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Effect of ginsam, a vinegar extract from *Panax* ginseng, on body weight and glucose homeostasis in an obese insulin-resistant rat model

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Abstract

Extracts of ginseng species show antihyperglycemic activity. We evaluated the antihyperglycemic and antiobesity effects of ginsam, a component of *Panax* ginseng produced by vinegar extraction, which is enriched in the ginsenoside Rg3. Otsuka Long-Evans Tokushima Fatty rats, an obese insulin-resistant rat model, were assigned into 1 of 3 groups (n = 8 each): controls (isotonic sodium chloride solution, 5 mL/d), rats given 300 mg/(kg d) ginsam, and rats given 500 mg/(kg d) ginsam. An intraperitoneal 2-hour glucose tolerance test was performed at the end of the 6-week treatment. After 8 weeks, body and liver weights, visceral fat measured by computed tomography, and fasting glucose and insulin concentrations and lipid profiles were recorded. Insulin-resistant rats treated with ginsam had lower fasting and postprandial glucose concentrations compared with vehicle-treated rats. Importantly, overall glucose excursion during the intraperitoneal 2-hour glucose tolerance test decreased by 21.5% ($P < .01$) in the treated rats, indicating improved glucose tolerance. Plasma insulin concentration was significantly lower in ginsam-treated rats. These changes may be related to increased glucose transporter 4 expression in skeletal muscle. Interestingly, when the data from both ginsam-treated groups were combined, body weight was 60% lower in the ginsam-treated rats than in the controls ($P < .01$). Liver weight and serum alanine aminotransferase concentrations were also lower in the ginsam-treated rats. These effects were associated with increased peroxisome proliferator–activated receptor γ expression and adenosine monophosphate–activated protein kinase phosphorylation in liver and muscle. Our data suggest that ginsam has distinct beneficial effects on glucose metabolism and body weight control in an obese animal model of insulin resistance by changing the expression of genes involved in glucose and fatty acid metabolism.

1. Introduction

Traditionally, ginseng is believed to improve health and increase metabolism, particularly by Asian populations. *Panax* ginseng has several pharmacologic and physiologic effects that are being disclosed gradually. Various clinical and pharmacologic effects associated with its use have been reported, such as anticancer activity, protection against circulatory shock, promotion of hematopoiesis, and modulation of immune functions and cellular metabolic processes involving carbohydrates, fats, and proteins [1-4].

Ginseng has saponin and nonsaponin components. The saponin fraction comprises a dammarane backbone with several side chains, including glucose, arabinose, xylose, and rhamnose [5]. This is termed *ginsenoside-Rx* according to the polarity of its side chains (Fig. 1). Ginsenoside, which is considered the biologically active fraction of *Panax* ginseng, is a mixture of triterpene glycosides. The major components of ginsenosides belong either to the protopanaxadiol or protopanaxatriol groups [6].

White ginseng has 4 specific ginsenosides that have malonyl chains. In contrast, red ginseng has 13 specific

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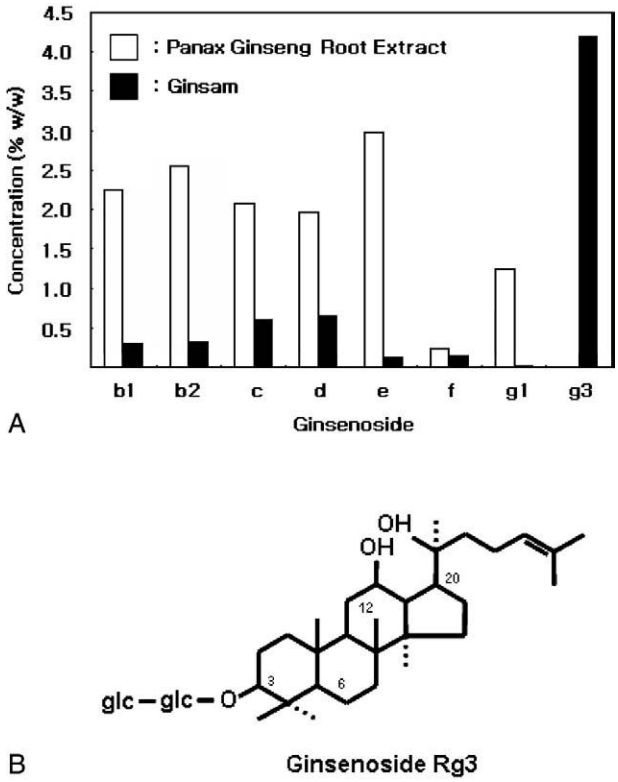

