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# Bifidus Fermentation Increases Hypolipidemic and Hypoglycemic Effects of Red Ginseng

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**Abstract** Antihyperlipidemic and antihyperglycemic effects of Red Ginseng (RG, steamed and dried root of *Panax ginseng* C.A.Meyer, family Araliaceae), major component of which is ginsenoside Rg3, and *Bifidodoterium*-fermented RG (FRG), major component of which is ginsenoside Rh2, were investigated. Orally administered RG and FRG potently reduced the serum triglyceride levels in corn-oil-induced hypertriglycemidemic mice as well as total cholesterol and triglyceride levels in Triton WR-1339-induced hyperlipidemic mice. Of the saponin and polysaccharide fractions of RG and FRG, the polysaccharide fraction inhibited postprandial blood glucose elevation of maltose- or starch-loaded mice and reduced the blood triglyceride levels in corn-oil-induced hypertriglycemidemic mice. The saponin fraction and its ginsenosides Rg3 and Rh2 reduced blood triglyceride and total cholesterol levels in Triton WR1339-induced hyperlipidemic mice. The inhibitory effect of FRG and its main constituents against hyperlipidemia and hyperglycemia in mice were more potent than those of RG. These findings suggest that hypolipidemic and hypoglycemic effects of RG can be enforced by Bifidus fermentation and FRG may improve hyperlipidemia and hyperglycemia.

**Keywords:** *Panax ginseng*, red ginseng, fermentation, hypolipidemic activity, hypoglycemic activity

Fermentation decomposes organic materials in the absence of air (oxygen). Some of these products (for example, alcohol and lactic acid) are of importance to humans, and fermentation has therefore been used for their manufacture on an industrial scale. These processes are performed by lactic acid bacteria, such as *Bifidobacterium* sp. and *Lactobacillus* sp., and some molds, such as *Saccharomyces* sp. [11, 16, 21, 28]. These microbes transform some components of foods as well as convert sugars to alcohol and lactic acid. For example, lactic acid bacterial fermentation of ginseng produces lactic acid as well as compound K, which is transformed from ginsenosides Rb1, Rb2, and Rc and exhibits potent cytotoxicity against tumor cells [2, 29].

Ginseng (root of *Panax ginseng* C.A. Meyer, family Araliaceae) is widely used in Asian countries as a traditional medicine for enhancing body strength, recovering physical balance, and stimulating metabolic function [1]. When it is steamed, it is called Red Ginseng (RG) [6]. RG contains polysaccharides and ginsenosides such as Rg3, Rb1, Rb2, and Rc as main constituents [17]. The ginsenoside Rg3, which is a representative constituent in RG, is produced from protopanaxadiol ginsenosides by steaming of raw ginseng. When RG is fermented by *Bifidobacterium* H-1, ginsenoside Rg3 is transformed to ginsenoside Rh2, which is a representative constituent in fermented RG (FRG) [3, 4]. Compared with ginsenoside Rg3, ginsenoside Rh2 exhibits potent cytotoxicity against tumor cells, antiallergic effect against mast cells, and antiinflammatory activity in microglial cells [4, 20, 23]. However, the antihyperlipidemic and antihyperglycemic effects of FRG and its constituents have been thoroughly studied.

Therefore, in the present study, RG was fermented by *Bifidobacterium* H-1, which is potently able to ferment RG and transform ginsenoside Rg3 to ginsenoside Rh2, and the hypolipidemic and hypoglycemic activities of RG and FRG investigated.

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## MATERIALS AND METHODS

### Materials

Triton WR-1339 and corn oil were purchased from Sigma Chemical (St. Louis, MO, U.S.A.). Cholesterol and triglyceride assay kits were from Asan Pharmaceutical Co. Ltd. (Korea). Orlistat (Xenical) and lovastatin were kindly donated by Dr. N. J. Kim of the Korea Herbal Research Institute, Kyung Hee Medical Center, Kyung Hee University, Korea.

