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Full-length article

Antihyperglycemic effects of total ginsenosides from leaves and stem of *Panax ginseng*

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Key words

Panax ginseng; total ginsenosides; diabetes mellitus; hyperglycemia; obesity; *ob/ob* mice

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Abstract

Aim: The antihyperglycemic effects of the total ginsenosides in Chinese ginseng (TGCG), extracted from leaves and the stem, were evaluated in diabetic C57BL/6J *ob/ob* mice. **Methods**: Animals received daily intraperitoneal injections of TGCG (100 and 200 mg/kg) or oral administration (150 and 300 mg/kg) for 12 d. Fasting blood glucose levels and body weight were measured after fasting the animals for 4 h. Peripheral glucose use was also measured using an intraperitoneal glucose tolerance test. **Results**: In the injection group, a high dose of TGCG (200 mg/kg) significantly lowered the fasting blood glucose levels in *ob/ob* mice on d 12 (153±16 mg/dL *vs* 203±9.8 mg/dL, $P<0.01$, compared to vehicle-treated group). In the oral group, blood glucose decreased notably with a dose of TGCG (300 mg/kg) on d 12 (169.1±12.6 mg/dL *vs* 211.6±13.8 mg/dL, $P<0.05$, compared to the vehicle-treated group). Glucose tolerance was also improved markedly in *ob/ob* mice. Furthermore, a significant reduction in bodyweight ($P<0.05$) was observed after 12 d of TGCG (300 mg/kg) treatment in mice from the oral group. **Conclusion**: The results indicated that in a diabetic *ob/ob* mouse model TGCG was endowed with significant anti-hyperglycemic and anti-obesity properties. Therefore, the total ginsenosides extracted from Chinese ginseng leaves and the stem may have some potential for treating diabetes.

Introduction

Diabetes mellitus is a devastating disease affecting approximately 8% of the total population in the USA and 3% of the population world wide, 90% of which suffer from type 2 diabetes[1]. Diabetes is a chronic metabolic disease that has a significant impact on the patients' quality of life as well as on the health care system. The incidence of diabetes is increasing rapidly, which will lead to a worldwide increase in the cost of management of the disease and its complications. Generally, diabetes is classified into two major categories: type 1 diabetes (formerly known as insulin-dependent diabetes mellitus, or IDDM), and type 2 diabetes (formerly known as non-insulin dependent diabetes mellitus, or NIDDM)[1,2]. Although the two types of diabetes have distinct pathogeneses, hyperglycemia and various life-threatening complications resulting from long-term hyperglycemia are common to both[3–7].

The drugs currently available for type 2 diabetes have a number of limitations, such as significant side effects and high rates of secondary failure. As the knowledge of the heterogeneity of this disorder increases, there is a need to look for more effective agents with fewer side effects[8]. This has led to the search for alternative therapies that may have a similar degree of efficacy without the troublesome side effects associated with conventional drug treatment. The identification of compounds with antihyperglycemic activity from medicinal plants may provide an opportunity to develop a new class of antidiabetic agents. According to previous reports, ginseng is one of the most important and valuable plants with antidiabetic properties[9].

Ginseng is a perennial herb of the *Araliaceae* family, cultivated in China, Japan, Korea, and Russia, as well as in the

USA and Canada. Ginseng has been used as a tonic remedy in traditional Chinese medicine for several thousands of years[10]. The pharmacological properties of ginseng are mainly attributed to ginsenosides, the active constituents that are found in the extracts of different species of ginseng[11,12]. Over 80 years ago, Japanese scientists observed that ginseng root extracts had antidiabetic properties[13,14]. Sub-sequently, the blood glucose-lowering effect of ginseng root was investigated by other researchers[15-19]. It has been reported that both Chinese ginseng (*Panax ginseng* C A Meyer) and American ginseng (*Panax quinquefolium* L) roots possess antihyperglycemic properties[18,20,21]. A limitation of using ginseng root, however, is its high cost. Other parts of the ginseng plant, namely; berries, leaves, and the stem, can also be harvested and could yield additional herbal material and improve the cost-efficiency of ginseng cultivation. Recently, we have demonstrated the antihyperglycemic properties of Chinese ginseng berry and root extract, American ginseng berry and leaf extract, polysaccharide fractions from American ginseng berry, and ginsenoside Re in diabetic *ob*/*ob* mice[22–28]. Moreover, our past data indicated that American ginseng leaf extract, with its high ginsenoside yield, could be an inexpensive alternative to the root in the treatment of diabetes[27]. In the present study, the total ginsenosides in Chinese ginseng (TGCG) were evaluated for antihyperglycemic and antiobesity properties in order to further examine the antidiabetic properties of the Chinese ginseng plant.