Fig. 1. Comparison of ginsenoside concentration between common *Panax* ginseng root extract and ginsam (upper panel). Chemical structure of the ginsenoside Rg3 (lower panel).

ginsenosides, such as Rg3, Rg5, and Rh1. In particular, the saponin fraction of Korean red ginseng has shown antioxidant, antinociceptive, and anticancer effects in in vitro and in vivo experiments [1,7-10]. In addition, ginsenosides from *Panax* ginseng decrease blood pressure in animals and humans with hypertension [11,12]. The blood pressure–lowering effect of ginsenosides is thought to be associated with the inhibition of vascular tone and induction of nitric oxide synthase [11].

Several clinical and laboratory studies support the claim that *Panax* ginseng and other ginseng species (eg, *Panax quinquefolium* or American ginseng) possess antihyperglycemic activity [1,13-16]. One study showed that 12 weeks of treatment with rootlets of Korean red ginseng decreases postchallenge glucose concentration and increases insulin sensitivity [13]. However, because hemoglobin A_{1c} level did not change, further research is needed to investigate the clinical efficacy.

Two studies showed that ginseng berry extracts exhibit potent antihyperglycemic and antiobesity effects in obese animal models [17,18]. Interestingly, a recent study showed that a wild ginseng ethanol extract had preventive effects against diabetes and obesity [19]. However, these studies did not investigate the mechanisms responsible for the antidiabetic or antiobesity effects of ginseng. In addition, whether the enrichment of a ginsenoside component might produce significantly more potent antihyperglycemic or weight-lowering activity than other extracts has not been explored. Thus, identifying the active compounds of ginseng with antihyperglycemic or antiobesity activities may provide an opportunity to develop a new class of antidiabetic agent.

Prosapogenin, a hydrolyzed form of saponin, has been shown recently to be a biologically more active compound [11]. In a preliminary study, we used vinegar extraction to produce ginsam, which is enriched in the ginsenoside Rg3, from *Panax* ginseng (Fig. 1). We found that ginsam reduced glucose concentration and body weight, but the sample size was small. The purpose of the current study was to assess the effect of ginsam on body weight and glucose homeostasis in an obese animal model of type 2 diabetes mellitus using Otsuka Long-Evans Tokushima Fatty (OLETF) rats.

2. Materials and methods

2.1. Animals

Twenty-four 5-week–old male OLETF rats, an obese animal model of insulin resistance, were donated by the Otsuka Pharmaceutical (Tokushima, Japan). They were allowed to grow to 24 weeks of age, when obesity and insulin resistance develop. The OLETF rats were held in the Preclinical Laboratory of Seoul National University for the study duration. All animals were handled in compliance with the Guide for Experimental Animal Research of the Laboratory, Clinical Research Institute, Seoul National University Hospital.

We divided the OLETF rats into 3 groups (n = 8 each): controls (isotonic sodium chloride solution, 5 mL/d), rats given 300 mg/kg of ginsam per day (GS300), and rats given 500 mg/kg of ginsam per day (GS500). Rats were fed with ginsam extract or isotonic sodium chloride solution for 8 weeks using an oral Zonde needle (Natsume, Tokyo, Japan) at 9:00 AM to 10:00 AM. No irritability or restlessness was observed after drug or vehicle administration. No noticeable adverse effects (eg, respiratory distress, abnormal locomotion, or catalepsy) were observed in any animals after the drug or vehicle treatment. All rats were maintained in plastic cages in an air-conditioned room at 22°C ± 2°C and 55% ± 10% humidity.

2.2. Measurements of diet and water consumption

The animals were all allowed free access to water and a pellet diet (Han Sam R&D, Seoul, Korea). Diet and water consumption was measured twice a week during the study period.

2.3. Measurements of obesity

2.3.1. Total body weight and liver weight

Rats were weighed twice a week at the same time in the morning. After sacrifice at the study end point, liver weight was measured for each rat.

