

Original Research

Null and Opposing Effects of Asian Ginseng (*Panax ginseng* C.A. Meyer) on Acute Glycemia: Results of Two Acute Dose Escalation Studies

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Key words: complementary and alternative medicine, ginseng, postprandial, glucose, insulin

Objective: We have repeatedly reported that a batch of American ginseng with a specific ginsenoside (glycosidal saponin) profile decreases acute postprandial glycemia. We investigated whether Asian ginseng is able to replicate this glycemia-lowering efficacy in two separate acute dose escalation studies.

Methods: Each study was conducted in a separate sample of 11 healthy subjects (gender:8M:3F and 6M:5F, age: 29 ± 2 y and 27 ± 3 y, BMI: 28.5 ± 2.1 kg/m² and 26.9 ± 1.4 kg/m²) using a randomized, single-blind, placebo-controlled, multiple-crossover design. Treatments consisted of 0 (placebo), 1, 2, and 3 g of Asian ginseng for the first study and 0 (placebo), 3, 6, and 9 g Asian ginseng for the second study administered 40 minutes before a 75g-OGTT protocol with blood drawn at -40, 0, 15, 30, 45, 60, 90, and 120 minutes. Ginsenosides were analyzed by HPLC-UV.

Results: Neither the main effect of pooled-treatment, nor dose, nor either factors interaction with time was significant for incremental plasma glucose and insulin. But the diagnostically and therapeutically relevant two-hour plasma glucose (2h-PG) value was significantly higher for pooled Asian ginseng treatment than placebo (5.46 ± 0.31 versus 4.99 ± 0.30 mmol/L, $p = 0.050$). Ginsenoside analyses showed that the Asian ginseng contained up to 96% lower and sevenfold higher quantities of various ginsenosides and their ratios than our previous efficacious batch of American ginseng.

Conclusions: Asian ginseng showed both null and opposing effects on indices of acute postprandial plasma glucose and insulin. This is in contrast to our findings with American ginseng. One explanation may be the marked ginsenoside differences. Practitioners and consumers should be aware of ginseng's variable effects.

INTRODUCTION

The prevalence of use of complementary and alternative medicine (CAM) is high among people with diabetes [1–2] and those seeking to prevent chronic diseases that include diabetes [3]. This is despite deficient safety and efficacy evidence and adequate legislation to support claims. This unsupported demand has prompted a call for rigorous scientific evaluations [4–6]. To meet this call, a growing database of studies investigating the effects of ginseng in diabetes has emerged. Various

in vitro and animal models of diabetes indicate that ginseng species including Asian (*Panax ginseng* C.A. Meyer), American (*Panax quinquefolius* L), and San-chi (*Panax notoginseng* [Burk.] F.H. Chen) ginsengs improve carbohydrate metabolism [8–10]. Human evidence has confirmed this benefit. Although complicated by energy restriction and weightloss, a Finnish study reported that an unidentified ginseng species decreased fasting glycemia and HbA_{1c} in subjects with type 2 diabetes and postprandial glycemia following a 75 g oral glucose tolerance test (75g-OGTT) in a subset of these subjects after eight

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Dr. Vuksan has received research and travel funding from Chai-Na-Ta Corp., Langley, BC; MuscleTech Research and Development Incorporated, Mississauga, ON; the Ontario Ginseng Growers Association, Simcoe, ON; Ginseng Growers of Canada, Simcoe, ON; Ontario Ministry of Agriculture, Toronto, ON, the Korean Ministry of Agriculture, Seoul, South Korea; and BioSapogen Inc, Seoul, South Korea.

Journal of the American College of Nutrition, Vol. 22, No. 6, 524–532 (2003)

Published by the American College of Nutrition

weeks' administration [11]. We also showed that a single batch of American ginseng consistently decreased postprandial glycemia in people with [12,13] and without diabetes [12,14,15] after acute administration. Collectively, these data have led the American Diabetes Association in its 2002 Evidence-Based Nutrition Principles and Recommendations to recognize ginseng as one of the best-studied CAMs in diabetes research [7].

