

## Anti-hyperglycemic effect of the polysaccharides fraction from American ginseng berry extract in *ob/ob* mice

J.T. Xie<sup>1,2</sup>, J.A. Wu<sup>1,2</sup>, S. Mehendale<sup>1,2</sup>, H.H. Aung<sup>1,2</sup>, and C.-S. Yuan<sup>1,2,3</sup>

<sup>1</sup>Tang Center for Herbal Medicine Research

<sup>2</sup>Departments of Anesthesia & Critical Care

<sup>3</sup>Committee on Clinical Pharmacology and Pharmacogenomics, The Pritzker School of Medicine, The University of Chicago, USA

### Summary

In this study, we evaluated the anti-hyperglycemic effect of a polysaccharides fraction from American ginseng berry extract in diabetic *ob/ob* mice. All animals received daily intraperitoneal injections of polysaccharides at 150 mg/kg body wt. ( $n = 5$ ), polysaccharides at 50 mg/kg body wt. ( $n = 5$ ), or vehicle ( $n = 5$ ) for 10 consecutive days. On Day 5, as compared to the vehicle-treated mice ( $230.5 \pm 13.5$  mg/dl, mean  $\pm$  S.E), mice from both treated groups showed significantly lower fasting blood glucose levels ( $187.4 \pm 20.5$  mg/dl and  $187.4 \pm 17.1$  mg/dl), respectively (both  $P < 0.05$ ). On Day 10, compared to the vehicle group ( $240.1 \pm 12.3$  mg/dl), the 50 mg/kg dose group were at  $188.4 \pm 12.6$  mg/dl ( $P < 0.05$ ), and the 150 mg/kg dose group were normoglycemic ( $148.8 \pm 17.6$  mg/dl,  $P < 0.01$ ). Those *ob/ob* mice treated with vehicle did not, however, show significant changes in fasting blood glucose levels. Data from the intraperitoneal glucose tolerance test (IPGTT) showed that, compared to Day 0, there was a significant improvement in glucose tolerance in animals who received the 50 and 150 mg/kg polysaccharide doses, and the area under the curve (AUC) decreased 15.5% ( $P < 0.05$ ) and 28.2% ( $P < 0.01$ ), respectively. Interestingly, after cessation of polysaccharide treatment, the fasting blood glucose levels stayed lower, and returned to control concentration on Day 30. We also observed that the polysaccharides fraction did not affect body weight changes in *ob/ob* mice. Our data suggest that the polysaccharides fraction from American ginseng berry extract has a potential clinical utility in treating diabetic patients.

**Key words:** American ginseng, ginseng berry, polysaccharides fraction, anti-hyperglycemic, diabetic *ob/ob* mice

### ■ Introduction

Ginseng root is a valuable herb in oriental medicine and has long been used as a remedy for a number of disorders. The root of ginseng has been utilized for over 2,000 years, in the belief that it is a panacea, tonic, roborant, and promotes longevity. The efficacy of ginseng root was known in the West by the eighteenth century, and the study of ginseng has a long history (Huang, 1999).

Historical records reveal that in traditional medical systems, a disease corresponding to type-2 diabetes was treated with plant extracts (Ackerknecht, 1982). Several reports have demonstrated that *Panax ginseng* C. A. Meyer (Asian ginseng) root has hypoglycemic effect both in normal and alloxan-induced hyperglycemic animals (Wang and Lei, 1957; Huang, 1999). *Panax quinquefolius* L. (American ginseng), another

common species of ginseng, is grown in the northern U.S. and Canada, but is also cultivated in France and northern China (Bensky and Gamble, 1993). Previous *in vitro* and *in vivo* animal studies (Kimura, 1980; Yokozawa et al. 1985; Kimura et al. 1999) and clinical trials (Sotaniemi et al. 1995; Vuksan et al. 2000a, 2000b) support the claim that the roots of Asian ginseng and American ginseng possess anti-hyperglycemic activities. Recently, we observed that extract of the berry (or fruit) of American ginseng has significant anti-hyperglycemic and anti-obesity effects in diabetic *ob/ob* mice (Xie et al. 2002a). In *ob/ob* mice, the *ob* gene was transferred from the stock of origin onto the B/6 genomic background and is located on chromosome 6 (Shafrir, 1992). Animals that are homozygous for the mutation exhibit morbid obesity and metabolic abnormalities that phenotypically resemble type 2 diabetes in humans.