2.3.2. Abdominal obesity

Visceral fat can be assessed in rats by computed tomography (CT) and is significantly correlated with

insulin sensitivity [20-22]. The visceral fat areas were quantified by a noncontrast CT scan (Somatom Sensation 16; Siemens, Munich, Germany). The relevant parameters were 120 kV (peak), 150 mA, 3-mm slice thickness, and 3-mm reconstruction interval under 1.8% to 2% isoflurane in O_2 anesthesia at the study end point. With the rats in a supine position, CT slice scans were acquired at the upper margin of the L3 vertebra to measure the amount of abdominal and visceral fat at a single level. Adipose tissue attenuation was determined by measuring the mean value of all pixels within the range of −250 to −50 HU. The images were converted into files compatible with a commercial software program (Rapidia; 3DMED, Seoul, Korea). To assess visceral adipose tissue volume, each abdominal image was edited by erasing the image exterior to the innermost abdominal wall muscles with a mouse-driven cursor; and the resulting images were saved in separate files. The amount of visceral fat was calculated by a radiologist.

2.4. Biochemical parameters

After the rats had fasted for 12 hours overnight at the study end point, rats were killed with a lethal dose of pentobarbital; and blood samples were drawn from the abdominal aorta. Plasma was separated immediately by centrifugation (3000 rpm, 10 minutes, at 4°C). Total cholesterol and triglyceride concentrations were determined by enzymatic procedures (Hitachi 747 chemistry analyzer; Hitachi, Tokyo, Japan). Plasma glucose concentration was measured using a glucose oxidase method (YSI 2300-STAT; Yellow Springs Instrument, Yellow Springs, OH) immediately after the blood was drawn. Serum insulin concentration was measured using insulin-specific radioimmunoassay kits (Linco, St Louis, MO). The homeostasis model assessment insulin resistance index (HOMA-IR) and β-cell function (HOMA-β) were measured to evaluate insulin resistance and pancreatic β-cell function.

2.5. Characterization of glucose metabolism

Fasting glucose concentration was measured after a 10-hour fast at baseline (0) and after 7, 14, 21, 28, 35, 42, 49, and 56 days. Postprandial glucose concentration was measured 2 hours after refeeding on days 3, 10, 17, 24, 31, 38, 45, and 52. Rats were subjected to an intraperitoneal glucose tolerance test (IPGTT) after the 6 weeks of treatment. After the 12-hour fasting glucose concentration was measured, each animal was injected intraperitoneally with 1.5 g/kg of a 50-mol/L glucose solution. Blood samples (about 10 μL) were collected from an incision in the tail at 30, 60, 90, and 120 minutes after the glucose load. Plasma glucose concentration was measured using reagent strips read in a glucose meter (YSI 2300-STAT). The area under the curve for glucose ($AUC_{glucose}$) was calculated using the trapezoid rule for glucose data from 0 to 120 minutes.

2.6. Immunoblot assays for peroxisome proliferator–activated receptor γ, phosphospecific adenosine monophosphate–activated protein kinase, and glucose transporters in liver and muscle

Liver and muscle (gastrocnemius muscle) tissues were harvested at the end of the study and subjected to immunoblotting analysis. Tissue samples were homogenized in lysis buffer, and the protein concentration was determined using a protein assay kit (Pierce Biotechnology, Rockford, IL). Proteins (20-μg aliquots) were separated on a sodium dodecyl sulfate–polyacrylamide electrophoresis gel and transferred to a polyvinylidene difluoride membrane (Millipore, Billerica, MA). The membrane was blocked with phosphate-buffered saline plus 0.3% Tween-20 containing 5% dry milk and incubated with primary antibody overnight at 4°C. After 3 washes with phosphate-buffered saline plus 0.3% Tween-20, the membrane was reblocked and incubated with secondary antibody for 1 hour at room temperature. The primary antibodies used were anti–peroxisome proliferator–activated receptor (PPAR) γ antibody (1:500 dilution; Santa Cruz Biotechnology, Santa Cruz, CA), anti–phosphospecific adenosine monophosphate–activated protein kinase (AMPK) antibody (1:100 dilution, Santa Cruz Biotechnology), anti–glucose transporter (GLUT) 1 antibody (1:1000 dilution, Santa Cruz Biotechnology), anti–GLUT2 antibody (1:500 dilution; Chemicon, Temecula, CA), and anti–GLUT4 antibody (1:500 dilution, Santa Cruz Biotechnology). The secondary antibody was horseradish peroxidase–conjugated antirabbit immunoglobulin G (1:4000 dilution; Promega, Madison, WI). Band density was quantified using a densitometer (Bio Image analyzer, CN-115, ETX-20MX, Marne-La-Valle, France) and normalized to that of β-actin or total AMPK.

