%) | | | |
|--------|----------------------|-------------------|----------------------|-------------------|-------------------|
| | | Liver | Spleen | Kidney | Pancreas |
| NC | 24.60 ± 0.47^c | 2.95 ± 0.16^b | 0.16 ± 0.03^{ns} | 0.61 ± 0.03^c | 0.42 ± 0.01^b |
| DM | 40.04 ± 1.52^b | 4.39 ± 0.33^a | 0.15 ± 0.04 | 1.13 ± 0.15^a | 0.55 ± 0.09^a |
| FRG100 | 43.60 ± 1.93^b | 4.19 ± 0.30^a | 0.20 ± 0.04 | 1.04 ± 0.15^b | 0.46 ± 0.09^b |
| FRG200 | 44.57 ± 0.41^a | 4.33 ± 0.23^a | 0.16 ± 0.04 | 1.04 ± 0.09^a | 0.48 ± 0.02^a |

Mean values with different superscripts in the same column are significantly different ($p < 0.05$).

NC ($n=6$), normal control group; DM ($n=6$), diabetic mellitus group; FRG100 ($n=6$), diabetic group fed with 100 mg/kg of FRG extracts; FRG200 ($n=6$), diabetic group fed with 200 mg/kg of FRG extracts.

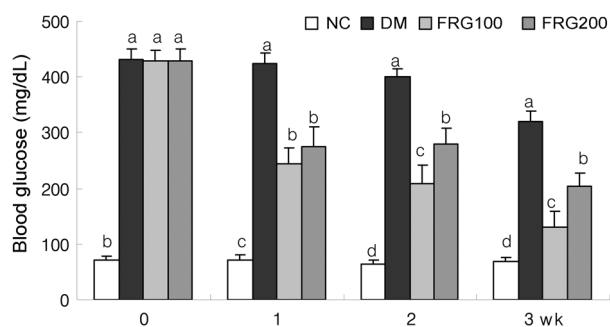


Fig. 3. Changes in the blood glucose levels during the 3-week period in streptozotocin-induced diabetic rats after fermented red ginseng (FRG) extracts administration. NC ($n=6$), normal control group; DM ($n=6$), diabetic mellitus group; FRG100 ($n=6$), diabetic group fed with 100 mg/kg of FRG extracts; FRG200 ($n=6$), diabetic group fed with 200 mg/kg of FRG extracts. Mean values with different superscripts in the same column are significantly different ($p<0.05$).

demonstrated a significant reduction in blood glucose levels.

Changes in plasma insulin concentration

The plasma insulin concentration was 24.56 ng/mL in the NC group and 6.58 ng/mL in the DM group, with the NC group showing a more significant increase in plasma insulin concentrations than the DM group. While the FRG groups had a more significant increase in insulin concentration than the DM group, no significant difference between the groups at different FRG concentrations was observed (Table 3). This may be attributable to the decrease in insulin secretion because of STZ-induced pancreatic β -cell destruction, followed by FRG sample administration, which helped the pancreatic cells to recover and increase the plasma insulin concentration [26]. The 100 mg/kg FRG group had a greater reduction in blood glucose levels than the 200 mg/kg FRG group, because of the greater increase in the insulin concentration of the 100 mg/kg FRG group, leading to a greater reduction in blood glucose levels. Thus, the FRG sample and its ability to reduce the

blood glucose level were used to illustrate that the increase in insulin concentration significantly affected the blood glucose level.

Inhibition of small intestinal disaccharidase activity

In comparison with the NC group, the DM group had a significant increase in disaccharidase activity, and the FRG groups had a significantly decreased disaccharidase activity, compared with the DM group (Fig. 4). Moreover, the 100 mg/kg FRG group showed a more significant inhibition of disaccharidase activity than the 200 mg/kg FRG group. This was in agreement with the results that the 100 mg/kg FRG group had a more significantly increased insulin concentration than the 200 mg/kg FRG group, thereby significantly decreasing the blood glucose level.

Generally, in animal models with STZ-induced diabetes, morphological, functional, and metabolic substitution take place in the small intestine, with an increase in small intestinal disaccharidase activity to stimulate glucose absorption there [36]. In this study, an increase in disaccharidase activity in the DM group was observed following FRG administration and a subsequent decline in enzyme activities and suppression of blood glucose level increase. Thus, FRG fermented by *Lactobacillus* may be an excellent candidate to inhibit disaccharidase activity and lower blood glucose levels.

Changes in plasma lipid concentrations

Following FRG administration, the total plasma cholesterol concentration was 60.29 \pm 5.65 mg/dL in the NC group, compared with 92.86 \pm 4.03 mg/dL in the DM group, a significant difference. The plasma cholesterol concentration in the FRG groups decreased, compared with that in the DM group. In terms of the 100 mg/kg FRG group, the plasma cholesterol concentration was 78.07 \pm 8.59 mg/dL, which was significantly lower than in the DM group (Table 3). The increase in the total

