Red ginseng powder fermented with probiotics exerts antidiabetic effects in the streptozotocin-induced mouse diabetes model

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ABSTRACT
Context: Red ginseng (heat-processed *Panax ginseng*) is a well-known alternative medicine with pharmacological antidiabetic activity. It exerts pharmacological effects through the transformation of saponin into metabolites by the intestinal microbiota. Given that intestinal conditions and intestinal microflora vary among individuals, the pharmacological effects of orally administered red ginseng likely may vary among individuals.

Objective: To overcome this variation and produce homogeneously effective red ginseng, we evaluated the antidiabetic effects of probiotic-fermented red ginseng in a mouse model.

Materials and methods: The antidiabetic efficacy of orally administered probiotic-fermented red ginseng was assessed in ICR mice after induction of diabetes using streptozotocin (170 mg/kg body weight). Samples were given orally for 8 weeks, and indicators involved in diabetic disorders such as body weight change, water intake, blood glucose, glucose tolerance and various biochemical parameters were determined.

Results: Oral administration of probiotic-fermented red ginseng significantly decreased the level of blood glucose of about 62.5% in the fasting state and induced a significant increase in glucose tolerance of about 10.2% compared to the control diabetic mice. Additionally, various indicators of diabetes and biochemical data (e.g., blood glycosylated haemoglobin level, serum concentrations of insulin, and α-amylase activity) showed a significant improvement in the diabetic conditions of the mice treated with probiotic-fermented red ginseng in comparison with those of control diabetic mice.

Discussion and conclusion: Our results demonstrate the antidiabetic effects of probiotic-fermented red ginseng in the streptozotocin-induced mouse diabetes model and suggest that probiotic-fermented red ginseng may be a uniformly effective red ginseng product.

Introduction
The incidence of diabetes mellitus, a typical metabolic disease, has been increasing recently. Diabetes is caused by an absolute (type 1 diabetes) or relative (type 2 diabetes) lack of insulin, and the continued hyperglycaemia due to diabetes causes abnormalities in lipid, protein, and sugar metabolism (Kannel & McGee 1979). It also causes various complications, including cardiovascular diseases, decreased renal function, atherosclerosis, blurred vision due to retinal bleeding, foot ulcers and peripheral neuropathies (Amos et al. 1997). Although it is difficult to ‘cure’ diabetes completely, controlling the level of blood glucose is possible. Thus, treating diabetes has focused on preventing diabetic complications and/or suppressing further development of the disease by controlling the level of blood glucose (Amos et al. 1997). Because the ability to fundamentally cure diabetes using insulin or oral hypoglycaemic agents is technically limited and because there are financial burdens as well as the side effects associated with the prolonged intake of medicines, the use of natural products with fewer side effects is strongly recommended. With advances in alternative medicine, there have been many studies on the effects of natural products on antidiabetic activity, and various functional foods for diabetes patients are under development (Oh et al. 2005; Han et al. 2010). In fact, a study conducted in the United States and Australia found that 34.5–48.5% of diabetes patients had used at least one ‘folk’ medicine along with other medications (MacLennan et al. 1996).

Red ginseng, which is acquired by steaming and then drying fresh ginseng *Panax ginseng*, is a functional food known to be effective in various applications. Its ability to improve the postprandial glucose levels in blood may be especially relevant to diabetes patients (Vuksan et al. 2000, 2008; Sievenpiper et al. 2006). Red ginseng contains various physiological substances, including the ginseng saponins (Sanada et al. 1974; Kimura et al. 2006). Red ginseng has been used as a functional food for diabetes patients (Yokozawa et al. 1985; Shin 2010). The saponin components of red ginseng are poorly absorbed into the body directly after administration; they are first converted to metabolites by...
intestinal microorganisms, such as *Bifidobacterium* spp., *Lactobacillus* spp., and *Saccharomyces* spp., which facilitate the major pharmacological action of red ginseng, although the efficiency of absorption varies depending on body conditions (Trinh et al. 2007; Yang et al. 2007; Liu et al. 2015). Although the metabolic processing of ginseng saponins by microbiota is complicated, and the possibility of further metabolism of fermented red ginseng by intestinal microbiota cannot be excluded, it can be assumed that the biological changes in red ginseng in the anerobic state are similar to those in the intestines, where intestinal microorganisms use fermentation to transform the components of red ginseng into final metabolites. Furthermore, fermentation of red ginseng may help in producing a uniformly effective product that is readily absorbed in a way that is independent of the individual’s intestinal condition (Kong et al. 2008). Fermentation is one technology capable of improving the physiological activity of natural products. For example, fermentation improves the functionality of green tea (Feng et al. 2002; Kuo et al. 2005; Lee et al. 2012). Additionally, it has been shown that the physiological activities of many natural goods are improved through fermentation (Kusznierekicz et al. 2008; Han et al. 2011). Thus, we prepared a probiotic-fermented red ginseng powder and confirmed its efficacy in diabetes mellitus in the streptozotocin (STZ)-induced diabetes mouse model.

