Korean red ginseng (*Panax ginseng*) improves insulin sensitivity and attenuates the development of diabetes in Otsuka Long-Evans Tokushima fatty rats

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**Abstract**

Ginseng has been reported to ameliorate hyperglycemia in experimental and clinical studies; however, its mechanism of action remains unclear. In this study, we investigated the metabolic effects and putative molecular mechanisms of Korean red ginseng (KRG, *Panax ginseng*) in animal models for type 2 diabetes mellitus (T2DM) and peripheral insulin-responsive cell lines. Korean red ginseng was administered orally at a dose of 200 mg/(kg d) to Otsuka Long-Evans Tokushima fatty rats for 40 weeks. Initially, chronic administration of KRG reduced weight gain and visceral fat mass in the early period without altering food intake. The KRG-treated Otsuka Long-Evans Tokushima fatty rats showed improved insulin sensitivity and significantly preserved glucose tolerance compared with untreated control animals up to 50 weeks of age, implying that KRG attenuated the development of overt diabetes. KRG promoted fatty acid oxidation by the activation of adenosine monophosphate–activated protein kinase (AMPK) and phosphorylation of acetyl–coenzyme A carboxylase in skeletal muscle and cultured C2C12 muscle cells. Increased expression of peroxisome proliferator–activated receptor–γ coactivator–1α, nuclear respiratory factor–1, cytochrome c, cytochrome c oxidase–4, and glucose transporter 4 by KRG treatment indicates that activated AMPK also enhanced mitochondrial biogenesis and glucose utilization in skeletal muscle. Although these findings suggest that KRG is likely to have beneficial effects on the amelioration of insulin resistance and the prevention of T2DM through the activation of AMPK, further clinical studies are required to evaluate the use of KRG as a supplementary agent for T2DM.

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**1. Introduction**

*Panax ginseng* CA Meyer has been widely used for more than 2000 years in Asia as a traditional medicine and dietary supplement. Red ginseng is produced by steaming and drying fresh ginseng. During this process, ginsenosides undergo chemical changes that confer the potential to induce special physiologic activities [1]. Although many clinical and experimental studies have reported that ginseng has a hypoglycemic effect [2-6], most of these studies have shown only a short-term effect; the exact mechanism of action for this effect still remains unclear.

Insulin resistance is considered a major health risk contributing to the development of other metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM),
hyperlipidemia, hypertension, and cardiovascular disease [7,8]. Consequently, insulin-sensitizing agents such as thiazolidinediones and metformin are important for reducing the risk of metabolic syndrome, T2DM, and associated complications. Recently, thiazolidinediones and metformin were both reported to have stimulatory effects on the activation of adenosine monophosphate–activated protein kinase (AMPK) and peroxisome proliferator–activated receptor–γ coactivator–1α (PGC-1α) [9,10].

Skeletal muscle is a potential target for antiobesity and antidiabetes therapies because it constitutes approximately 40% of the body’s mass and is an important site for the uptake and oxidation of both glucose and fatty acids [11]. In obesity, fatty acid metabolism in skeletal muscle is compromised, resulting in the accumulation of intramyocellular lipids, a condition associated with insulin resistance and the development of T2DM [12]. In addition, mitochondrial dysfunction is another important cause of insulin resistance and metabolic syndrome [13].

Adenosine monophosphate–activated protein kinase is thought to be an important regulator of glucose and fat metabolism and is activated under cellular stress, typically in response to changes in the intracellular AMP–adenosine triphosphate ratio [14,15]. Recent reports have shown that the activation of AMPK increases fatty acid oxidation and glucose uptake in skeletal muscle [16]. Remarkably, PGC-1α has been shown to be a key intermediate molecule involved in the mitochondrial biogenesis pathway and the activation of AMPK in skeletal muscle [17]. Recent evidence indicates that PGC-1α also plays a role in the regulation of muscle glucose metabolism through the activation of glucose transporter 4 (GLUT4) by coactivation of myocyte enhancer factor–2 (MEF-2) [18,19]. In this regard, therapeutic strategies that target skeletal muscles to stimulate fatty acid oxidation or mitochondrial biogenesis may have beneficial effects on whole-body energy expenditure and insulin sensitivity.