### Preparation of KRG and F-KRG

RG was prepared by steaming the root of *Panax ginseng* C.A. Meyer (cultured for 4 years at Keumsan, Chungcheungnam-do, Korea) at 98–100°C for 4 h and dried for 5 h at 60°C. The RG was extracted with 70% ethanol, evaporated, and freeze-dried (yield 55%). The RG extract was fermented by *Bifidobacterium* H-1 as previously reported [5]. The fermented RG (FRG) was centrifuged at 10,000 ×*g* for 0.5 h, evaporated, and freeze-dried (yield 99%). The freeze-dried RG and FRG were stored at 4°C and used when necessary. The contents of ginsenosides Rb1, Rg3, and Rh2 in RG and FRG prepared in the present study were 0.67, 0.55, and 0.03% and 0.01, 0.13, and 0.83%, respectively. The ginsenoside contents were analyzed by HPLC according to a previously reported method [14]. The contents of their acidic polysaccharides were 13.4 and 12.1%, respectively. The polysaccharide contents were assayed by the method of Kim *et al.* [13].

### Preparation of Polysaccharide and Saponin Fractions and Isolation of Ginsenosides Rg3 and Rh2

RG and FRG (10 g) were dissolved in 100 ml of distilled water, extracted with BuOH three times, and the BuOH fractions were combined, evaporated, suspended in distilled water, and then freeze-dried. It was used as a saponin fraction. The residual water layer was precipitated by the addition of the same volume of cold ethanol. The precipitate was dissolved in distilled water and then dialyzed against water for 5 days. The dialysate was freeze-dried and then it was used as a polysaccharide fraction.

Ginsenosides Rg3 and Rh2 were isolated from RG and FRG, respectively, according to our previously reported method [3, 5].

### Animals

Male ICR mice (20–25 g) were purchased from Orient Charles River Co. (Republic of Korea). The mice were housed in wire cages at 20–22°C, with 50±10% humidity, fed a commercial diet (Orient Charles River Co., Republic of Korea), and allowed water *ad libitum*. These mice were kept for at least 7 days before experiments. All procedures relating to the animals and their care conformed to the International Guidelines for the Principles of Laboratory Animals Care (NIH publication no. 85–23, revised 1985) and Guiding Principles for the Care and Use of Laboratory Animals of Kyung Hee University, Korea.

### Hyperlipidemic Activity Assay

Male ICR mice (20–25 g) were purchased from Orient Charles River Co. (Republic of Korea) and fed a commercial diet (Orient Charles River Co., Republic of Korea). These animals were kept for at least 7 days prior to the experiments. To evaluate the hypolipidemic effect, two kinds of hyperlipidemic mouse models were established.

First, a hyperlipidemic model based on corn oil was established according to the method of Lee *et al.* [19]. Five mice were used per group. Corn oil (1 g/kg) was orally administered 2 h after each test sample was administered orally. Two hours after the administration of corn oil, blood samples of the mice were drawn by cardiac puncture under ether anesthesia.

Second, a hyperlipidemic model based on Triton WR-1339 was also established according to the method of Lee *et al.* [19]. Triton WR-1339 was injected at the end of the regular 16 h fasting period as a 10% solution in saline at a dose of 200 mg/kg body weight into the tail veins of mice under light ether anesthesia. Six mice were used per group. These mice were anesthetized with ether 18 h after Triton WR-1339 injection and 1–1.5 ml of blood was withdrawn by cardiac puncture. Sera were obtained by centrifugation (1,500 ×*g*, 10 min). Tested samples, lovastatin and orlistat, were administered orally once a day for 3 days. The final administration of the samples was performed 1 h before Triton WR-1339 injection. Serum cholesterol and triglyceride levels were measured using commercial assay kits.

### Hyperglycemic Activity Assay

A postprandial hyperglycemic mouse model was established according to the method of Choi *et al.* [7, 24]. Each group had 5 mice. All mice were fasted for 16 h and then substrate (maltose or starch) dissolved in distilled water was orally administered. Test samples and acarbose were orally administered. Individual substrates (maltose or starch) and samples dissolved in distilled water were injected orally. Before the administration of test samples and 30 min after their administrations, blood glucose levels were measured using an Accu-chek blood glucose meter (Roche, Diagnostic GmbH, Germany).

### Statistical Analysis

All the data were expressed as mean±standard deviation, and statistical significance was analyzed by one-way ANOVA followed by a Student-Newman-Keuls test.