2.7. Statistical analysis

Data are expressed as the mean ± SD. All data were found to have a normal distribution by probability-probability plot. Significant differences between groups were evaluated using Student *t* test and analysis of variance (ANOVA) with Tukey post hoc test. Associations between variables were analyzed using Pearson correlation. Differences were considered significant at P less than .05.

3. Results

3.1. Weights of total body and liver

During the study, weight gain tended to be lower in the ginsam-treated groups than in controls (Fig. 2A). This lesser weight gain was apparent in the first 2 to 3 weeks of the study and persisted to the study end point. At the study end point, compared with the control group, the mean body weight was 38.8 g (5.7%, $P = .045$) lower in the GS300 group and 43.0 g lower (6.3%, $P = .029$) in the GS500 group. When comparing the weight change from baseline to the study

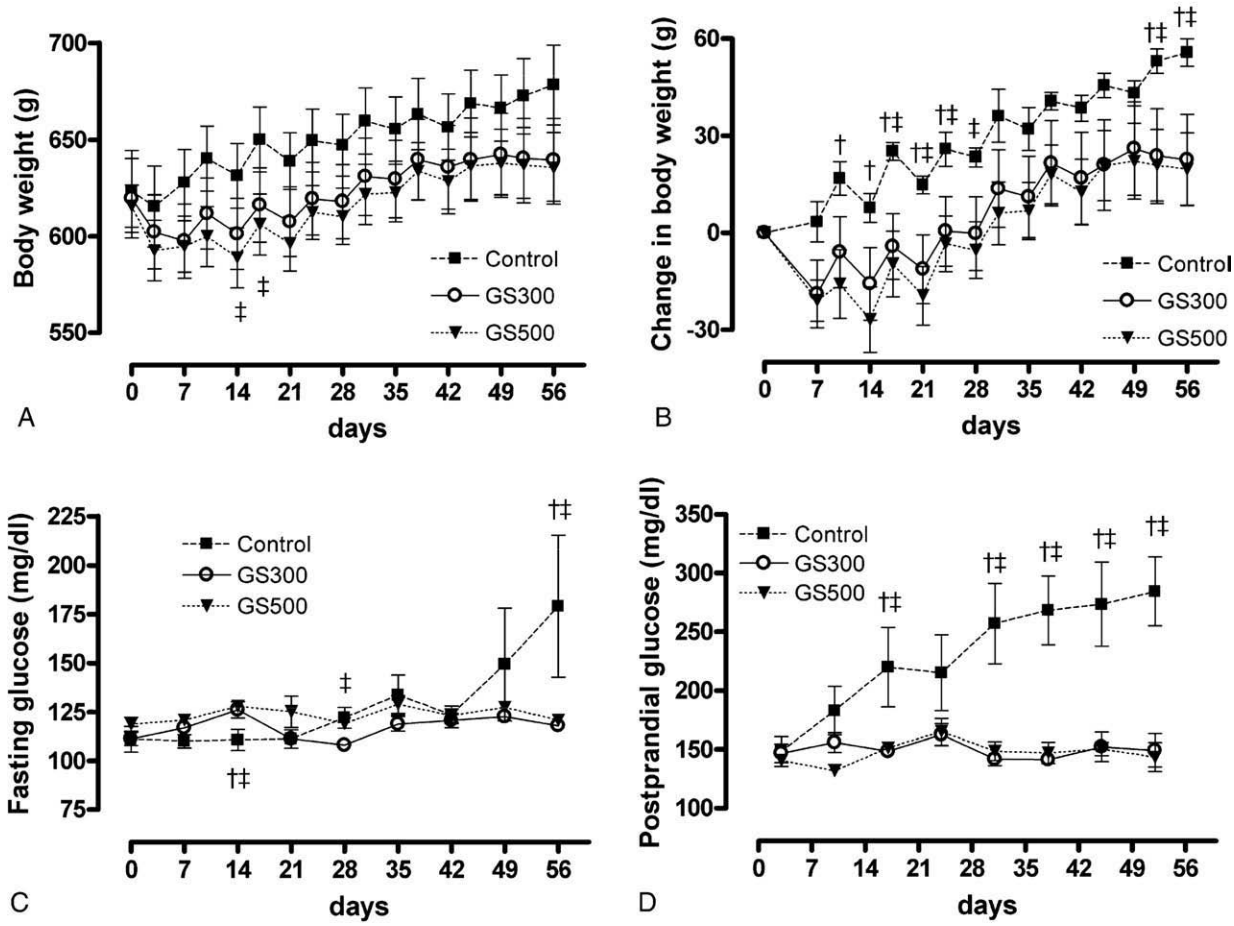

Fig. 2. Body weight (A), change in body weight (B), fasting glucose (C), and postprandial glucose concentrations (D) over the study period. $^{\dagger}P < .05$ control vs GS500; $^{\ddagger}P < .05$ control vs GS300.

end point, weight gains were more than 60% lower in the GS300 or GS500 group than in the control group ($P < .05$) (Table 1 and Fig. 2B). In addition, the mean ± SD weights of the liver were significantly lower in the ginsam-treated rats than in the controls: 10.66 ± 1.09 g in the GS300 group and 9.68 ± 0.56 g in the GS500 group vs 12.78 ± 0.94 g in the control group (both $P < .05$). There was a nonsignificant trend for reduced food intake in the ginsam-treated groups compared with the controls (control = 30.3 g/d, GS300 = 28.8 g/d, and GS500 = 29.6 g/d; $P = .132$).

3.2. Measurement of visceral fat amount

The GS300 and GS500 rats tended to have lower visceral fat content measured at the L3 level by CT than the controls, with borderline significance ($.05 < P < .1$) (Table 1).

3.3. Glucose concentration