**Materials and methods**

**Preparation of probiotic-fermented ginseng powder and experimental materials**

A commercial red ginseng extract powder was obtained from Kunbo Inc. (Jinan, Korea). The powder was suspended in water and fermented for 20 days with *Lactobacillus plantarum* (KPC11611P) at 35–40°C, then extracts were freeze-dried and administered orally. Qualitative analyses of the ginsenoside composition of the probiotic-fermented red ginseng was performed by high-performance liquid chromatography; changes in the ginsenoside composition before and after fermentation have been described previously (Jang et al. 2016). All chemicals were purchased from Sigma Chemical Co. (St. Louis, MO), unless otherwise specified.

**Experimental animals**

Six-week-old male ICR mice were purchased from Orient Bio, Inc. (Sungnam, Korea) and maintained under specific pathogen-free conditions with *ad libitum* access to food and water. Experimental procedures involving laboratory animals were approved by the Institutional Animal Care and Use Committee of the Chonbuk National University (Approval Number: CBU 2015-0004) and followed the guidelines suggested by the committee.

**Diabetes induction**

To set up the experimental insulin-dependent diabetes mellitus mouse model, we used the STZ-induced model. Usually, after fasting for 12 h, mice with an average body weight of 30 g were injected intraperitoneally with STZ (170 mg/kg body weight, a dose to induce diabetes in 85% of the treated mice) in 0.1 M citrate buffer (pH 4.0). At 4 days after STZ injection, the mice were fasted for 12 h, and blood was drawn from their tail vein; mice with glucose levels higher than 250 mg/dL were selected as diabetes-induced mice and were randomly assigned to the experimental groups.

**Animal experiments**

Experimental animals were divided into five groups with eight mice in each: the untreated group (Normal), the STZ-induced diabetic group (Control), the STZ-induced diabetic group treated with probiotics only (PB), the STZ-induced diabetic group treated with red ginseng (GS), and the STZ-induced diabetic group treated with probiotics-fermented red ginseng (GS+PB). The normal and control groups were given distilled water (DW), whereas the PB group was given 3 × 10^9 CFU of probiotics per mouse, and the GS and GS+PB groups were given 150 mg/kg body weight of red ginseng and probiotic-fermented red ginseng, respectively. All samples were orally given in 0.4 mL volume once per day for 8 weeks. During the experimental period, body weight and water intake were measured once every 7 and 3 days, respectively.

**Analysis of blood glucose and glucose tolerance levels**

Levels of blood glucose were measured once every 2 weeks using a blood glucose strip (Accu-Chek, Roche Diagnostics GmbH, Mannheim, Germany) after a 12 h fasting period. A glucose tolerance test was performed by measuring levels of blood glucose with the blood glucose strip at 15, 30, 45, 60, 90, 120, and 180 min after intraperitoneal administration of glucose solution (2 g/kg body weight) after a 12 h fasting period at the 8th week of the experimental period.

**Analysis of other indicators related to diabetes**

To measure the levels of glycated haemoglobin in blood, blood samples were collected at the 8th week of the experiment and injected into a glycated haemoglobin (HbA1c) analytical cartridge (Bio-Rad, Hercules, CA). The level of HbA1c was measured using the Bio-Rad Variant II Turbo system.