The aim of this study was to examine the effect of Korean red ginseng (steamed and dried P. ginseng CA Meyer; KRG) administration on whole-body insulin activity in an obese T2DM animal model. In addition, we sought to further investigate the mechanism by which KRG improves insulin sensitivity and prevents the development of diabetes.

2. Research design and methods
2.1. Animals and diets

Ten-week-old male Otsuka Long-Evans Tokushima fatty (OLETF) rats and control nondiabetic Long-Evans Tokushima Otsuka (LETO) rats were obtained from Otsuka Pharmaceutical (Tokushima, Japan). The rats were maintained at ambient temperature (22°C ± 1°C) with 12-hour light-dark cycles and free access to water and food. In our preliminary study, OLETF rats received a daily oral administration of KRG (Korean Tobacco and Ginseng, Daejon, Korea) for 16 weeks. Our preliminary experiments revealed that the antihyperglycemic effect of KRG was dose dependent (data not shown); 200 mg/kg was subsequently chosen as the daily amount of KRG supplied to the rats. The OLETF rats were divided randomly into 2 groups, with 1 group of rats receiving 200 mg/(kg d) orally for 40 weeks. After pretreatment with KRG for 4 weeks, food intake and body weight were monitored once per week. After 50 weeks, the rats were killed for tissue sampling. Interscapular brown adipose tissues (BAT); abdominal subcutaneous, epididymal, and peritoneal white adipose tissues; and skeletal muscle (gastrocnemius) were isolated and immediately freeze-clamped in liquid nitrogen and stored at −70°C. All procedures were approved by the Institutional Animal Care and Use Committee at the Yonsei Institute for Life Sciences.

2.2. Glucose tolerance and insulin tolerance tests

An oral glucose tolerance test (OGTT) was performed after an overnight fast in the OLETF rats at 10, 18, 25, 36, 42, and 50 weeks of age. Blood glucose levels were determined using a glucose analyzer (Accu-Chek; Roche Diagnostics, Basel, Switzerland) after oral administration of glucose (2 g/kg body weight) by gavage. At 32 weeks of age, an insulin tolerance test (ITT) was performed after an intraperitoneal injection of insulin (1 U/kg of body weight; Novolet; Novo Nordisk, Bagsværd, Denmark).

2.3. Biochemical analyses

Blood samples were obtained from the heart at the time of killing and were immediately centrifuged at 5000 g for 5 minutes. Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol were determined using an ADVIA 1650 (Bayer, West Haven, CT). Plasma hemoglobin A1c (HbA1c) levels were measured and serum insulin concentrations were determined using a rat radioimmunoassay kit (Linco Research, St Louis, MO).

2.4. Western blot analysis

Tissue samples were homogenized in buffer (20 mmol/L Tris base [pH 8.0], 3 mol/L NaCl, 1 mmol/L MgCl2, 2 mmol/L CaCl2, 1% NP-40, 100 mmol/L NaF, 2 mmol/L sodium orthovanadate, 1 mmol/L dithiothreitol, 2.5 mmol/L phenylmethylsulfonyl fluoride, 10 mg/mL aprotinin, and 10 mg/mL leupeptin) at 4°C. Homogenates were incubated on ice for 30 minutes and then centrifuged at 13 000g for 20 minutes at 4°C. The supernatant was considered the cytosolic fraction. To obtain the membrane protein fraction, the pellet was resuspended in lysis buffer including 0.3% Triton X-100, incubated for 1 hour at 4°C, and then centrifuged at 55 000 rpm for 20 minutes at 4°C. This supernatant was considered the membrane fraction. Protein samples were separated by sodium dodecyl sulfate–
polyacrylamide gel electrophoresis, transferred to a polyvinylidene difluoride membrane, and then blocked with 5% skimmed milk. Membranes were incubated with primary antibodies against GLUT4 (Chemicon, Temecula, CA), cytochrome phospho-AMPK (Thr172), total AMPK (Cell Signaling Technology, Danvers, MA), total acetyl–coenzyme A carboxylase (ACC), phospho-ACC (Ser79), PGC-1α, nuclear respiratory factor–1 (NRF-1), MEF-2 (Santa Cruz Biotechnology, Santa Cruz, CA), cytochrome c oxidase–4 (COX-4), cytochrome c (Cell Signaling Technology), and uncoupling protein 1 (UCP-1, Chemicon), and subsequently with the corresponding secondary antibodies. Results were visualized using an enhanced chemiluminescence detection system (Amersham Pharmacia, Uppsala, Sweden) and quantified with a LuminolInager and TINA software.