Fasting glucose concentration increased in the control group from the seventh week, but there was no such increase in the ginsam-treated groups (Fig. 2C). At the study end point, 4 control rats, 0 GS300 rat, and 1 GS500 rat had a glucose concentration greater than 130 mg/dL. The 2-hour postprandial glucose concentration increased substantially from the second week to the study end point in the control group, but not in the ginsam-treated groups, whose glucose concentrations were maintained at around 150 mg/dL (Fig. 2D).

3.4. Biochemical parameters at the end of treatment

Total cholesterol and high-density lipoprotein cholesterol concentrations were lower in the ginsam-treated groups than in the controls, but triglyceride concentration did not differ significantly between groups (Table 1). The ginsam-treated groups tended to have lower low-density lipoprotein cholesterol concentrations than the controls, but this was not significant.

Fasting plasma glucose concentration and the HOMA-IR values were lower in the ginsam-treated groups than in the controls ($P < .05$). The mean fasting plasma insulin concentration was lower in the GS300 group than in the control group ($P < .05$). The HOMA-β values did not differ significantly between the 3 groups at the end of the treatment. Liver enzyme activities, particularly alanine aminotransferase (ALT), were lower in the ginsam-treated rats than in the controls ($P < .05$).

Table 1
Body weight, visceral fat, biochemical parameters, and insulin resistance index in an obese rat model of insulin resistance at the end of 8 weeks of ginsam treatment

	Control	GS300	GS500	P*
Weight (g)	678.3 ± 20.7	639.5 ± 21.5	635.3 ± 18.6	
Weight change from baseline (g)	55.7 ± 4.2	22.6 ± 14.0	19.6 ± 11.2	A,B
Visceral fat (mm^2)	4952.8 ± 310.6	4319.7 ± 330.6	4123.0 ± 414.5	
Fasting glucose (mg/dL)	179.0 ± 88.7	118.0 ± 5.1	120.8 ± 8.0	A,B
Fasting insulin (pg/mL)	379.8 ± 165.5	238.1 ± 51.4	284.8 ± 57.7	A
HOMA-IR	190.0 ± 159.2	69.1 ± 13.3	85.2 ± 19.9	A,B
HOMA-β	1458.1 ± 533.3	1587.1 ± 474.6	1795.6 ± 365.3	
Total cholesterol (mg/dL)	111.7 ± 12.1	98.4 ± 6.7	93.0 ± 12.9	A,B
Triglyceride (mg/dL)	149.5 ± 80.7	151.9 ± 57.4	101.8 ± 39.7	
HDL cholesterol (mg/dL)	31.0 ± 2.4	27.6 ± 2.1	26.0 ± 3.0	A,B
LDL cholesterol (mg/dL)	50.8 ± 12.2	40.5 ± 9.1	46.7 ± 8.5	
AST (IU/L)	98.3 ± 40.0	70.4 ± 13.4	64.5 ± 24.1	B
ALT (IU/L)	71.3 ± 22.6	42.3 ± 10.4	33.6 ± 8.5	A,B