## RESULTS

### Antihyperlipidemic Effect of RG and FRG

To evaluate the effect of fermentation on the hypolipidemic effect of RG, the antihyperlipidemic effect of RG and FRG in corn-oil-induced hypertriglyceridemic mice was investigated (Fig. 1). The oral administration of corn oil increased the serum triglyceride level, but did not elevate serum cholesterol levels. The treatment of RG and FRG significantly reduced the serum triglyceride level increased by corn oil. The polysaccharide fractions prepared from RG and FRG also reduced serum triglyceride levels (Table 1). The polysaccharide fraction from FRG more potently reduced the serum triglyceride level than that of RG. That of FRG at 50 mg/kg reduced the serum triglyceride level by 84%. However, saponin fractions of RG and FRG and their ginsenosides Rg3 and Rh2 did not exhibit the triglyceride-lowering effect.

The hypolipidemic effect of RG and FRG in Triton WR-1339-induced hyperlipidemic mice was also investigated (Fig. 2). The treatment of Triton WR-1339 significantly increased serum triglyceride and total cholesterol levels, but decreased the serum HDL-cholesterol level. The treatment of RG and FRG reduced serum triglyceride and total cholesterol levels, but increased the serum HDL-cholesterol level.

To understand the active components of RG and FRG, we also investigated the hypolipidemic effect of their saponin and polysaccharide fractions (Table 2). The saponin and polysaccharide fractions reduced serum triglyceride and total cholesterol levels. The saponin fractions of RG and FRG and ginsenosides Rg3 and Rh2 isolated from them also reduced serum triglyceride and total cholesterol levels. However, the polysaccharide fractions did not reduce serum total cholesterol level and weakly reduced the serum

**Table 1.** Effect of RG, FRG, and their constituents on serum triglyceride and total cholesterol in corn-oil-induced hypertriglyceridemic mice.

| Group | Dose (mg/kg) | Serum level (mg/dl) | |
|---|---|---|---|
| | | Triglyceride | Total cholesterol |
| Normal | - | 115.6±5.6[a] | 129.4±10.7 |
| Control | - | 165.6±4.6[#] | 135.7±14.4 |
| RG polysaccharide Fr | 10 | 144.1±20.6 | 140.5±15.2 |
| RG polysaccharide Fr | 20 | 122.3±16.3* | 132.0±17.6 |
| FRG polysaccharide Fr | 10 | 141.9±12.7 | 138.2±10.9 |
| FRG polysaccharide Fr | 20 | 123.4±13.8* | 131.6±15.2 |
| RG saponin Fr | 10 | 163.0±17.7 | 136.2±21.6 |
| RG saponin Fr | 20 | 177.3±20.5 | 133.5±10.3 |
| FRG saponin Fr | 10 | 147.3±21.6 | 140.3±16.3 |
| FRG saponin Fr | 20 | 157.7±21.0 | 127.4±17.9 |
| Ginsenoside $Rg_3$ | 10 | 164.3±15.8 | 136.6±15.5 |
| Ginsenoside $Rg_3$ | 20 | 174.5±18.7 | 132.1±12.8 |
| Ginsenoside $Rh_2$ | 10 | 144.8±18.0 | 133.7±16.4 |
| Ginsenoside $Rh_2$ | 20 | 151.3±23.9 | 129.4±21.7 |
| Xenical | 10 | 120.6±5.7* | 126.3±14.8 |

[#]Statistically significant compared with data of normal group ([#]$p<0.05$).
*Statistically significant compared with data of control group (*$p<0.05$).