2.5. Cell culture

C2C12 cells were obtained from the American Type Culture Collection (Manassas, VA) and maintained at 37°C in a 5% CO2 humidified atmosphere in Dulbecco modified Eagle medium containing 10% fetal bovine serum. As the myoblasts became confluent inducing differentiation of C2C12 cells, medium containing 2% horse serum was used. Experimental treatments commenced after 4 to 7 days, by which time nearly all of the myoblasts present had fused to form myotubes.

2.6. Measurement of fatty acid oxidation

C2C12 cells were grown for 6 days in Dulbecco modified Eagle medium supplemented by 0.1% fetal bovine serum. Before measurement, cells were washed 3 times with Dulbecco phosphate-buffered saline. Fatty acid oxidation was measured by quantifying the production of 3H2O from (9, 10) palmitate as described previously[20].

2.7. Statistical analysis

Data were compared using the Student t test or by analysis of variance using the SPSS 14.0 program (SPSS Institute, Chicago, IL) where appropriate. Data are presented as mean ± standard error. Statistical significance was defined as P less than .05.

3. Results

3.1. Effects of KRG on biochemical profiles in OLETF rats

The biochemical characteristics of the LETO and OLETF rats are shown in Table 1. Administration of KRG significantly changed metabolic parameters in OLETF rats. Fasting glucose and insulin levels at 25 weeks were much lower in the KRG-treated groups (Fig. 1A). Between control and KRG-treated OLETF rats until the age of 32 weeks (Fig. 1A).

| Table 1 Effects of KRG on biochemical profiles in OLETF rats |
|-----------------|-----------------|-----------------|
|                 | LETO (n = 10)   | OLETF (n = 20)  | OLETF + KRG (n = 20) |
| Fasting glucose (mmol/L) | 5.82 ± 0.79 | 7.22 ± 0.47* | 6.56 ± 0.22* |
| Insulin (ng/mL) | | | |
| 25 wk  | 0.45 ± 0.03 | 1.35 ± 0.12* | 0.75 ± 0.05* |
| 42 wk  | 0.63 ± 0.03 | 0.84 ± 0.04* | 1.65 ± 0.07*† |
| HbA1c (%) | | | |
| 25 wk  | 4.25 ± 0.05 | 6.77 ± 1.41* | 5.07 ± 0.54‡ |
| 42 wk  | 4.33 ± 0.09 | 9.22 ± 0.69* | 5.08 ± 0.56‡ |
| Total cholesterol (mmol/L) | 2.09 ± 0.14 | 3.02 ± 0.57* | 2.18 ± 0.27‡ |
| Triglycerides (mmol/L) | 0.57 ± 0.05 | 2.66 ± 0.97* | 1.42 ± 0.47‡|
| HDL cholesterol (mmol/L) | 0.74 ± 0.04 | 0.76 ± 0.13 | 0.65 ± 0.01 |
| LDL cholesterol (mmol/L) | 0.51 ± 0.02 | 0.82 ± 0.17* | 0.63 ± 0.07‡ |
| hsCRP (mg/L) | 0.14 ± 0.01 | 0.17 ± 0.04* | 0.15 ± 0.01† |
| AST (IU/L) | 139.5 ± 19.8 | 112.5 ± 17.5 | 121.6 ± 10.7 |
| ALT (IU/L) | 44.0 ± 2.3 | 48.6 ± 8.5 | 45.3 ± 3.2 |
| BUN (mg/dL) | 17.2 ± 1.6 | 15.4 ± 2.5 | 15.3 ± 2.5 |
| Creatinine (mg/dL) | 0.71 ± 0.04 | 0.61 ± 0.03 | 0.64 ± 0.02 |