Materials and methods

Animals Adult male, diabetic C57BL/6J *ob*/*ob* mice were used in the present study, and were purchased from Jackson Laboratory (Bar Harbor, ME, USA). The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Chicago. Animals were housed under controlled conditions with a 12-h light/dark cycle. Animals had free access to standard rodent pellet food (Zeigler Bros, Gardners, PA, USA) and water *ad libitum*, except when fasted before experiments. After 2–3 weeks of acclimation under these conditions, animals were grouped for the experiment.

Thirty-four diabetic *ob*/*ob* mice, 10–16 weeks old, weighing 58.2±0.6 g, were randomly divided into two groups used for the experiments: Group 1, Injection Group (*ip*) including high-dose TGCG group (200 mg/kg, n=7), low-dose TGCG group (100 mg/kg, n=6), and vehicle group (n=6); and Group 2, Oral Group (ig) including high-dose TGCG group (300 mg/kg, n=5), low-dose TGCG group (150 mg/kg, n=5), and vehicle group (n=5). Dose selection was based on previous reports[22]. The TGCG solution was injected intraperitoneally or orally administered once a day. Vehicle group animals received an equivalent volume of saline. No irritation or restlessness was observed following administration of the test solutions. All mice were housed in the same conditions during all experiments.

TGCG preparation The dried TGCG extracts were a gift from Mr Qing-hua ZHANG at Nankai University in Tianjin, China. Leaves and stems of *Panax ginseng* were purchased from Jilin Province in China. TGCG was analyzed using HPLC in our laboratory. The dried TGCG were dissolved in saline and vortexed for 2 min at room temperature before use.

Blood glucose levels As in our previous studies[22, 23, 27], fasting blood glucose levels (measured by Glucose Analyzer, Hemocue, Angelholm, Sweden) and bodyweight were measured after fasting the animals for 4 h (starting from 09:00) on d 0 (before treatment), d 5, and d 12. Blood glucose levels were determined from tail vein blood samples at 13:00 using the Glucose Analyzer.

Glucose tolerance test To evaluate the peripheral glucose use, an intraperitoneal glucose tolerance test (IPGTT) was performed on d 0 and d 12. On the test days, animals were fasted for 4 h starting from 09:00 followed by an ip administration of glucose (2 g/kg). Blood glucose levels were determined in blood samples from the tail vein at 0 (prior to glucose administration), 30, 60 and 120 min after glucose administration.

Statistical analysis Data are expressed as mean±SEM. Statistical significance between vehicle-treated versus drug-treated mice, and between before treatment versus after treatment were determined by a paired Student's t-test. A value of $P<0.05$ was considered statistically significant.

Results

HPLC assay Figure 1 shows the HPLC-UV (202 nm) chromatogram of TGCG. The analyzed results were Rb1 (0.32%), Rb2 (1.45%), Rc (1.68%), Rd (2.60%), Re (20.42%), Rg1 (14.60%), and Rg2 (4.64%). The rank order of the quantity of ginsenoside was Re>Rg1>Rg2>Rd>Rc>Rb2>Rb1. The results show that ginsenosides Re and Rg1 in TGCG are much higher than other ginsenosides.