The generalizability of this research is obscured by uncertainty about which individual components or their combinations are responsible for the reductions observed. Most of ginseng's antihyperglycemic activity has been attributed to ginsenosides (steroidal triterpene glycosides of which more than thirty have been identified). Total and isolated protopanaxadiol (PPD) ginsenosides (Rb₁, Rb₂, Rc, Rd, Rg₃) and protopanaxatriol (PPT) ginsenosides (Rg₁, Re, Rf, Rg₂, Rh₁) have been shown to increase glucose disposal significantly *in vitro* [17–19]. An Asian ginseng berry extract with high levels of Re [20,21] and an extract of Re alone [21] have also shown hypoglycemic effects in db/db and ob/ob mice respectively. Finally, the human studies from our laboratory have demonstrated that only an American ginseng with a specific ginsenoside profile decreases acute postprandial glycemia [22]. Whether other ginseng species with marked differences in their ginsenoside profiles are able to replicate this acute glycemia-lowering efficacy in humans is unknown. To investigate this possibility, we conducted two acute dosing studies of the most popular commercial ginseng species [23], Asian ginseng, following the same protocol used in our earlier work [12–16].

METHODS

Participants

Healthy participants without previously diagnosed dysglycemia were recruited separately for each study from faculty and students at the University of Toronto and hospital advertisements. Fourteen participants were enrolled in the first study and 11 participants were enrolled in the second study. Informed written consent was obtained from the participants before beginning the studies. Of the 14 participants enrolled in the first study, 11 (gender: 8M:3F, age: 29 ± 2y, BMI: 28.5 ± 2.1 kg/m²) completed the study. One withdrew due to a time conflict, a second was excluded due to subsequently diagnosed glucose intolerance, and a third was removed due to an apparent allergic reaction following the first test. In the case of this last subject, although she had been able to consume American ginseng without incident five days earlier and a follow-up skin test with the same batch of Asian ginseng was negative, she was withdrawn from the study and advised to avoid ginseng of any species. Of the 11 participants enrolled in the second study, all 11 (gender: 6M:5F, age: 27 ± 3 y, BMI: 26.9 ± 1.41 kg/m²) completed the study. Two of these participants also completed the first study. Both studies were approved by the Research Ethics Board at St Michael's Hospital.

Design

The two studies were conducted seven months apart each using a randomized, single-blind, placebo-controlled, multiple-crossover design. By this design, the participants for each study did all ginseng and placebo treatments on separate days and in random order. In the first study, the first recruited group of participants received four "low-dose" treatments: 0 (placebo), 1, 2, and 3 g of Asian ginseng. In the second study, the second recruited group of participants received four "high-dose" treatments: 0 (placebo), 3, 6, and 9 g of Asian ginseng. The design for each study was powered to achieve 93%, 100%, and 85% power (1-β) for plasma insulin (PI) and 99%, 100%, and 100% power for plasma glucose (PG) at a 5% significance level (α) in 10 healthy participants when an F test is used to test the effect of the factor dose at the four levels indicated for each study, the factor time at eight levels (-40, 0, 15, 30, 45, 60, 90, 120 minutes), and their interaction respectively. These calculations assumed that the actual SD among the appropriate means was 16.77 pmol/L (an effect size of 0.22), 106.92 pmol/L (an effect size of 1.43), and 21.01 pmol/L (an effect size of 0.28) respectively for incremental PI and 0.224 mmol/L (an effect size of 0.28), 1.47 mmol/L (an effect size of 1.84), and 0.58 mmol/L (an effect size of 0.73) respectively for incremental PG.

Treatments

The batches of Asian ginseng and placebo were identical in both studies. The Asian ginseng was three-year-old powdered whole root (Korean Ministry of Agriculture and Forestry, Seoul South Korea) encapsulated in gel capsules at 500 mg. To ensure stability, the encapsulated ginseng was stored in a cool, dry, dark location over the course of the study and used within nine months of production. The placebo consisted of corn-flour encapsulated identically. Attempts were made to match the treatments within each study. The energy and carbohydrate content of the placebo were designed to approximate that of the Asian ginseng. The number of capsules was also kept equal among the treatments by adding placebo capsules to the lower doses.

Protocol

The protocol was identical for both studies. It followed the World Health Organization (WHO) guidelines for the administration of a 75 g oral glucose tolerance test (75g-OGTT) [24]. Participants attended the Risk Factor Modification Centre at St. Michael's hospital twice following a 10-to-12-hour overnight fast. A minimum of three days separated each visit to minimize carry-over effects. Each participant was instructed to maintain the same dietary and exercise patterns the evening before each test and consume a minimum of 150 g of carbohydrate each day over the three days prior to the test. To ensure compliance, participants completed a questionnaire detailing pre-session