Levels of blood insulin were measured using a mouse insulin ELISA kit (ALPCo Diagnostics, Salem, NH) at the 8th week of the experiment with sera prepared from blood drawn from mice fasted for 12 h. The same sera samples were also used in the analysis of α-amylase concentrations using a QuantiChrom α-amylase assay kit (BioAssay Systems, Hayward, CA).

**Biochemical analyses of the sera**

To analyze serum components biochemically, samples were collected from the mice in the 8th week of the experiment after a 12-h fasting period. Sample analyses for various indicators, including levels of albumin, total protein, lactate dehydrogenase (LDH), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), creatinine, high-density lipoprotein (HDL), total cholesterol, triglyceride and blood urea nitrogen (BUN), were performed at the Green Cross Reference Lab. (Yongin, Korea).

**Statistical analysis**

Statistical analyses were performed using the SPSS software version 16.0 (San Rafael, CA). Results are presented as means ± standard deviations (SDs). To examine the statistical significance of
the results, analysis of variance (ANOVA) was performed, and differences were considered statistically significant when \( p \)-values between groups were <0.05.

**Results**

**Oral administration of probiotic-fermented red ginseng is effective in reducing increased water intake in mice with STZ-induced diabetes**

We observed changes in body weight in the experimental mice three times, once every 20 days after STZ-mediated diabetes induction (Figure 1(A)). Compared with the untreated group (Normal) of mice, which showed continued increases in body weight, the mice treated with probiotic alone (PB) had unchanged and consistent body weights. In contrast, the body weights of the mice treated with probiotic-fermented red ginseng (GS + PB) decreased slightly at the first measurement and quickly recovered to levels comparable to those of the PB group. However, the STZ-induced diabetes group (Control) showed decreased body weights that were about one-third of those of the normal group on day 60 after diabetes induction.

We next measured the amount of water intake, because increased water intake is a physiological characteristic of diabetes. As expected in a typical diabetic state, in the 8th week of the experiment, the amount of water consumed by a mouse in 5 days was increased significantly (\( p < 0.001 \)), by ~9-fold compared with that of normal untreated mice, in the control diabetic group. The amount of water intake in the GS group of mice was significantly lower (\( p < 0.05 \)) than that in the control diabetic group. More importantly, the amount of water intake in the GS + PB group was significantly lower to a large degree (\( p < 0.01 \)) than in the GS group (Figure 1(B)).

**Oral administration of probiotic-fermented red ginseng is effective in reducing increased levels of blood glucose and enhancing low glucose tolerance in the diabetic group of mice**

Blood glucose level is the most important indicator of diabetic status. To assess the effects of oral administration of GS + PB on diabetes, the level of blood glucose was determined (Figure 2(A)). The blood glucose level in the GS + PB group of mice was significantly lower (198.0 ± 85.6 mg/dL; \( p < 0.01 \)) compared with the increased blood glucose level (515.0 ± 74.1 mg/dL) observed in the control diabetic group of mice. In contrast, although it was relatively lower than that in the control diabetic group of mice, the blood glucose level of the PB group of mice was not reduced significantly.

We next measured how efficiently the high concentration of intraperitoneally introduced glucose was cleared from the blood (Figure 2(B)). Although blood glucose increased rapidly at 30 min after glucose injection in the normal group of mice, the level was significantly lower than that in control diabetic mice, and the level decreased rapidly to background levels. All mice, in which diabetes was induced, showed inefficient blood glucose clearance compared with the normal group. Importantly, blood glucose levels measured at 3 h after glucose injection were significantly lower (\( p < 0.05 \)) in the GS + PB group of mice versus in the control diabetic mice. However, blood glucose levels in the PB group of mice was similar to that in the control diabetic group during the test period.