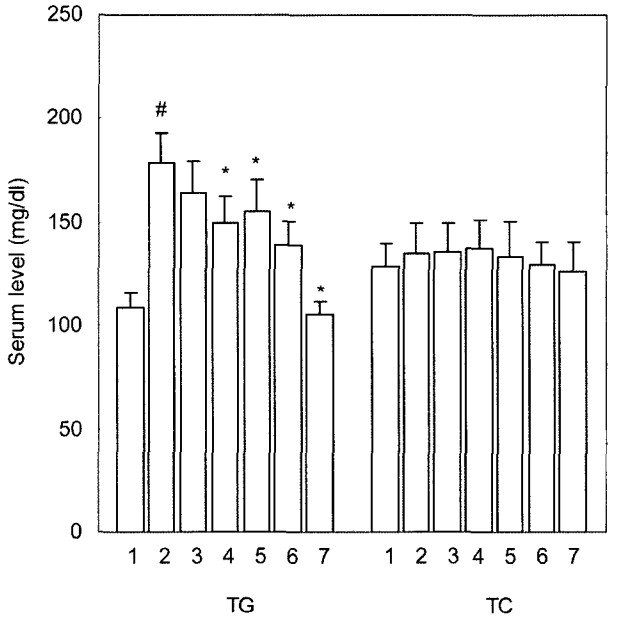


**Fig. 1.** Antihyperlipidemic effect of RG and FRG extracts on corn-oil-induced hypertriglyceridemic mice.
RG, FRG, or oristat (1, normal; 2, control; 3, 20 mg/kg of RGR; 4, 50 mg/kg of RG; 5, 20 mg/kg FRG; 6, 50 mg/kg of FRG; 7, xenical) were orally administered to hyerptriglyceridemic mice. [#]Significantly different compared with data of normal group ([#]$p<0.05$).*Significantly different compared with data of control group (*$p<0.05$).

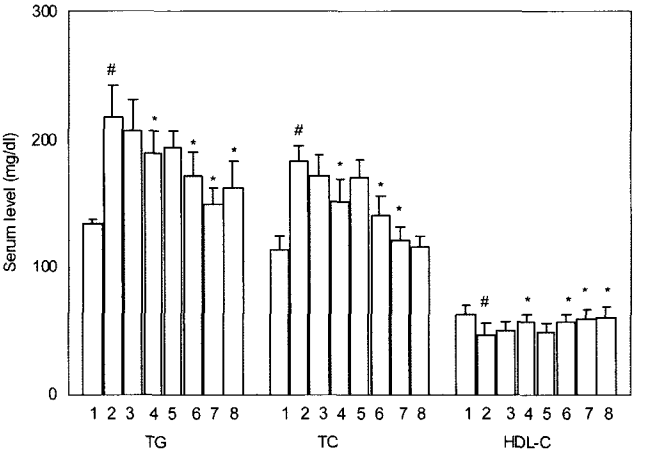


**Fig. 2.** Antihyperlipidemic effect of RG and FRG extracts on Triton WR1339-induced hyperlipidemic mice.
RG, FRG or oristat (1, normal; 2, control; 3, 20 mg/kg of RGR; 4, 50 mg/kg of RG; 5, 20 mg/kg FRG; 6, 50 mg/kg of FRG; 7, xenical; 8, lovastatin) were orally administered to hyerplipidemic mice. [#]Significantly different compared with data of normal group ([#]$p<0.05$).*Significantly different compared with data of control group (*$p< 0.05$).

**Table 2.** Effect of RG, FRG, and their constituents on serum triglyceride, total cholesterol, and high-density lipoprotein (HDL)-cholesterol in Triton WR-1339-induced hyperlipidemic mice.

| Group | Dose (mg/kg) | Serum level (mg/dl) | | |
|---|---|---|---|---|
| | | Triglyceride | Total cholesterol | HDL-cholesterol |
| Normal | – | 133.6±4.3 | 122.9±9.9 | 73.3±7.6 |
| Control | – | 217.6±25.6# | 205.0±14.9# | 48.5±7.0# |
| RG polysaccharide Fr | 10 | 199.0±30.3 | 202.4±16.7 | 50.9±7.5 |
| RG polysaccharide Fr | 20 | 207.2±24.3 | 195.2±24.7 | 53.9±8.6 |
| FRG polysaccharide Fr | 10 | 204.5±26.5 | 198.6±19.5 | 52.6±9.5 |
| FRG polysaccharide Fr | 20 | 212.6±30.7 | 200.5±21.9 | 54.7±9.1 |
| RG saponin Fr | 10 | 197.1±21.9 | 179.0±25.8* | 66.1±4.6* |
| RG saponin Fr | 20 | 172.4±19.0* | 164.7±24.7* | 69.4±11.0* |
| FRG saponin Fr | 10 | 192.3±16.7 | 175.7±22.0* | 66.0±9.1* |
| FRG saponin Fr | 20 | 160.3±20.5* | 151.8±15.8* | 71.8±12.7* |
| Ginsenoside $Rg_3$ | 10 | 187.2±26.2 | 180.8±21.9 | 62.1±13.3 |
| Ginsenoside $Rg_3$ | 20 | 167.1±17.0* | 154.5±17.8* | 72.8±15.3* |
| Ginsenoside $Rh_2$ | 10 | 185.3±20.9* | 172.9±18.0* | 67.2±11.0* |
| Ginsenoside $Rh_2$ | 20 | 156.7±13.8* | 144.9±11.2* | 74.2±12.6* |
| Lovastatin | 10 | 163.0±20.7* | 129.8±15.6* | 75.2±14.5* |
| Xenical | 10 | 149.5±14.0* | 139.5±15.5* | 71.4±15.7* |