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase.
* ANOVA and post hoc test were used: A and B; mean significant difference between 2 groups: A = control vs GS300, and B = control vs GS500 ($P < .05$ in all cases).

3.5. IPGTT at the end of 6-week treatment

Glucose values were significantly lower in GS500 rats than controls at all times during the 120-minute IPGTT study. Mean glucose concentration was nonsignificantly lower in the GS300 group than in the controls. The glucose concentration at 120 minutes of the IPGTT was lower in the GS300 group than in the controls, with borderline significance ($P = .059$). The glucose concentration tended to be lower in the GS500 group than in the GS300 group, but this was not significant except for the value at 30 minutes, which showed a lower glucose concentration in GS500 rats than in GS300 rats (Fig. 3A). Ginsam treatment improved glucose intolerance, as indicated by the decreased $AUC_{glucose}$ after the IPGTT (Fig. 3B).

3.6. Protein expression of PPARγ and GLUTs and phosphorylation of AMPK

Western blot analysis performed after 8 weeks of treatment with ginsam showed a marked increase in the protein levels of PPARγ and phosphorylation of AMPK in liver and gastrocnemius muscle in the GS300 and GS500 groups compared with the control group; this increase was dose dependent (Fig. 4). In addition, ginsam produced a dose-dependent decrease in GLUT2 expression in liver and increase in GLUT4 expression in muscle. Glucose transporter 1 expression did not differ between groups in the liver or muscle tissues.

4. Discussion

We found that ginsam, which is enriched in the ginsenoside Rg3 from a *Panax* ginseng, had a glucose-lowering and antiobesity effect and improved insulin resistance in an obese rat model of prediabetes. The GS300 and GS500 groups gained significantly less weight than the controls. This difference in weight gain was apparent within the first 2 to 3 weeks of ginsam treatment and persisted to the study end point.

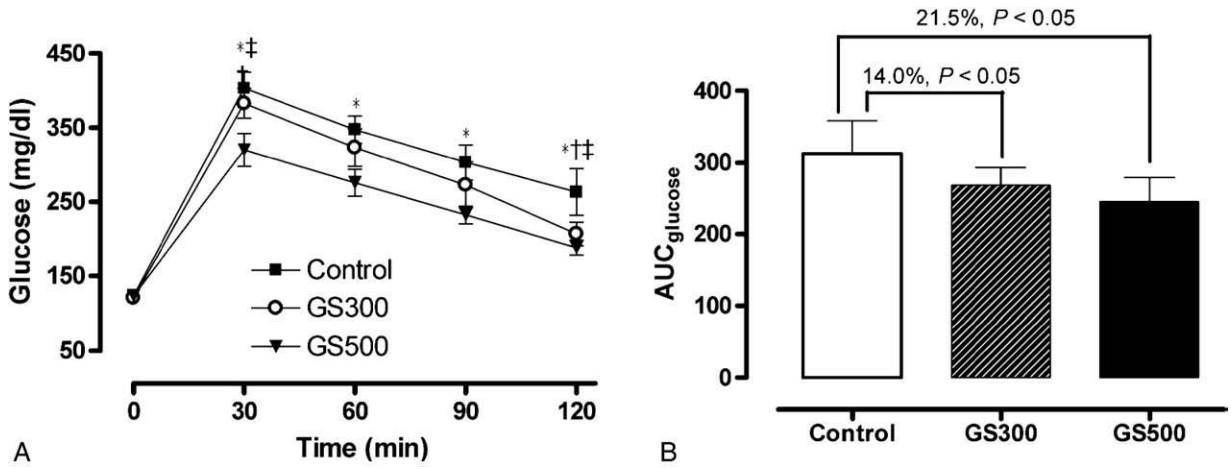

Fig. 3. Glycemic profiles (A) and $AUC_{glucose}$ (B) of ginsam-treated and control rats measured by IPGTT at the end of the 6 weeks of treatment. *$P < .05$ control vs GS500; †$.05 < P < .1$ control vs GS300; ‡$P < .05$ GS300 vs GS500 (ANOVA and Tukey post hoc comparison).