Plasma fasting glucose was measured at 25 weeks. LDL indicates low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

in KRG-treated OLETF rats at both 25 and 42 weeks. There were significant differences in lipid profiles between untreated OLETF rats and rats that were administered KRG, except for HDL cholesterol. Other biochemical indexes such as AST, ALT, BUN, and creatinine were not statistically different between the 2 groups.

3.2. KRG reduces visceral fat mass gains and improves insulin sensitivity in OLETF rats

To investigate the in vivo metabolic effects of KRG on diabetes, KRG was administered to OLETF rats for 40 weeks; and body weight and epididymal and peritoneal fat mass were measured. The incremental body weight gain was greater in the control OLETF rats than in the LETO or KRG-treated OLETF rats until the age of 32 weeks (Fig. 1A). However, only untreated OLETF rats showed a decrease in body weight after the age of 32 weeks. Treatment of OLETF rats with KRG significantly reduced visceral fat mass gains by approximately 20% (Fig. 1B). There was no significant difference in food intake between control and KRG-treated OLETF rats (Fig. 1C). Body temperatures of KRG-treated OLETF rats were higher than those of control rats (36.69°C ± 0.17°C vs 36.42°C ± 0.24°C, P < .05), indicating increased basal metabolism in the treated groups (Fig. 1D). Next, we assessed insulin sensitivity by ITT in OLETF rats. Korean red ginseng administration resulted in a significant amelioration of insulin tolerance in OLETF rats (Fig. 1E).

3.3. KRG attenuates the development of overt diabetes in OLETF rats

To assess whether the administration of KRG delayed the onset of overt diabetes, we performed serial OGTT in
OLETF rats at 10, 18, 25, 36, 42, and 50 weeks of age (Fig. 2). Over time, blood glucose levels increased gradually over 40 weeks; and all untreated OLETF rats developed overt diabetes after 36 weeks. After receiving KRG for more than 36 weeks, KRG-treated rats exhibited much improved glucose tolerance, which was preserved up to 50 weeks, compared with untreated rats. These results indicate that the administration of KRG may delay the deterioration of glucose tolerance and partially prevent the development of T2DM in OLETF rats.

3.4. KRG promotes fatty acid oxidation by the activation of AMPK in vivo and in vitro

Activated AMPK is known to inhibit ACC by direct phosphorylation to increase $\beta$-oxidation of fatty acids in

Fig. 2. Effects of KRG on glucose tolerance in OLETF rats. The effects of KRG on the development of diabetes in OLETF rats were investigated by performing OGTTs in 10- (A), 18- (B), 25- (C), 36- (D), 42- (E), and 50-week-old (F) OLETF rats. Data are presented as the mean ± SD in the LETO (n = 10), OLETF (n = 20), and OLETF + KRG groups (n = 20). $^*P$ less than .05 compared with untreated OLETF rats.
mitochondria. We examined the activities of AMPK and its downstream target, ACC, in the skeletal muscle of OLETF rats to elucidate the molecular mechanism of KRG effects on insulin sensitivity and lipid metabolism. Phosphorylation of AMPK and ACC was significantly increased in the gastrocnemius muscle of KRG-treated OLETF rats as compared with control rats (Fig. 3A). To determine the direct effect of KRG on the activities of AMPK and ACC in vitro, Western blotting was performed on C2C12 cells treated with 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and metformin, which are known to be AMPK activators (Fig. 3B). Treatment of C2C12 cells with AICAR, metformin, or KRG for 24 hours induced the phosphorylation of AMPK and ACC and promoted a significant increase in the oxidation of palmitate (40% relative to control) (Fig. 3C). Collectively, these findings suggest that KRG may stimulate fatty acid oxidation by enhancing the activity of AMPK that leads to an inhibition of ACC.