#Statistically significant compared with data of normal group (#$p<0.05$).
*Statistically significant compared with data of control group (*$p<0.05$).

triglyceride level. Of the isolated ginsenosides, ginsenoside Rh2 more potently reduced the serum total cholesterol level, but more potently increased the serum HDL-cholesterol level than ginsenoside Rg3.

### Antihyperglycemic Effect of RG and FRG

To evaluate the effect of fermentation on the hypoglycemic effect of RG, the RG and FRG were orally administered to fasted mice, then maltose or starch were loaded, and the blood glucose levels were measured (Fig. 3). The RG and FRG extracts inhibited the increment of acute postprandial blood glucose levels in mice. RG and FRG more potently inhibited the increment of blood glucose levels in starch-loaded mice than in maltose-loaded mice. FRG more strongly lowered the blood glucose level compared with that of RG. In starch-loaded hyperglycemic mice, the inhibitory effect

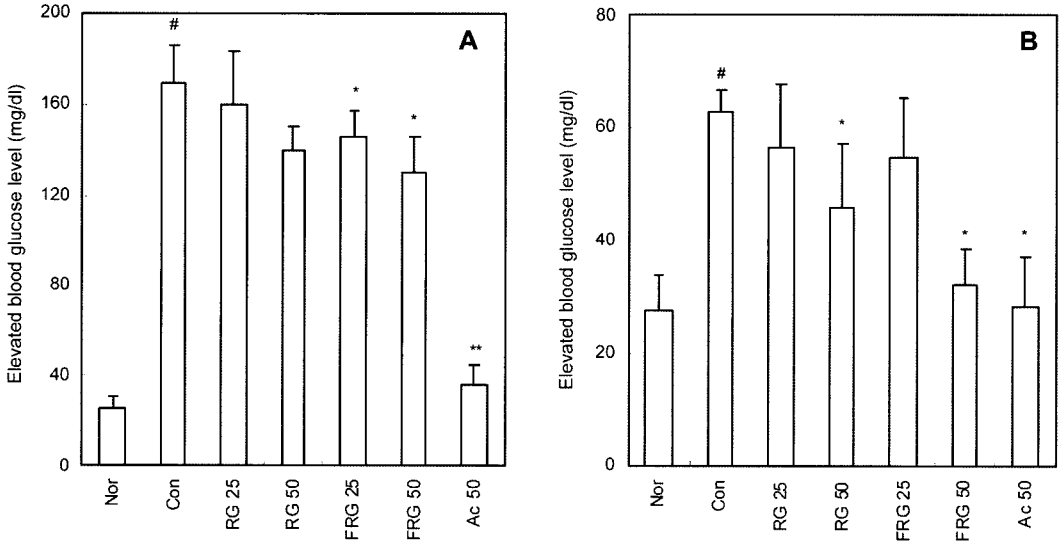


**Fig. 3.** Effect of RG and FRG extracts on postprandial blood glucose levels of maltose (**A**) or starch (**B**) loaded mice.
The samples (Con, control treated with vehicle; RG25, 25 mg/kg of RG; RG50, 50 mg/kg of RG; FRG25, 25 mg/kg of FRG; FRG50, 50 mg/kg of FRG; Ac 50, 50 mg/kg acarbose) were orally administered to sugar-loaded mice (Con). The normal group was treated with vehicle alone instead of sugar. #Significantly different compared with data of normal group (#$p<0.05$). *Significantly different compared with data of control group (*$p<0.05$).