information about their diet and lifestyle patterns and submitted to measurements of their body weight and total body fat, assessed by infrared-interactance using a FUTREX-5000® (FUTREX Inc., Gaithersburg, MD). Upon commencement of the OGTT, participants had a catheter inserted into a forearm vein that was secured by tape and kept patent by saline. From this device a fasting 7mL-blood sample was obtained in a plasma tube. Treatment capsules were then administered with exactly 300 mL of tap water. Participants gave another blood sample after 40 minutes. This was followed by consumption of the 75 g oral glucose load (75g-Glucodex®, Technilab, Quebec, Canada) over exactly five minutes. Additional blood samples were drawn at 15, 30, 45, 60, 90, and 120 minutes after the start of the load. Adverse symptom monitoring during each clinic visit and in the intervening washout days (≥ 3 days) was assessed by subjective seven-point bipolar visual analogue scales.

Ginseng Analyses

The ginsenoside profile of the Asian ginseng was measured using standard techniques. The ginsenosides compose principally a family of steroids called dammarane-type triterpene glycosides with either (20*S*)-protopanaxadiol (PPD) or (20*S*)-protopanaxatriol (PPT) as the aglycone. The four main PPD ginsenosides (Rb₁, Rb₂, Rc, Rd) and three main PPT ginsenosides (Rg₁, Re, Rf) were analyzed using HPLC-UV techniques developed for the American Botanical Council (ABC) Ginseng Evaluation Program [25]. The HPLC conditions included: chromatograph—Beckman HPLC system; column—a reverse-phase Beckman ultrasphere C-18, 5 μ m octadecylsilane, 250 \times 4.6 mm column; mobile phase—de-ionized water and acetonitrile; flow rate—1.3 mL/minute; UV detection—a module 168 diode-array detector set at 203 nm. The ginsenoside standards for Rg₁ and Re were provided by Dr. H. Fong, University of Illinois and the Rf, Rb₁, Rc, Rb₂, Rd standards were provided by Indofine Chemical Co., Somerville NJ.

Plasma Glucose and Insulin Analyses

All samples were separated by centrifuge and the plasma immediately frozen at -20°C pending analysis. Analyses of glucose concentration of each sample were done by the glucose oxidase method [26] and the insulin concentration, by double antibody radioimmunoassay [27], at the Banting and Best Diabetes Centre Core Laboratory, Toronto, Canada.

Statistical Analyses

Various indices of glucose and insulin regulation were derived from PG and PI during the OGTT. Incremental PG and PI curves, calculated as the change from baseline (-40 minutes), were plotted and the positive incremental area under the curve (AUC) was calculated [28]. Incremental values were used to control for baseline differences between the treatments.

Absolute values for peak-PG and peak-PI independent of time and 2h-PG were also assessed. Other derived indices included the whole body insulin sensitivity index (ISI) [28] and the early insulin secretion index, $\Delta\text{PI}_{30-0}/\Delta\text{PG}_{30-0}$ [30]. Both were calculated using absolute PG and PI values in derived equations for the OGTT. ISI was calculated using fasting PG (FPG) and PI (FPI) with mean OGTT outcome, according to the formula [29]: 10 000 divided by the square root of $([\text{FPG} \times \text{FPI}] \times [\text{mean-PG} \times \text{mean-PI}])$, where PG is expressed in mg/dL (0.0551 mmol/L) and PI in $\mu\text{U/mL}$ (6 pmol/L). The early insulin secretion index, $\Delta\text{PI}_{30-0}/\Delta\text{PG}_{30-0}$, was calculated as the change in PI from 0 minutes to 30 minutes divided by the change in PG over the same period [30]. Statistical analyses were then performed using the *Number Cruncher Statistical System* (NCSS) 2000 software (NCSS statistical software, Kaysville, Utah). Repeated measures two-way ANOVA assessed the interactive and independent effects of pooled-treatment (the mean of all Asian ginseng treatments) and pooled-time (the mean of all protocol time points) for the two studies combined and the interactive and independent effects of dose and time for each study separately on incremental PG and PI. If the interaction terms were significant, then repeated measures one-way ANOVA assessed differences in incremental PG and PI at each time point. This statistic also assessed differences in AUC-PG, AUC-PI, peak-PG and peak-PI, 2h-PG, ISI, and $\Delta\text{PI}_{30-0}/\Delta\text{PG}_{30-0}$. Adjustment for multiple pairwise comparisons in each case was done by the Tukey Kramer procedure. Paired student *t* tests assessed differences in subjective ratings of symptoms for both the clinical testing and washout periods. All results were expressed as mean \pm SEM and considered significant at $p \leq 0.05$.