3.5. Effects of KRG on the expression of GLUT4 and proteins related to mitochondrial biogenesis

We investigated whether AMPK activation induced by KRG treatment enhanced the expression of GLUT4 and mitochondrial enzymes in skeletal muscles or adipose tissues. Immunoblotting of proteins associated with mitochondrial biogenesis and glucose uptake was performed on the gastrocnemius muscle and BAT of LETO and OLETF rats (Fig. 4). The expression levels of PGC-1α, NRF-1, cytochrome c, and COX-4 were lower in the gastrocnemius muscle of untreated OLETF rats. However, expression levels of these proteins were significantly increased in OLETF rats treated with KRG. KRG also enhanced PGC-1α and UCP-1 expression in the BAT of OLETF rats. Furthermore, higher expression levels of GLUT4 and its transcription factor, MEF-2, were observed in the skeletal muscle of KRG-treated OLETF rats compared with untreated rats.

4. Discussion

Several studies investigating the antidiabetic effects of herbs have been performed to date. Among these herbs, *P* ginseng has been reported to have therapeutic effects in patients with diabetes [21,22]. Previous clinical trials have shown that the administration of ginseng induces a reduction in plasma glucose as well as HbA1c levels in T2DM patients.
Interestingly, researchers have noted that different ginseng batches have variable pharmacologic efficacies and that responses might be affected by the clinical characteristics of patients, such as body weight [24]. Furthermore, it has been demonstrated that ginseng has an antihyperglycemic effect in insulin-resistant or diabetic animal models, although most of the results have shown only short-term effects [2-4]. In the present study, we first demonstrated that long-term KRG administration prevented the development of hyperglycemia in a diabetes-prone animal model. In addition, biochemical parameters related to hepatic injury or nephrotoxicity were not elevated after the treatment, indicating that treatment with KRG was well tolerated and did not cause a toxic response. The exact mechanism of how ginseng ameliorates the symptoms of diabetes still remains elusive. Several studies have suggested that ginseng might be involved in reducing the digestion and absorption of dietary fat [25,26], improving insulin resistance [2-4], or stimulating insulin secretion [27]. The results of our ITT and OGTT studies demonstrated that KRG treatment improved insulin sensitivity and attenuated the development of T2DM in OLETF rats. The possible molecular mechanism of these effects is suggested by both in vivo and in vitro findings that KRG induced activation of AMPK, which leads to the phosphorylation of ACC, which in turn contributes to increased β-oxidation. Improved β-oxidation of fatty acids reduces the accumulation of long-chain fatty acyl-coenzyme A, fatty acid metabolites, and diacylglycerol, which leads to the activation of protein kinase C θ and subsequently insulin resistance [28,29]. In addition, fasting insulin concentrations were significantly increased in the KRG-treated OLETF rats at 42 weeks, implying that KRG may preserve the insulin secretory function of β-cells. Insulin immunostaining of the pancreas in OLETF rats revealed that KRG-treated rats tended to have larger islets than control rats (data not shown). Korean red ginseng treatment significantly reduced visceral fat mass and marginally inhibited weight gain in OLETF rats. The body weight of untreated OLETF rats compared with KRG-treated rats was much greater up to 32 weeks and then decreased gradually, which implies that a low plasma insulin level due to islet depletion rendered untreated rats catabolic, which led to weight loss. Decreases in free fatty acid flux from reduced adipose tissues induced by KRG may inhibit lipid accumulation in skeletal muscles, liver, and pancreatic β-cells, which are susceptible to lipotoxicity [30].