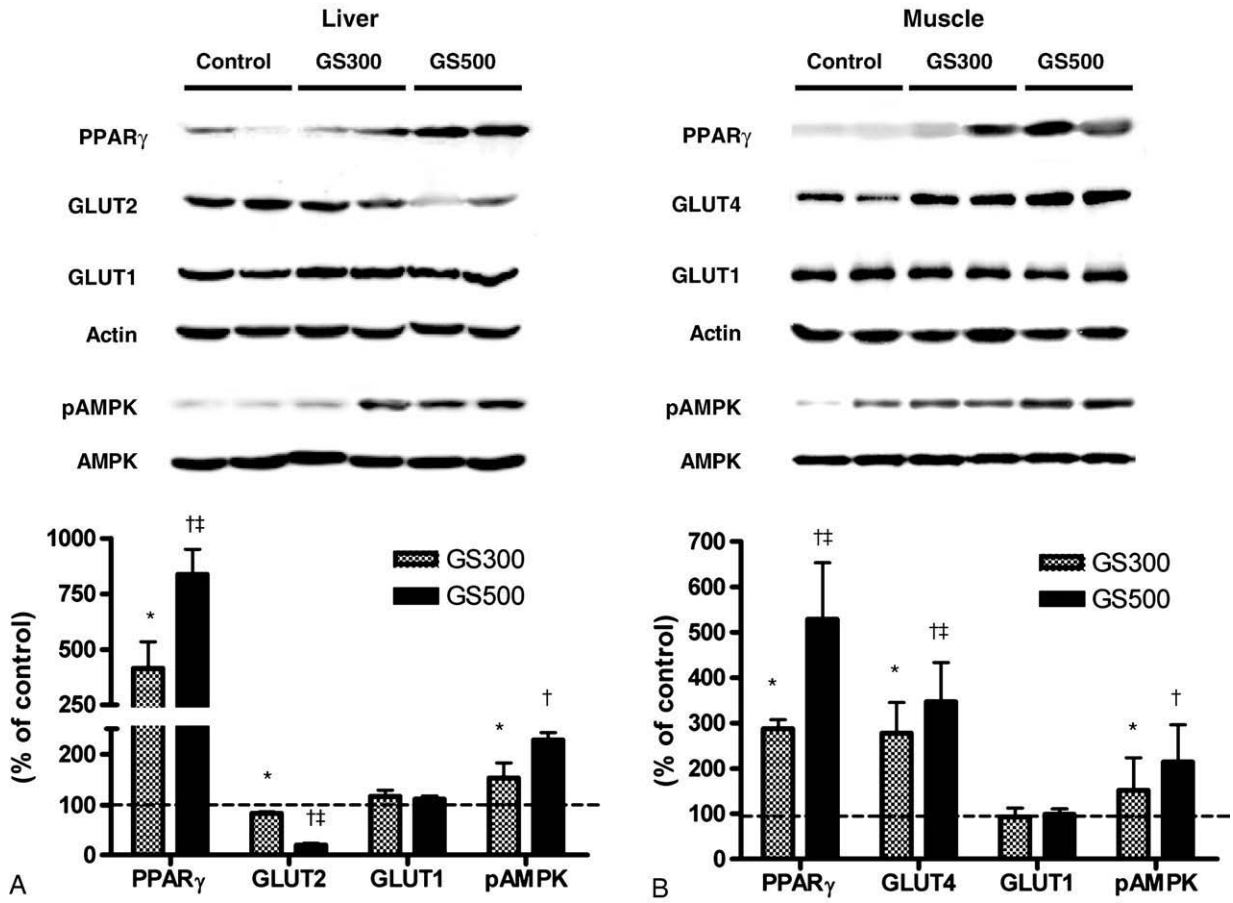

Fig. 4. Western blot analysis of PPARγ, GLUTs, and phosphospecific AMPK in liver and gastrocnemius muscle after 8 weeks of treatment with ginsam (GS300 and GS500) or isotonic sodium chloride solution. Band density was quantified using a densitometer and normalized to that of β-actin or total AMPK. *$P < .05$ control vs GS300; †$P < .05$ control vs GS500; ‡$P < .05$ GS300 vs GS500.