**Table 3.** Inhibitory effect of RG, FRG, and their constituents on blood glucose elevation in maltose- or starch-loaded mice.

| Group | Dose (mg/kg) | Elevated blood glucose concentration (mg/dl) | |
|---|---|---|---|
| | | maltose | starch |
| Normal | - | 25.4±4.8 | 22.4±4.5 |
| Control | - | 169.0±16.8# | 61.2±8.3# |
| RG polysaccharide Fr | 10 | 152.2±18.9 | 47.4±7.2* |
| RG polysaccharide Fr | 20 | 120.8±14.0* | 37.6±7.5* |
| FRG polysaccharide Fr | 10 | 142.8±12.9 | 44.4±8.3* |
| FRG polysaccharide Fr | 20 | 109.8±13.2* | 32.2±8.4* |
| RG saponin Fr | 10 | 167.2±17.5 | 55.6±9.4 |
| RG saponin Fr | 20 | 137.2±21.5* | 50.4±10.4 |
| FRG saponin Fr | 10 | 148.2±21.4 | 55.4±10.8 |
| FRG saponin Fr | 20 | 133.6±21.1* | 50.0±11.6 |
| Ginsenoside $Rg_3$ | 10 | 155.8±25.7 | 55.4±9.5 |
| Ginsenoside $Rg_3$ | 20 | 146.6±24.3 | 50.0±8.5 |
| Ginsenoside $Rh_2$ | 10 | 152.4±29.3 | 51.8±6.0 |
| Ginsenoside $Rh_2$ | 20 | 138.0±26.1* | 48.2±11.7 |
| Acarbose | 10 | 82.6±9.2* | 47.0±7.7* |

#Statistically significant compared with data of normal group (#$p<0.05$).
*Statistically significant compared with data of control group (*$p<0.05$).

of FRG at a dose of 50 mg/kg was comparable with that of a commercial acarbose.

To understand what kinds of the constituents in RG could exhibit the hypoglycemic effect, the saponin and polysaccharide fractions from RG and FRG were prepared and their antihyperglycemic effects were measured (Table 3). Them, the oral administration of the polysaccahride fractions from RG and FRG showed a lowering effect of the blood glucose level in maltose- or starch-loaded mice compared with the control group. A main constituent, ginsenoside Rg3, from the saponin fraction of RG did not exhibit the lowering effect of the blood glucose level. However, ginsenoside Rh2 from that of RG had a weak lowering effect of the blood glucose level. Of the polysaccharides, the polysaccharide fraction of FRG more potently lowered the blood glucose level than RG, but the difference was not significant.

## DISCUSSION

Lipid metabolism normally maintains an elegant balance between synthesis and degradation [10]. When the balance is lost, hypertriglyceridemia and hypercholesterolemia may develop. This can cause a variety of serious diseases, such as arteriosclerosis, hypertension, obesity, diabetes, functional depression of some organs, etc. [9]. Diabetes mellitus is characterized by hyperglycemia. An abnormally elevated blood glucose level causes oxidative stress and is linked to diabetic complications affecting the eye, kidney, nerve, and blood vessels. Therefore, to prevent and cure arteriosclerosis and diabetes, inhibitors against hyperlipidemia and hyperglycemia have been developed, but improvement of these diseases is too difficult. Therefore, traditional herbal medicines have been developed against these diseases. Among them, the effectiveness of ginseng has received increasing attention.

Ginseng, which contains saponins and polysaccharides, has been used to help blood circulation, improve physical conditions, and extend life by its prolonged use as a traditional medicine and ingested daily at more than 1 g (>100 mg as saponin) per human. Recently, many researchers have attempted to certify its pharmacological effects. Recently, Waki *et al.* [30], Sievepiper *et al.* [26], and Sotaniemi *et al.* [27] reported that RG improved blood glucose and insulin regulation in non-insulin-dependent diabetic mellitus patients. Lee *et al.* [18] reported that ginsenoside Rh2, a main constituent of RG, increases insulin secretion in animal experiment. In addition, Oshima *et al.* [22] reported that panaxans from ginseng exhibited the lowering effect of blood glucose and liver glycogen. Nevertheless, the studies on the effective constituents of RG for hyperglycemia have not been thoroughly studied.