Effect of TGCG on blood glucose levels in injection group Blood glucose levels in C57BL/6J *ob/ob* mice after 4 h fasting were measured on d 0, d 5, and d 12 after daily ip administration of TGCG or vehicle. As shown in Figure 2, diabetic *ob*/*ob* mice had remarkably high baseline fasting blood glucose levels (>200 mg/dL), which decreased significantly after administration of high-dose of TGCG. For example, on d 5 blood glucose levels were 179.0±12.7 mg/dL

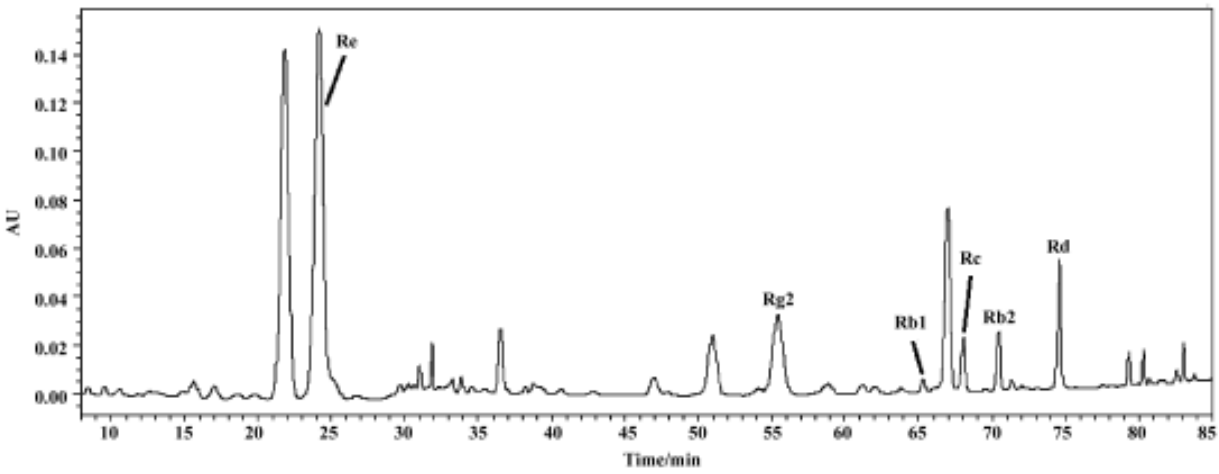

Figure 1. Chromatogram of total ginsenosides of Chinese ginseng (TGCG) extracted from leaves and stem.

(P<0.05) compared to the vehicle group, 192.0±10.7 mg/dL. On d 12, the high-dose group were normoglycemic (153.0± 16.8 mg/dL) compared to the vehicle group (203.0±9.8 mg/dL, P<0.01). At the low-dose (100 mg/kg), however, the blood glucose decreased from 203.0±15.0 mg/dL to 189.0±20.0 mg/dL on d 5 and 170.0±9.0 mg/dL on d 12 (P<0.05). Figure 2 also indicates that mice in the vehicle group did not show any remarkable changes in blood glucose levels. In contrast, TGCG inhibited blood glucose level in a dosage-dependent manner. The blood glucose lowering effect of TGCG was comparable to Chinese and American ginseng berry extracts and ginseng leaf extracts[22–28].

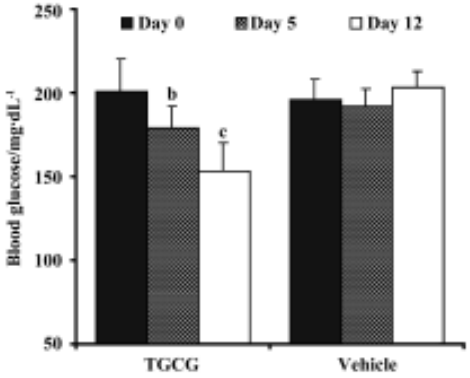

Figure 2. Effect of total ginsenosides of Chinese ginseng (TGCG; 200 mg/kg, ip, n=7) and vehicle (n=6) on fasting blood glucose in *ob*/*ob* mice. ^bP<0.05, ^cP<0.01 *vs* vehicle group.