Ginseng roots consist of a number of active constituents, such as ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids (Li and Zhang, 1986; Cao, 1989; Lee, 1992; Attele et al. 1999). These constituents are also found in ginseng berry, in different proportions (Zhang and Jiang, 1981; Liu et al. 1988; Wang et al. 2000; Hao et al. 2000). It has been shown that polysaccharides from ginseng root possess a hypoglycemic effect in alloxan-induced hyperglycemic mice (Konno and Hikino, 1987). However, the effect of polysaccharides fraction from the berry of American ginseng in diabetic *ob/ob* mice has not been investigated. The present study was designed to evaluate anti-diabetic effect of polysaccharides fraction from American ginseng berry extract in diabetic *ob/ob* mice.

## Materials and Methods

### Animals

The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Chicago. Male C57BL/6J *ob/ob* mice were obtained from Jackson Laboratory (Bar Harbor, ME). Mice were housed in environmentally controlled conditions with a 12-h light/dark cycle. All animals had free access to standard rodent pellet food (Zeigler Bros., Gardners, PA) and water *ad libitum*, except when fasted before experiments. Animals of 10–15 weeks of age were used in the study.

### Preparation of polysaccharides fraction from American ginseng berry extract

Fresh American ginseng berry was obtained from a ginseng farm in Wausau, WI. In brief, 500 g of berry was mixed with 500 ml organic solvent. After removal

of the seeds, 356 g pulp was collected. An additional 500 ml organic solvent was added, and the solution was heated and refluxed. This procedure was repeated three times. The organic solvent was then evaporated and the solution was filtered. The filtered solution contained both polysaccharides and ginsenosides.

The remaining solution was loaded onto a Dialon HP-20 gel column (Supelco, VA), and the passed solution collected. Afterwards, the column was washed with distilled water several times, until the color of the solution disappeared. All collected solutions were mixed and filtered to obtain the polysaccharides fraction (Ma et al. 1998; Sung et al. 2000). Finally, the extract was lyophilized. The extraction rate was approximately 2% from the fresh ginseng berry.

### Experimental protocol

Fifteen *ob/ob* mice received daily intraperitoneal (IP) injections, and were divided into three groups. The first drug group ( $n = 5$ ) received 150 mg/kg body wt. of polysaccharides fraction of American ginseng berry extract. The second drug group ( $n = 5$ ) received 50 mg/kg body wt. of polysaccharides fraction. The third vehicle group ( $n = 5$ ) received vehicle (0.9% NaCl). No noticeable irritation or restlessness was observed following administration of the extract or vehicle solutions.

As our previous reports (Attele et al. 2002; Xie et al. 2002b), fasting blood glucose levels and body weight were measured after fasting the animals for 4 h (starting from 9:00 AM) on Day 0 (before treatment), Day 5, and Day 10. Blood glucose levels were determined from the tail vein blood samples at 1:00 PM using a Glucose Analyzer (Hemocue AB, Angelholm, Sweden). After cessation of consecutive 10-day administration, fasting blood glucose levels and body weights were measured every five days, until the effect of polysaccharides disappeared.

Intraperitoneal glucose tolerance test (IPGTT) was performed on Day 0 and Day 10. On days of the test, animals fasted for 4 h (starting from 9:00 AM), followed by an IP administration of glucose (2 g/kg body wt.). 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  $\pm$  standard error. Statistical significance between vehicle-treated mice vs. drug-treated mice and between before treatment and after treatment were determined by paired Student's *t* test. A value of  $P < 0.05$  was considered statistically significant.