The OLETF rats have been described as cholecystokinin-1 receptor knockout models and are known to be hyperphagic because of elevated levels of neuropeptide Y messenger RNA expression in the hypothalamus. In our study, food intake did not differ between control and KRG-treated rats. Therefore, we hypothesize that the observed reduction of weight gain in the treated group in the initial treatment period (<32 weeks) might be due to increases in energy expenditure rather than decreases in food intake. Although the measurement of energy expenditure and oxygen consumption was not performed in our study, we observed that KRG-treated OLETF rats exhibited elevated body temperatures, consistent with a report studying ginseng berry [2]. However, the present study differs in that we used

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**Fig. 4. Effects of KRG on the expression of proteins related to mitochondrial biogenesis and glucose utilization.** A, Effects of KRG on the expression of metabolic proteins in gastrocnemius muscle. Western blot analyses showed enhanced expressions of PGC-1α, NRF-1, MEF-2, cytochrome c, COX-4, and GLUT4 in gastrocnemius muscle. B, Effects of KRG on the expression of PGC-1α and UCP-1 in BAT. Interscapular BAT was removed, lysed, and immunoblotted with antibodies specific for PGC-1α and UCP-1. •P less than .05 compared with LETO rats; †P less than .05 compared with untreated OLETF rats.
ginseng root extract instead of ginseng berry. Furthermore, we demonstrated a concurrent increase in the expression of genes related to the control of energy expenditure, such as PGC-1α and UCP-1, in BAT from the rodents. These results imply that KRG treatment may also contribute to enhanced energy expenditure in adipose tissue.

It has been suggested that treatment with ginseng extract enhances capillary density and mitochondrial contents in gastrocnemius muscle and attenuates mitochondrial impairment in the heart muscle [31,32]. Our data showed that KRG treatment significantly increased the expressions of PGC-1α, NRF-1, cytochrome c, and COX-4, which are involved in mitochondrial biogenesis in skeletal muscle. These results indicate that the prolonged uptake of KRG expanded the oxidative capacity of skeletal muscle with greater aerobic potential in a manner similar to physical exercise.

The activation of AMPK induces metabolic changes in skeletal muscle by various pathways. One of these pathways is the fast process in which activated AMPK rapidly phosphorylates ACC and thereby increases palmitate oxidation in skeletal muscle. Another pathway is the chronic action of AMPK, which enhances insulin sensitivity and glucose uptake via GLUT4 translocation and promotes mitochondrial biogenesis by the activation of PGC-1α in skeletal muscle, leading to improved oxidative metabolism [14]. We have shown that long-term KRG treatment enhanced MEF-2 and GLUT4 protein expression in gastrocnemius muscle, implying that KRG may play a potential role in increasing glucose utilization and glucose disposal in the skeletal muscle of OLETF rats.

It has been reported that most of the pharmacologic actions of ginseng are attributed to ginsenosides, which are able to act on a wide range of tissues [33]. Besides ginsenosides, Panax ginseng root extract contains nonginsenoside constituents such as lipophilic compounds and phenolic substances (maltol, salicylic acid, and vanillic acid), which exert diverse pharmacologic effects. Although the major potent substance of KRG is not yet fully elucidated, we presume that various components in KRG may play cooperative roles in the regulation of glucose and lipid metabolism in OLETF rats.

In summary, we have demonstrated that the improvement in insulin sensitivity and prolonged protection against the development of overt diabetes after KRG administration may be due to (1) increased energy expenditure with loss of adipose tissue, (2) activation of the fatty acid oxidation pathways by increased AMPK activity, (3) enhanced mitochondrial function by upregulation of mitochondrial biogenesis, and (4) augmented GLUT4-mediated glucose utilization in skeletal muscle. Furthermore, KRG administration increased adaptive thermogenesis, possibly contributing to increased energy expenditure and decreased weight gain. As a result, KRG may reduce glucotoxicity and lipotoxicity in pancreatic β-cells, which are thought to be secondary effects in the improvement of insulin resistance.

Ultimately, these effects could prevent the development of overt T2DM (Fig. 5).

In conclusion, KRG may be a potentially useful agent for the treatment of metabolic syndrome and the prevention of T2DM. Because the exact mechanisms by which KRG prevents diabetes remain to be investigated, future studies are required to identify precisely which components of KRG exhibit therapeutic functions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2009.03.015.

References