**Oral administration of probiotic-fermented red ginseng is effective in reducing increased levels of HbA1c**

HbA1c represents glycated haemoglobin and the level of HbA1c increases when blood glucose level increases. We measured levels of HbA1c in the blood to assess the effects of GS + PB administration (Figure 3). The HbA1c blood level was increased significantly (\( p < 0.01 \)) in the control diabetic mice; in comparison, this level was significantly reduced (\( p < 0.01 \)) in the GS + PB-treated group. However, the PB-only-treated group of mice also showed significantly (\( p < 0.05 \)) reduced level of HbA1c compared with the control diabetic group of mice.

**Oral administration of probiotic-fermented red ginseng is effective in restoring blood insulin levels and a-amylase activity**

We next assessed the effects of the oral administration of GS + PB on the levels of blood insulin (Figure 4(A)). As shown in the figure, the level of blood insulin in the control diabetic group was significantly lower (\( p < 0.001 \)) than it was in the
normal untreated mice; this result was expected, because STZ
induction to induce diabetes is known to exert toxic effects on
insulin-producing \(\beta\)-cells. Importantly, although oral administra-
tion of GS\(^+\)PB significantly increased the levels of blood insulin
(\(p < 0.05\)), its ability to completely restore such levels seemed
somewhat limited, which might have been caused by STZ medi-
ated permanent damage to \(\beta\)-cells.

It is known that a low serum \(\alpha\)-amylase level is associated
with diabetes and that insulin restores the level of \(\alpha\)-amylase
(Kim et al. 1990; Lee et al. 2011). The level of blood \(\alpha\)-amylase
in control diabetic mice was significantly (\(p < 0.05\)) lower than
that in the normal untreated mice (Figure 4(B)). Additionally,
oral administration of GS + PB restored the level of \(\alpha\)-amylase to
a significant extent (\(p < 0.05\)).

**Oral administration of probiotic-fermented red ginseng is
effective in restoring various biochemical indicators
associated with diabetes**

We next performed biochemical analysis on various parameters,
including albumin, total protein, LDH, GOT, GPT, creatinine,
HDL, total cholesterol, and triglycerides. The level of GOT in the
control diabetic mice (874 ± 128 U/L) was significantly
(\(p < 0.05\)) than in the normal untreated group of mice
(606 ± 120 U/L); the latter level was significantly higher (\(p < 0.01\))
than it was in the GS + PB-treated group of mice (371 ± 143 U/L).
Similarly, the GPT level in the control diabetic group of mice
(725 ± 395 U/L) was significantly higher (\(p < 0.05\)) than that in
the normal untreated mice (170 ± 128 U/L). Most other indicators that were changed in the
control diabetic mice in comparison with the normal untreated
mice were restored to levels similar to those in the normal mice
after oral administration of GS + PB (data not shown). Finally,
we performed a BUN accumulation experiment, as BUN is an
indicator of renal function (Figure 5). The BUN blood levels in
control diabetic mice were significantly higher (\(p < 0.05\)) than
those in the normal untreated mice; the BUN level was signifi-
cantly (\(p < 0.05\)) decreased in the groups that received oral GS
and GS + PB, whereas there was no significant difference in the
PB-only-treated mice.