In this study, we investigated the inhibitory effect of RG and its polysaccharide and saponin fractions on the postprandial blood glucose level of sugar-loaded mice. Orally administered RG potently inhibited blood glucose elevation after loading with maltose or starch. The inhibitory effect of the polysaccharide fraction was stronger than the saponin fraction. To understand whether the hypoglycemic effect of RG can be increased by fermentation, we fermented RG by *Bifidobacterium* H-1 and investigated its antihyperglycemic effect. However, the hypoglycemic effects of the saponin and polysaccharide fractions isolated from RG and those of FRG have not been thoroughly studied.

To confirm whether or not ginsenosides of RG and FRG could exhibit the hypoglycemic activity, we isolated the representative constituent, ginsenoside Rg3 of RG and ginsenoside Rh2 of FRG, which was transformed from ginsenoside Rg3 by H-1 [5], and investigated their hypoglycemic effects. The ginsenoside Rg3 from the saponin fraction of RG did not lower the blood glucose level, but the ginsenoside Rh2 from that of RG weakly lowered it. Sievenpiper *et al.* [26] reported that RG improves non-insulin-dependent diabetic mellitus patients and Lee *et al.* [18] reported that ginsenoside Rh2 increases insulin secretion in animal experiment. These findings suggest that the hypoglycemic activity of RG and FRG may be due to the inhibition of blood glucose elevation by their polysaccharides and/or the stimulation of insulin secretion by their ginsenosides.

Kim *et al.* [15] reported that RG exhibited antihypercholesterolemia in humans. Ismail *et al.* [12]

reported that RG lowered blood cholesterol level in animal models. Cui *et al.* [8] reported that ginseng extract reduced blood total cholesterol and triglyceride levels in hepatectomized rats. Cho *et al.* [6] reported that ginsenoside Re exhibited a hypolipidemic effect in streptozotocin-induced diabetic rats. Rho *et al.* [25] reported that polyacetylenes from RG inhibited acyl-CoA cholesterol acyltransferase. Nevertheless, we could not understand what kinds of constituents in RG are effective for hyperlipidemia.

Therefore, we isolated saponin and polysaccharide fractions from RG and FRG and investigated their antihyperlipidemic effects. RG potently improved hyperlipidemia in corn-oil- or Triton WR-1339-induced mice. Therefore, to understand whether the hypolipidemic effect of RG can be increased by fermentation, those of RG and FRG were also investigatged. FRG showed a more potent hypolipidemic activity than RG. We separated saponin and polysaccharide fractions from RG and FRG and also investigated their antihyperlipidemic effects. The polysaccharide fractions of RG and FRG weakly reduced serum triglyceride in Triton WR-1339-induced hyperlipidemic mice, but potently inhibited serum triglyceride levels in corn-oil-induced hyperlipidemic mice. However, these polysaccharide fractions did not reduce serum cholesterol levels.

Saponin fractions of RG and FRG potently reduced serum tiglyceride and total cholesterol levels increased in Triton WR-1339-induced hyperlipidemic mice. The FRG saponin fraction more potently reduced the blood total cholesterol level and increased the blood HDL-cholesterol level. The isolated ginsenosides Rg3 and Rh2 also potently reduced serum total cholesterol and triglyceride levels. Of the ginsenosides, ginsenoside Rh2, which was transformed from ginsenoside Rg3, more potently improved hypercholesterolemia.

These findings suggest that the hypotriglyceridemic effect of polysaccharides of RG and FRG may be due to the inhibition of triglyceride absorption, and the hypocholesterolemic effect of the saponin fractions, particularly ginsenosides, may be due to the inhibition of biosynthesis of cholesterol and triglyceride, such as HMG-CoA reductase and acyl-CoA: cholesterol acyltransferase. In addition, RG, FRG, and their constituents saponins and polysaccharides did not significantly increase serum ALT and AST. Based on these findings, we suggest that the hypolipidemic and hypoglycemic effects of RG can be enforced by fermentation and FRG can improve hyperlipidemia and hyperglycemia.

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