Effects of TGCG on glucose tolerance test in injection group Glucose tolerance was evaluated by IPGTT, prior to and 12 d after treatment with TGCG. As shown in Figure 3A (high-dose group, 200 mg/kg) and Figure 3B (vehicle group), on d 0, *ob*/*ob* mice demonstrated basal hyperglycemia. This hyperglycemia was exacerbated by the ip glucose load and failed to return to baseline after 120 min, indicating glucose intolerance. After 12-d treatment with TGCG 200 mg/kg the overall glucose tolerance was improved remarkably. Figure 3A also shows that the area under the curve (AUC) decreased by 42% (from 830.4 mg·mL^{-1}·min^{-1} on d 0 to 486.3 mg·mL^{-1}·min^{-1} on d 12, P<0.01) after treatment. In the vehicle group (Figure 3B), however, the AUC decreased less than 10% (from 590.6 mg·mL^{-1}·min^{-1} on d 0 to 533.9 mg·mL^{-1}·min^{-1} on d 12, P>0.05).

Effect of TGCG on blood glucose levels in oral group We also evaluated the effects of orally administered (oral gavage) TGCG (150 and 300 mg/kg) on blood glucose in *ob/ob* mice. As shown in Table 1, after the TGCG high-dose treatment (300 mg/kg), fasting blood glucose levels significantly decreased from 209.8±16.7 mg/dL (d 0) to 186.2±11.0 mg/dL (d 5, P<0.05), and 169.1±12.6 mg/dL (d 12, both P<0.05, compared to vehicle group). In the low-dose group (150 mg/kg), blood glucose was lowered significantly on d 12 (183.5±10.9 mg/dL, P<0.05 *vs* vehicle group). The results showed that TGCG (150 and 300 mg/kg) caused anti-hyperglycemic effects after oral administration.

Effect of TGCG on body weight in oral group The aver-

Table 1. Effects of oral administration of total ginsenosides in Chinese ginseng (TGCG) on fasting blood glucose in *ob/ob* mice. ^bP<0.05 *vs* vehicle group.

		Blood glucose/mg·dL^{-1}		
	n	d 0	d 5	d 12
TGCG 150 mg/kg	5	214.0±21.1	201.7±16.1	183.5±10.9^b
TGCG 300 mg/kg	5	209.8±16.7	186.2±11.0^b	169.1±12.6^b
Vehicle	5	210.3±14.6	212.5±10.8	211.6±13.8

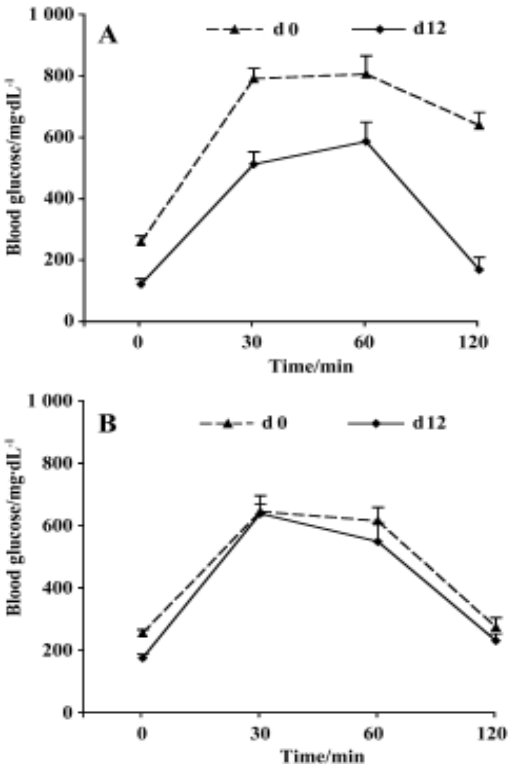

Figure 3. Effect of total ginsenosides in Chinese ginseng (TGCG) and vehicle on intraperitoneal glucose tolerance test in *ob*/*ob* mice before (d 0) and after a 12-d treatment (d 12). (A) TGCG (200 mg/kg, ip, n=7); (B) vehicle (n=6).

age bodyweight of adult *ob/ob* mice is almost twice as great as their lean littermates. As shown in Figure 4, the body weight of *ob/ob* mice in the oral vehicle group had a tendency to increase from d 0 (57.9±2.3 g) to d 12 (59.1±1.1 g). In contrast, in the oral administration of TGCG high-dose group (300 mg/kg), the body weight decreased from 60.8±0.5 g (d 0) to 57.2±1.0 g (P<0.05 compared to d 0) after 12-d TGCG