## Results

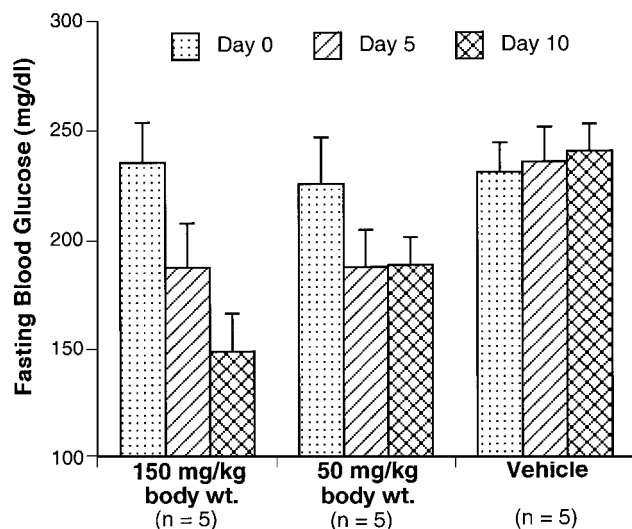
### Effect of the polysaccharides fraction on fasting blood glucose levels

As shown in Fig. 1, diabetic *ob/ob* mice had remarkably high baseline fasting blood glucose levels. The polysaccharides fraction of American ginseng berry extract at doses of 50 and 150 mg/kg body wt. decreased fasting blood glucose levels significantly. On Day 5, as compared to the vehicle-treated mice ( $230.5 \pm 13.5$  mg/dl), polysaccharides-treated animals had significantly lower fasting blood glucose levels ( $187.4 \pm 20.5$  mg/dl in the 50 mg/kg group and  $187.4 \pm 17.1$  mg/dl in the 150 mg/kg group; both  $P < 0.05$ ). On Day 10, as compared to the vehicle group ( $240.1 \pm 12.3$  mg/dl), the 50 mg/kg group were  $188.4 \pm 12.6$  mg/dl ( $P < 0.05$ ), and the 150 mg/kg group were normoglycemic ( $148.8 \pm 17.6$  mg/dl,  $P < 0.01$ ). However, those *ob/ob* mice treated with vehicle did not show significant changes in fasting blood glucose levels.

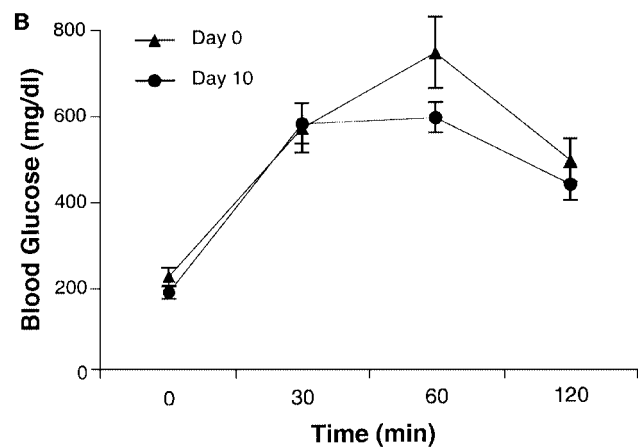
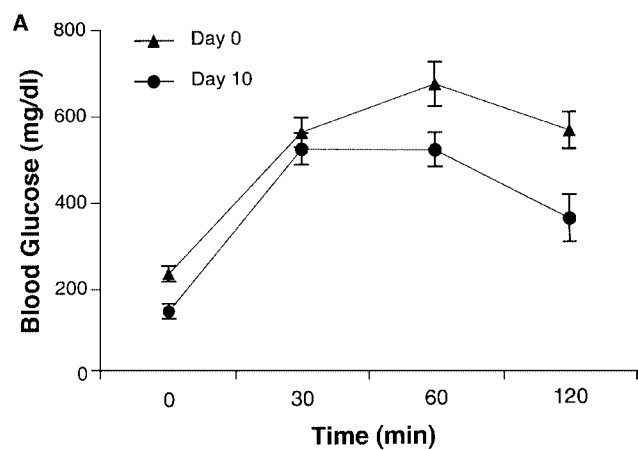
### Effects of the polysaccharides fraction on the glucose tolerance test