Table 3. Effects of fermented red ginseng (FRG) extracts on plasma insulin, total cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride contents in streptozotocin-induced diabetic rats for 3 weeks

| | Insulin (ng/mL) | Total cholesterol (mg/dL) | HDL-cholesterol (mg/dL) | Triglyceride (mg/dL) |
|--------|-------------------------------|--------------------------------|-------------------------------|--------------------------------|
| NC | 24.56 \pm 1.80 ^a | 60.29 \pm 5.65 ^c | 60.54 \pm 6.14 ^b | 53.57 \pm 5.5 ^{bc} |
| DM | 6.58 \pm 0.51 ^c | 92.86 \pm 4.03 ^a | 63.11 \pm 8.9 ^{ab} | 104.47 \pm 4.48 ^a |
| FRG100 | 10.4 \pm 1.08 ^b | 78.07 \pm 8.59 ^b | 73.30 \pm 12.7 ^a | 51.64 \pm 4.58 ^c |
| FRG200 | 8.56 \pm 1.14 ^b | 84.50 \pm 6.64 ^{ab} | 78.16 \pm 9.04 ^a | 63.28 \pm 6.10 ^b |

Mean values with different superscripts in the same column are significantly different ($p<0.05$).

NC ($n=6$), normal control group; DM ($n=6$), diabetic mellitus group; FRG100 ($n=6$), diabetic group fed with 100 mg/kg of FRG extracts; FRG200 ($n=6$), diabetic group fed with 200 mg/kg of FRG extracts.

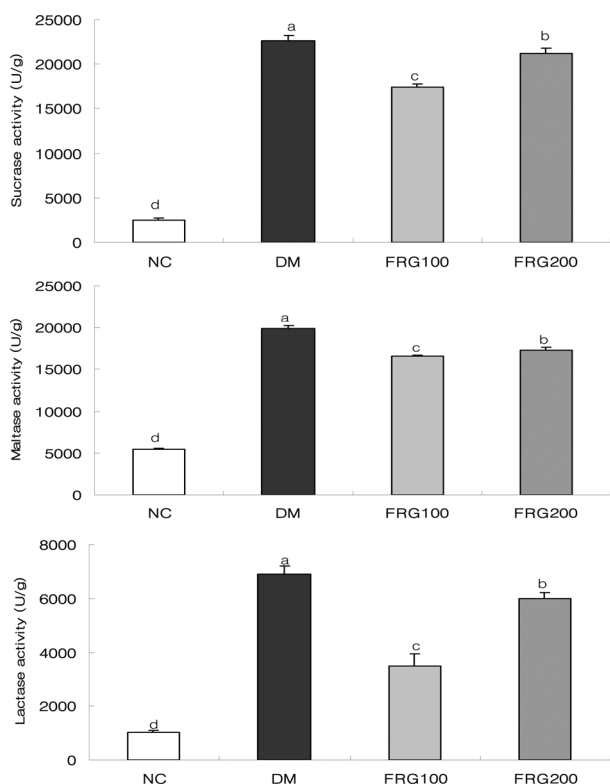


Fig. 4. Inhibitory effects of fermented red ginseng (FRG) extracts on disaccharidase activity in streptozotocin-induced diabetic rats. NC ($n=6$), normal control group; DM ($n=6$), diabetic mellitus group; FRG100 ($n=6$), diabetic group fed with 100 mg/kg of FRG extracts; FRG200 ($n=6$), diabetic group fed with 200 mg/kg of FRG extracts. Mean values with different superscripts in the same column are significantly different ($p<0.05$).

cholesterol level in the diabetes-induced group may be because of the inability of the rats to metabolize carbohydrates as an energy source, and the subsequent use of free fatty acids for energy and cholesterol synthesis [37]. Moreover, in a state of difficulty controlling glucose, a reduction in the activity of liver HMG-CoA reductase and an increase in the activity of intestinal HMG-CoA reductase occur, resulting in hypercholesterolemia [38]. Plasma HDL cholesterol increased more in the FRG groups than in the DM group, but not statistically significantly. Plasma HDL cholesterol was more significantly elevated in all the diabetic-induced groups, compared with the NC group. This observation was consistent with a report demonstrating that HDL cholesterol increased in the diabetes-induced group because of an increase in the total cholesterol level, and that in experiments with puffed RG, the HDL cholesterol level was also higher in the diabetes-induced group, compared with the normal group [38]. The plasma triglyceride concentration increased

significantly, from 53.57 ± 5.50 mg/dL in the NC group to 104.47 ± 4.48 mg/dL in the DM group, while it decreased significantly in the FRG groups. In hyperlipidemia, a major complication of diabetes, the rate at which plasma fatty acids become triglycerides is greater than normal, leading to an increase in the plasma triglyceride concentration [39]. The triglyceride concentration in diabetes also increased in this study, and the 100 mg/kg FRG group showed a significant decrease in the plasma triglyceride concentration, compared with the NC group. This result is consistent with a report that revealed that saponin components in ginseng stimulated the decline and excretion of plasma cholesterol, and improved lipid metabolism with treatment with either tissue cultured ginseng or puffed RG [33,40].

In summary, FRG, RG fermented by *Lactobacillus*, demonstrated blood glucose-lowering effects in oral glucose tolerance test, and increased insulin secretion that was reduced because of pancreatic β -cell destruction, caused by STZ administration. Consequently, the blood glucose levels decreased. Additionally, FRG plays a role in improving glucose metabolism and lipid metabolism by decreasing the plasma triglyceride concentration.

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