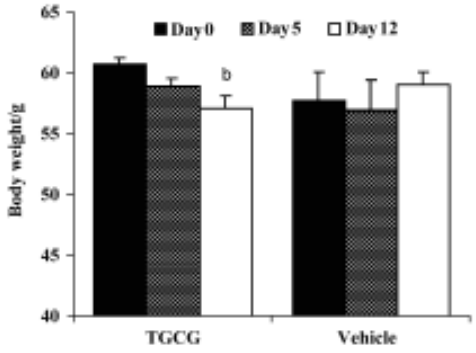

Figure 4. Effect of total ginsenosides of Chinese ginseng (TGCG; 300 mg/kg, ig, n=5) and vehicle (n=5) on body weight by oral administration in *ob/ob* mice. ^{b}P<0.05 *vs* d 0.

treatment. On d 5, however, the bodyweight was not significantly reduced (P>0.05 compared to d 0). The data indicated that TGCG (300 mg/kg, ig) possessed the effect of lowering the bodyweight in *ob*/*ob* mice. The body weight reduction activity of TGCG by oral administration was similar with Chinese and American ginseng berry extracts and ginseng leaf extracts by ip administration[22–28].

Discussion

Diabetes mellitus is a serious and chronic disease. Although oral antihyperglycemic agents and insulin are often successful in diabetes treatment, they have prominent side effects and fail to significantly alter the course of diabetic complications[8,29]. Therefore, there is an urgent need to look for more effective agents with fewer side effects, especially in medicinal plants. Previous records reveal that ginseng possesses anti-hyperglycemic properties[9]. The blood glucose-lowering effect of ginseng root has been studied[15–20,30]. According to our recent results, Chinese ginseng and American ginseng root, berry, and leaf extract, American ginseng berry polysaccharide fractions and their major active constituent ginsenoside Re, show anti-hyperglycemic properties in diabetic animals[22–28]. For a thorough study of the ginseng plant, other parts of ginseng should be analyzed for chemical composition, studied for biological activity and compared with ginseng root[31]. Recently in our laboratory, a comparison of constituent analyses among American ginseng root, berry, and leaf extract, using HPLC indicated that total ginsenosides (%) were different in ginseng berries, roots, and leaves. The total ginsenosides (%) in leaves are much higher than those in roots, and the content of ginsenoside Re in leaves is much higher than that in roots. The rank order of the quantity of total ginsenoside Re was leaves, berries, then roots[22–28]. Therefore, the ginseng leaf extract, with its high ginsenoside yield, has a promising potential to be an inexpensive alternative to the root in the treatment of diabetes. The major findings in the present study are as follows: (1) TGCG (200 and 100 mg/kg by ip and 300 and 150 mg/kg by ig) decreased fasting blood glucose levels significantly; (2) TGCG (200 mg/kg by ip) improved glucose tolerance; and (3) TGCG (300 mg/kg by ig) lowered the body weight in our experimental conditions.

As previous studies have shown the blood glucose lowering effects of ginseng root, berry, and leaf extracts individually[22–28]; the results from the present study indicate that TGCG also possesses an anti-hyperglycemic property. Both injection and oral administration of TGCG can decrease blood glucose. The results of IPGTT indicated that TGCG increased the peripheral glucose use and lowered blood glu-

cose levels. There are considerable amounts of data indicating that the chronic elevation of blood glucose causes many of the major complications of diabetes, including nephropathy, retinopathy, neuropathy, and macro- and microvascular damage[32]. Effective control of the blood glucose level, therefore, is a key step in preventing or reversing diabetic complications and improving the quality of life in both type 1 and type 2 diabetic patients[3–6]. Sustained reductions in hyperglycemia will decrease the risk of developing microvascular complications, and most likely reduce the risk of macrovascular complications[7]. The present data show TGCG not only lowers blood glucose in diabetic *ob/ob* mice, but also improves glucose tolerance. The anti-hyperglycemic effect and body weight reduction activity of TGCG may prove to be of clinical importance in improving the management of type 2 diabetes.