Glucose tolerance was evaluated using the IPGTT, prior to and 10 days after treatment with the polysaccharides fraction. As shown in Fig. 2A (150 mg/kg

body wt. group) and 2B (50 mg/kg body wt. group), on Day 0, *ob/ob* mice demonstrated basal hyperglycemia, and this hyperglycemia was exacerbated by the IP glucose load, and failed to return to baseline after 120 min indicating glucose intolerance. After 10-day treatment with polysaccharides at 150 and 50 mg/kg body wt., overall glucose tolerance improved remarkably. After 150 and 50 mg/kg body wt. polysaccharides treatment, the area under the curve (AUC) decreased 28.2% (from  $287.8$  mg/ml · min of Day 0 to  $206.7$  mg/ml · min of Day 10,  $P < 0.01$ ) and 15.5% (from  $249.6$  mg/ml · min of Day 0 to  $211.0$  mg/ml · min of Day 10,  $P < 0.05$ ), respectively.



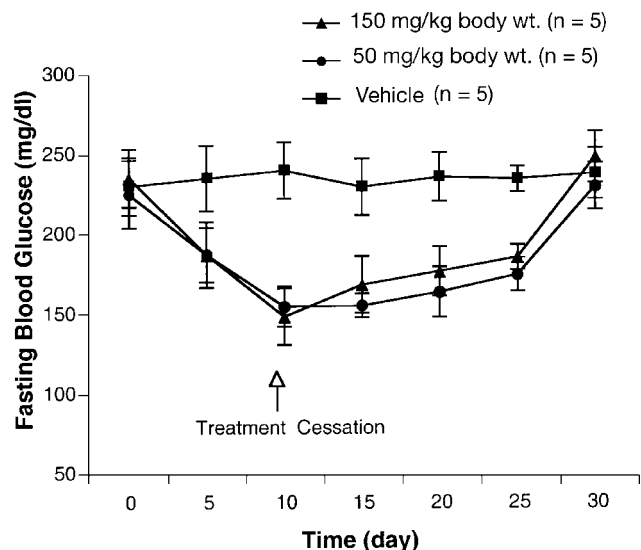
**Fig. 1.** Effect of the polysaccharides fraction from American ginseng berry extract on fasting blood glucose levels in diabetic *ob/ob* mice. The glucose levels decrease significantly in 50 mg/kg body wt. and 150 mg/kg body wt. polysaccharides-treated mice on Day 5 (both  $P < 0.05$  as compared to vehicle-treated mice) and Day 10 ( $P < 0.05$  and  $P < 0.01$  as compared to vehicle-treated mice, respectively).



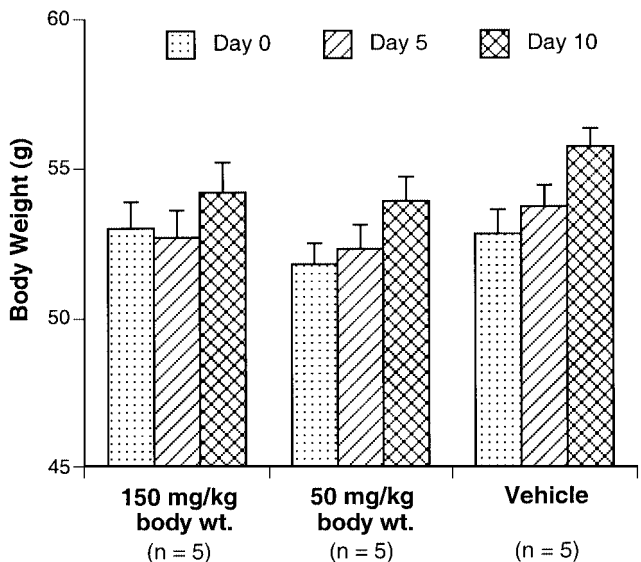
**Fig. 2.** Intraperitoneal glucose tolerance test in *ob/ob* mice before (Day 0) and after a 10-day treatment with polysaccharides fraction from American ginseng berry extract. (A) 150 mg/kg body wt. polysaccharides-treated mice ( $n = 5$ ). (B) 50 mg/kg body wt. polysaccharides-treated mice ( $n = 5$ ). There is a significantly higher rate of glucose disposal based on measurement of area under the plasma concentration curve (AUC) ( $P < 0.01$  and  $P < 0.05$  compared to Day 0, respectively).