The visceral fat amount measured by CT scans was also lower in the treatment groups compared with the controls, although the difference was only borderline significant, possibly because of the small number of study animals. Interestingly, at the end of study, the liver weight was significantly lower in ginsam-treated rats than in controls. In addition, ALT level, a measure of liver enzyme activity that increases in fatty livers and is associated with metabolic syndrome [23], was significantly lower in the ginsam-treated rats. Taken together, these effects on fat contents and liver enzyme activity indicate a general improvement in glucose metabolism.

Attele et al [18] showed that a berry extract of *Panax* ginseng has glucose-lowering and weight-lowering effects in mice. After daily intraperitoneal injections of *Panax* ginseng, the obese (*ob/ob*) mice showed significantly improved glucose tolerance, as shown by a 46% decrease in the overall glucose excursion ($P < .01$) compared with controls. They also found that the ginsenoside Re, a major constituent of *Panax* ginseng, played a significant role in this antihyperglycemic action. However, this antihyperglycemic effect was not associated with body weight changes. We note that Attele et al focused on Re, not Rg3, the main components of ginsam.

A recent study demonstrated that a wild ginseng ethanol extract has preventive effects on diabetes and obesity [19]. In this previous study, wild ginseng combined with a high-fat diet fed to mice significantly lessened body weight gain; reduced fasting glucose, triglyceride, and free fatty acid concentrations; and improved insulin resistance index in a dose-dependent manner. Adipocyte diameter was also significantly smaller in the treated group compared with the controls. However, this study could not identify the active component of ginseng inducing this favorable effect because the entire body of ginseng was used. In addition, the study did not investigate in detail the mechanisms responsible for the antidiabetic or antiobesity effects.

The active components of ginseng are considered to be ginsenosides, a group of steroidal saponins [24,25]. Ginsenosides are distributed in many parts of the ginseng plant, including the root, leaf, and berry. Different parts of the plant contain distinct ginsenoside profiles [25], and these parts may have different pharmacologic activities. Considering that ginsam, which was used in our study, was enriched with the ginsenoside Rg3, we suggest that Rg3 is a key component responsible for the antiobesity effects and improved glucose metabolism.

In our study, the improvement in glucose tolerance was associated with increased PPARγ and phosphospecific AMPK expression in skeletal muscle and liver, which play an important role in regulating glucose metabolism. Interestingly, treatment with ginsam decreased the GLUT2 protein level in the liver and increased the GLUT4 protein level in muscle tissue. These data suggest that ginsam plays a role in regulating glucose metabolism by changing the expression of genes involved in glucose and fat metabolism in metabolically active tissues.

We found no differences in fasting glucose concentration between groups except during the last week of the study. This is probably because we used 24-week–old OLETF rats, an age that is not old enough for the rats to show increased fasting glucose levels [26]. At the study end point, half of the control rats had a glucose concentration greater than 130 mg/dL, but only one in the GS500 group and none in the GS300 had glucose concentrations greater than this level. This suggests that ginsam treatment might have reduced fasting glucose concentration if the study duration had been extended. In the IPGTT, glucose concentrations were significantly lower in the ginsam-treated groups than in the controls; and this effect was dose dependent.

In summary, we found that ginsam, which is produced by vinegar extraction from *Panax* ginseng and enriched in the ginsenoside Rg3, had glucose-lowering and weight-lowering effects in an obese insulin-resistant animal model. These effects may be related to the increased GLUT4 protein level in skeletal muscle and increased PPARγ protein level and AMPK phosphorylation in liver and skeletal muscle. A potential limitation of our study is the *significantly smaller weight gain* in the ginsam-treated groups, which may have been responsible for the smaller liver size and improved glucose metabolism compared with controls. Our data suggest that ginsam has clinical use in treating obese patients with type 2 diabetes mellitus. Its potential in the prevention of type 2 diabetes mellitus and possibly obesity deserves further clinical trials.

Acknowledgment

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