The mechanisms for improved blood glucose levels associated with ginseng part extract, including TGCG, and its major active components, ginsenosides, may be multifaceted and remain unclear so far. According to previous studies, there are several plausible hypotheses that may work independently or concurrently.

First, inhibition digestion and increase of energy expenditure may be involved. Our results have demonstrated that ginseng berry extract significantly decreased food intake activity, which reduced the source of carbohydrates[22]. Energy expenditure values were obtained in *ob/ob* mice treated with vehicle or Chinese ginseng berry extract. After the 12-d treatment, there was a significant increase in energy expenditure in *ob/ob* mice ($P<0.01$). However, we also showed that ginseng berry extract increased body temperature significantly in *ob/ob* mice. Increases in body temperature suggested that the carbohydrate metabolism in mice was enhanced, consistent with the increased basal metabolic rate.

Second, there can be improvement in sensitivity to insulin and changes in blood insulin levels. Prospective studies of populations at high risk for type 2 diabetes suggest that in most patients, the initial inherited damage is insulin resistance[33,34]. The *ob/ob* mice mimic these characteristics of type 2 diabetes and demonstrate insulin resistance and hyperinsulinemia by 6 weeks of age[35]. Our study confirmed these characteristics, and showed reduced glucose disposal rates during the glucose clamp study in vehicle-treated *ob/ob* mice, which suggested insulin resistance was partly caused by reduced insulin receptor sensitivity. Treatment with ginseng extract improved peripheral insulin action as suggested by the significantly improved insulin-stimulated glucose disposal. Improvement in peripheral insulin sensitivity should increase tissue glucose uptake, lower blood glucose levels towards normal[23], and should also result in reduced insulin requirements. This is consistent with our present data, which demonstrate a significant reduction in serum insulin levels following treatment with ginseng extract, accompanied by improved peripheral insulin action.

While we have indicated a decreased serum insulin level with ginseng treatment, there are reports in the published literature that ginseng treatment increases serum insulin. Kimura *et al* indicated that administration of ginseng to alloxan-treated rats resulted in increased serum insulin levels[36,37]. Obviously, the effect of ginseng on the serum insulin level is dependent on the animal model used. The *ob/ob* mice show typical characteristics similar to type 2 diabetes mellitus, where impaired glucose tolerance is caused by decreased peripheral insulin sensitivity and a compensatory excess insulin release, which is corrected by ginseng treatment. However, alloxan-treated diabetic animal models are characterized by chemical destruction of pancreatic islets and a decreased insulin level. Ginseng treatment in this model caused stimulation of the residual islets and increased serum insulin and glucose-stimulated insulin secretion[38].

Because ginsenosides were shown to release nitric oxide (NO) from vascular tissues[39], and NO is known to stimulate glucose-dependent secretion of insulin in rat islet cells[40], ginseng extract may affect glucose transport, which is mediated by NO and thus modulates NO-mediated insulin secretion[41,42]. Ginseng may act through both mechanisms in exerting its antidiabetic effect; however, the more relevant mechanism in the type 2 diabetic model would be improved insulin sensitivity, thereby reducing insulin requirements and decreasing serum insulin.

The last hypothesis addresses the importance of antioxidants. It is clear that antioxidants are important in diabetes and circulating levels of radical scavengers were impaired throughout the progression of diabetes[43]. Therefore, the antioxidant character of ginseng extract may be a significant mechanism of antidiabetic properties. Recently, we used a cardiomyocyte culture model to measure the antioxidant effect of American ginseng berry extract[44] and ginsenoside Re (unpublished data). The results demonstrated that American ginseng berry extract and Re attenuated oxidant stress and protected cells from lethal oxidant damage. Therefore, American ginseng berry extract and ginsenoside Re have antioxidant properties. The antioxidant character of ginseng extract may be an important mechanism in the antidiabetic action.

In summary, our results have demonstrated that TGCG possesses anti-hyperglycemic and anti-obesity properties in diabetic *ob/ob* mice *in vivo*. We conclude that the total ginsenoside fraction of the leaf and stem extract could po-

tentially be developed into newer anti-diabetic agents subject to confirmation of its efficacy in clinical trials.

Acknowledgement

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