**Prolonged effect of the polysaccharides fraction on fasting blood glucose levels**

To observe whether there was an effect on fasting blood glucose concentration after cessation of polysaccharides treatment, we measured the blood glucose



**Fig. 3.** Prolonged hypoglycemic effect on fasting blood glucose levels in *ob/ob* mice treated with 150 and 50 mg/kg body wt. polysaccharides fraction from American ginseng berry extract. After 5 days (Day 15), 10 days (Day 20), and 15 days (Day 25) cessation of treatment, fasting blood glucose levels were significantly lower as compared to the vehicle group (all  $P < 0.01$ ).



**Fig. 4.** Effects of polysaccharides fraction on body weight changes in diabetic *ob/ob* mice. While there is a tendency to increase in body weight from Day 0 to Day 10 in mice receiving vehicle, polysaccharides treatment did not affect body weight changes.

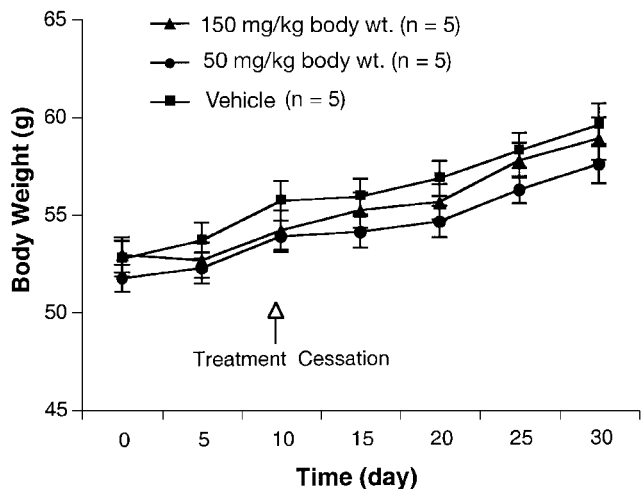
every five days until the levels returned to those measured prior to the treatment. Fig. 3 shows a prolonged effect in animals who received polysaccharides treatment. Fasting blood glucose levels were  $168.6 \pm 17.7$  (150 mg/kg) and  $155.6 \pm 7.4$  (50 mg/kg) on Day 15,  $176.8 \pm 15.4$  (150 mg/kg),  $163.8 \pm 15.7$  (50 mg/kg) on Day 20, and  $185.6 \pm 7.9$  (150 mg/kg) and  $174.8 \pm 10.4$  (50 mg/kg) on Day 25, respectively (all  $P < 0.01$  compared to the vehicle group).

**Effects of the polysaccharides fraction on body weight changes**

As shown in Fig. 4, the body weight of *ob/ob* mice in the vehicle-treated group had a tendency to increase from Day 0 to Day 10. This tendency of body weight increase was not affected by 150 or 50 mg/kg body wt. polysaccharides administration. After cessation of drug injection, a prolonged hypoglycemic effect was observed, as presented in Fig. 3. However, in our 30 days observation, body weight changes were not affected by polysaccharides treatment (Fig. 5).

**Discussion**

Type-2 diabetes is a major health problem, affecting approximately 5% of the total population of the U.S., and 3% of the population world-wide. Currently available drugs for type-2 diabetes have a number of limitations such as adverse effects and high rates of secondary failure (DeFronzo, 1999). These problems have led to the search for alternative therapies that may have



**Fig. 5.** Effect of polysaccharides on body weight changes in diabetic *ob/ob* mice. As compared to the vehicle group, polysaccharides administration did not affect body weight changes during and after treatment.

a similar degree of efficacy without the troublesome side-effects associated with the conventional drug treatment. The identification of compounds from medicinal plants with anti-hyperglycemic activity may also provide an opportunity to develop a new class of anti-diabetic agent.