RESULTS

Both study protocols were followed safely and without difficulty by the respective groups of participants. A minimum of 150 g of carbohydrate was consumed over the three days prior to each test. Baseline anthropometry and fasting plasma glucose and insulin were maintained. The participants consumed the placebo and Asian ginseng capsules in the self-standardized amount of time and the 75 g Glucodex® oral glucose load in the allotted five minutes for each test. There were also no differences among the placebo and Asian ginseng treatments in reported symptoms that included bloating, belching, nausea, dizziness, headache, diarrhea, flatulence polyuria, insomnia, anxiety, numbness, light-headedness, or drowsiness during the clinic visits or intervening washout periods.

Fig. 1 shows the PG and PI responses following a 75 g-OGTT for the mean of all doses of Asian ginseng over a 3–9 g dose range compared with the mean of two placebos from two studies. Two-way repeated measures ANOVA applied to these data demonstrated that there was a significant effect of pooled-time ($p < 0.0001$, $p < 0.00001$) but no effect of

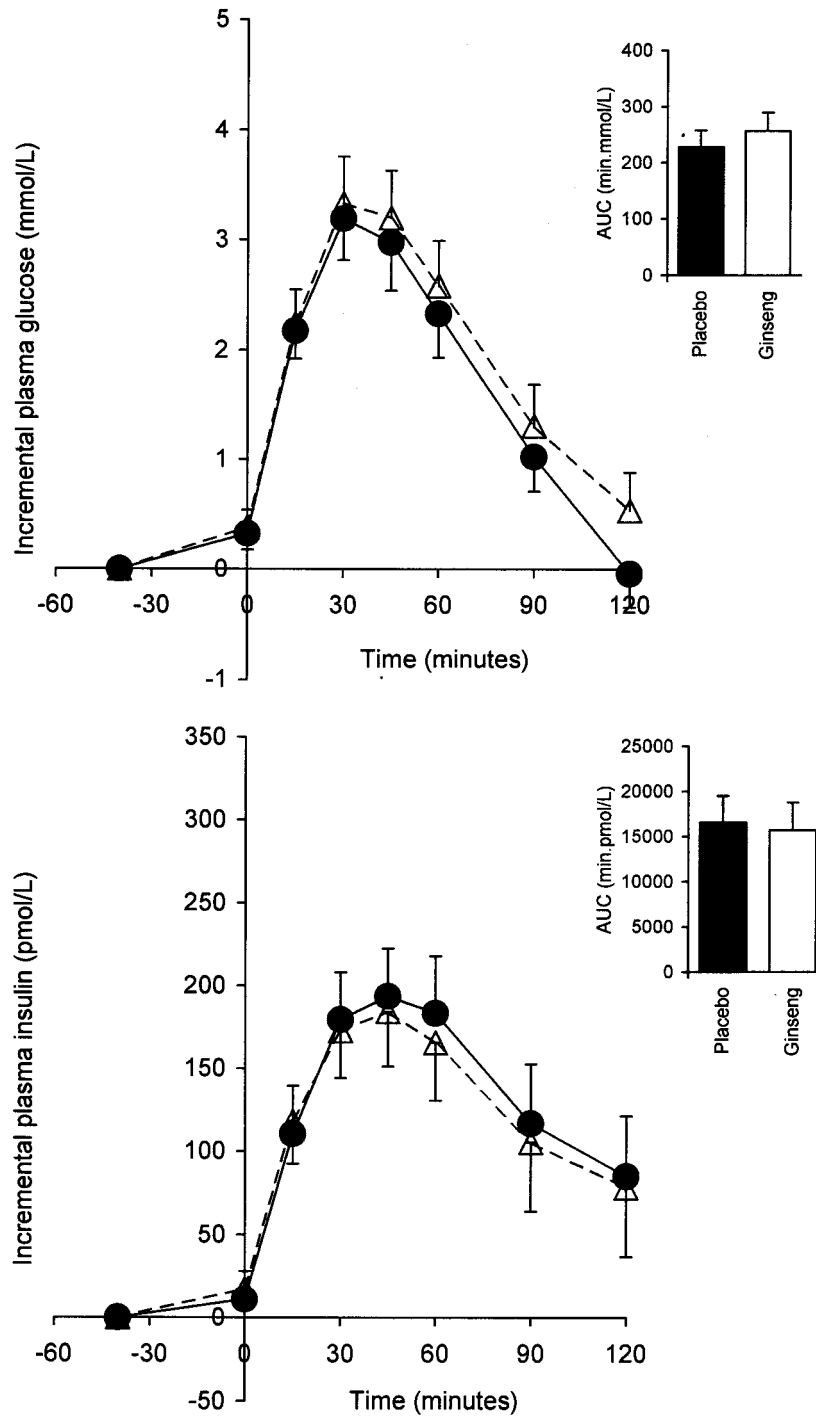


Fig. 1. The aggregate acute treatment effect of Asian ginseng on plasma glucose and insulin for two studies. The line plots and bars represent the incremental and AUC plasma glucose and insulin responses following the mean of two placebos (3 g and 9 g) (●) or the mean of doses from 1–9 g (1–3 g and 3–9 g) (△) taken 40 minutes before a 75 g oral glucose tolerance test (75 g-OGTT) in two studies each with 11 healthy, nondiabetic participants, in which each subject did all treatments in a single-blinded, randomized, multiple crossover design. Data are mean ± SEM.

pooled-treatment ($p = 0.12, p = 0.89$) on PG and PI respectively, with no interaction between pooled-time and pooled-treatment for either parameter ($p = 0.29, p = 0.93$). This was reflected in a lack of effect of pooled-treatment on AUC-PG ($p = 0.11$), AUC-PI

($p = 0.77$), peak-PG ($p = 0.59$), peak-PI ($p = 0.43$), ISI ($p = 0.93$), and $\Delta\text{PI}_{30-0}/\Delta\text{PG}_{30-0}$ ($p = 0.55$). But pooled-Asian ginseng significantly increased 2h-PG compared with pooled-placebo (5.46 ± 0.31 versus 4.99 ± 0.30 mmol/L, $p = 0.050$).