**Discussion**

STZ, a nitrosourea alkylating agent that has been used as a dia-
abetes inducer (Evans et al. 1965; Junod et al. 1967), selectively
destroyes \(\beta\)-cells, which, in turn, decreases the level of insulin in the
body and inhibits normal sugar metabolism, resulting in the
characteristic symptoms of hyperglycaemia. We used STZ to
induce type I diabetes in mice and assessed the functioning of
\(\beta\)-cells in STZ-mediated diabetes-induced mice by measuring
body weight, water intake, blood glucose, glucose tolerance,
blood serum insulin, \(\alpha\)-amylase and various biochemical indica-
tors. Additionally, the influence of oral administration of pro-
biotic-fermented red ginseng (GS + PB) on these indicators was
assessed to confirm the antidiabetic effect of this substance,
including its ability to produce a uniformly effective red ginseng
treatment of hyperglycaemia given that such levels reflect the HbA1c blood levels indicate the long-term effectiveness of this (Figure 2(B)). Moreover, data regarding the suppression of efficacy of GS product (Figure 2(A)). Glucose tolerance tests also confirmed the induced diabetes animal model, suggesting that, similar to red ginseng, this substance may be useful as an anti-hyperglycaemic related to fat and sugar metabolism in normal mice. These studies also reported that a diet with cultured ginseng powder lowers blood glucose levels in STZ-induced diabetic mice (Ng & Yeung 1985; Lee et al. 1997, 2003). Our current study confirmed that GS + PB effectively lowered blood glucose levels in the STZ-induced diabetes animal model, suggesting that, similar to red ginseng, this substance may be useful as an anti-hyperglycaemic product (Figure 2(A)). Glucose tolerance tests also confirmed the efficacy of GS + PB as an anti-hyperglycaemic product (Figure 2(B)). Moreover, data regarding the suppression of HbA1c blood levels indicate the long-term effectiveness of this treatment of hyperglycaemia given that such levels reflect the progression of diabetes over a 1–3-month period (Figure 3). Additionally, it has been reported that a 1% reduction in HbA1c decreases the occurrence of diabetic complications, such as myocardial infarction, by 14% and that of microvessel disease, such as retinopathy, by 37% (Stratton et al. 2000). Thus, it can be concluded that long-term blood glucose control is possible through taking GS + PB to reduce the dangers of diabetic complications.

The most important hormone in controlling sugar metabolism is insulin, which is produced by β-cells. Additionally, in diabetes, the mRNA available for α-amylase production in the exocrine acini of the colon decreases, thereby decreasing the synthesis of α-amylase; it has been reported that injection of insulin into diabetic mice increases the colonic excretion of α-amylase (Williams & Goldfine 1985). We observed that the level of insulin, which controls blood sugar levels, was increased significantly in the group receiving oral administration of GS + PB in comparison with in the control diabetic group (Figure 4(A)). Moreover, α-amylase secretion was increased significantly in the group receiving the oral administration of GS + PB compared with in the control diabetic group (Figure 4(B)). These results suggest that GS + PB positively affects the production of insulin by stimulating β-cells in the colon and improves sugar metabolism in peripheral tissues, thereby causing a sharp decline in blood glucose levels.

The main pharmaceutical component of ginseng is saponin, which is also known as ginsenoside. However, ginseng also has various non-saponin pharmacological components including acidic polysaccharides, polyacetylenes such as panaxyl, and organic compounds such as maltol. Parts of these components undergo chemical changes during the manufacturing process, generating saponin and other bioactive components (Christensen 2009). The saponin in ginseng is mostly malonyl-ginsenoside, and malonic acid is released from malonyl-ginsenoside, leaving trace saponins including Rg3, Rg2, Rh2, Rs1, Rs2 and Rh4. Although red ginseng goes through the same pharmacological changes and is not entirely different from ginseng, some reports have shown that the efficacy of red ginseng for enhancing blood
circulation, cancer suppression, and defence against various infections is superior to that of ginseng (Sung et al. 2009; Nam 2005). Interestingly, fermentation of red ginseng with probiotics reduces the total concentration of ginsenosides about 30%, suggesting that the fermentation process may aid the absorption of red ginseng by the intestine (Jang et al. 2016). Notably, the concentration of Rg3, which is a crucial component in the antidiabetic activity of red ginseng, increased about 3-fold after fermentation (Kang et al. 2013; Kim et al. 2015).

Conclusion
This study confirmed that GS + PB has an antidiabetic effect, as the results of our experiments confirmed improvements in the typical symptoms of diabetes, including increases in blood glucose levels, body weight loss, increased HbA1c, and decreased insulin density and ß-amylase activity, in STZ-induced diabetic mice. Additionally, the experiments showed that oral administration of GS + PB improved serum lipid levels and decreased levels of BUN in the blood. GS + PB may be particularly effective in decelerating the progression toward heart failure caused by diabetes by preventing the accumulation of BUN. Taken together, our results suggest that GS + PB may be useful for alleviating diabetic symptoms and can be used as a uniformly effective red ginseng product.

Disclosure statement
The authors have no conflict of interest to declare.

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