In this study, we observed that the polysaccharides fraction of American ginseng berry extract had a significant anti-hyperglycemic effect. Glucose tolerance also improved significantly after polysaccharides treatment. This was shown by overall glucose excursion, calculated as area under the curve during the two-hour intraperitoneal glucose tolerance test, which decreased up to 28% as compared to pre-treatment levels. Whether this improvement of glucose tolerance is due to an increase in insulin sensitivity remains to be tested in future experiments using body-wide hyperinsulinemic-euglycemic clamp technique (DeFronzo, 1999).

Previously, we observed that extract of ginseng berry had significant anti-hyperglycemic and anti-obese effects in *ob/ob* and *db/db* mice (Attele et al. 2002; Xie et al. 2002b). However, unlike ginseng berry extract, the polysaccharides fraction of the extract did not affect body weight in the *ob/ob* mice. Thus, the anti-hyperglycemic action of the polysaccharides fraction is independent of body weight changes. This suggests that other constituents in the berry extract have distinct pharmacological mechanisms affecting energy metabolism.

Past anti-diabetic activity data suggested that ginseng root may affect glucose transport, which is mediated by nitric oxide (NO), and thus modulate NO-mediated insulin secretion (Hasegawa et al. 1994; Ohnishi et al. 1996; Roy et al. 1998). It was shown recently that NO stimulates glucose-dependent secretion of insulin in rat islet cells (Spinas et al. 1998). In these studies, however, the investigators did not test which fraction of ginseng extract, for example, ginsenoside or polysaccharide fraction, are responsible for the observed effects.

Another possible action site for ginseng berry extract to contribute its hypoglycemic effect is in the gastrointestinal tract. Gastric vagal afferents are the primary neuroanatomical link between the stomach and the central nervous system. In a previous study, we reported that ginseng extract, via gastric vagal afferents, inhibited brainstem neuronal activity (Yuan et al. 1998). Suzuki et al. (1991) reported that gastric secretion *in vitro* was inhibited by ginseng (Suzuki et al. 1991). These results suggest that ginseng may slow the digestion of food and decrease the rate of carbohydrate absorption. Since we observed a significant prolonged hypoglycemic effect after cessation of polysaccharides fraction treatment in this study, it is unlikely that the delay in digestion after the treatment would last several weeks.

Yang et al. reported that intraperitoneal or subcutaneous injection of polysaccharides from ginseng root, at dose of 50–200 mg/kg body wt., reduced blood glucose and liver glycogen levels significantly in mice (Yang et al. 1990; Yang and Wang, 1991). These investigators proposed that the reduction of blood glucose and liver glycogen by polysaccharides may be due primarily to the increase of carbohydrate utilization and the decrease of glycogenesis. They also observed that the polysaccharides stimulated the release of insulin. The exact mechanisms of the polysaccharides fraction from American ginseng berry extract in *ob/ob* mice are yet to be determined.

Various components from ginseng polysaccharides have been reported. For example, heteroglycans composed of six monosaccharides (Liu et al. 1988) and a number of biologically active panaxans were isolated (Konno and Hikino, 1987; Konno et al. 1984; 1985) in alloxan-induced type-1 diabetic mice. Whether these components have a similar effect on type-2 diabetic mice is still unknown. The activity-guided polysaccharides fractionation approach will be useful in our future studies to identify the particular constituents responsible for the pharmacological effect observed in this study.

The present study demonstrated that the polysaccharides fraction from American ginseng berry extract has a significant anti-hyperglycemic activity. Our observation suggested that the polysaccharides may have a potential clinical utility in treating type-2 diabetic patients. On the other hand, due to a prolonged effect of the polysaccharides on fasting blood glucose levels observed in this study, the pharmacokinetics of the compound warrant future investigation. Caution should be taken due to the undesirable additive hypoglycemic effect occurring when other anti-hyperglycemic drugs are added after cessation of polysaccharides administration.

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## ■ Address

Chun-Su Yuan, Department of Anesthesia & Critical Care, The University of Chicago Medical Center, 5841 S Maryland Avenue, MC 4028, Chicago, Illinois 60637, USA  
Tel.: (773) 702-1916; Fax: (773)834-0601;  
e-mail: cyuan@airway.uchicago.edu