Fig. 2 shows the postprandial PG and PI responses following a 75g-OGTT with escalating doses of Asian ginseng in the first and second studies. Panel A compares the effect of 1, 2, or 3 g Asian ginseng with placebo on incremental PG and PI following a 75g-OGTT in the first study. Two-way repeated measures ANOVA applied to these data demonstrated that there was a significant effect of time ($p < 0.0001$, $p < 0.0001$) but no effect of dose ($p = 0.85$, $p = 0.75$) on PG and PI, with no interaction for either parameter ($p = 0.093$, $p = 0.79$). This was reflected in a lack of effect of dose on AUC-PG ($p = 0.90$), AUC-PI ($p = 0.82$), 2h-PG ($p = 0.17$), peak-PG ($p = 0.80$), peak-PI ($p = 0.91$), ISI ($p = 0.86$) and $\Delta\text{PI}_{30-0}/\Delta\text{PG}_{30-0}$ ($p = 0.73$). Panel B compares the effect of 3, 6, and 9 g Asian ginseng with placebo on incremental PG and PI following a 75 g-OGTT in the second study. Two-way repeated measures ANOVA applied to these data demonstrated that there was a significant effect of time ($p < 0.0001$, $p < 0.0001$) but no effect of dose ($p = 0.17$, $p = 0.86$) on PG and PI, with no interaction for either parameter ($p = 0.57$, $p = 0.52$). This was

reflected in a lack of effect of dose on AUC-PG ($p = 0.13$), AUC-PI ($p = 0.63$), 2h-PG ($p = 0.62$), peak-PG ($p = 0.45$), peak-PI ($p = 0.32$), $\Delta\text{PI}_{30-0}/\Delta\text{PG}_{30-0}$ ($p = 0.91$), and ISI, although it was approaching significance (5.4 ± 0.72 vs. 4.17 ± 0.60 vs. 5.07 ± 0.90 vs. 6.41 ± 0.83 , $p = 0.088$).

Table 1 shows the ginsenoside analysis for the Asian ginseng used in the present study and our original efficacious batch of American ginseng [12–16]. The composition of the present Asian ginseng batch and our original American ginseng batch were consistent with authentic *Panax ginseng* C.A. Meyer and *Panax quinquefolius* L respectively. Key ratios and the presence and absence of various ginsenosides are used in their authentication. A ratio of $\text{Rb}_1:\text{Rg}_1 < 3$ [31–33] and ratios of $\text{Rg}_1:\text{Re}$ and $\text{Rb}_2:\text{Rc} > 1$ [34] have been shown to be indicative of *Panax ginseng* C.A. Meyer. Conversely, the opposite is true for *Panax quinquefolius* L. [31–34]. The most powerful marker is the presence of Rf, a ginsenoside not found in American ginseng and distinctive for Asian ginseng [31–35]. Both batches met their respective criteria. These species-

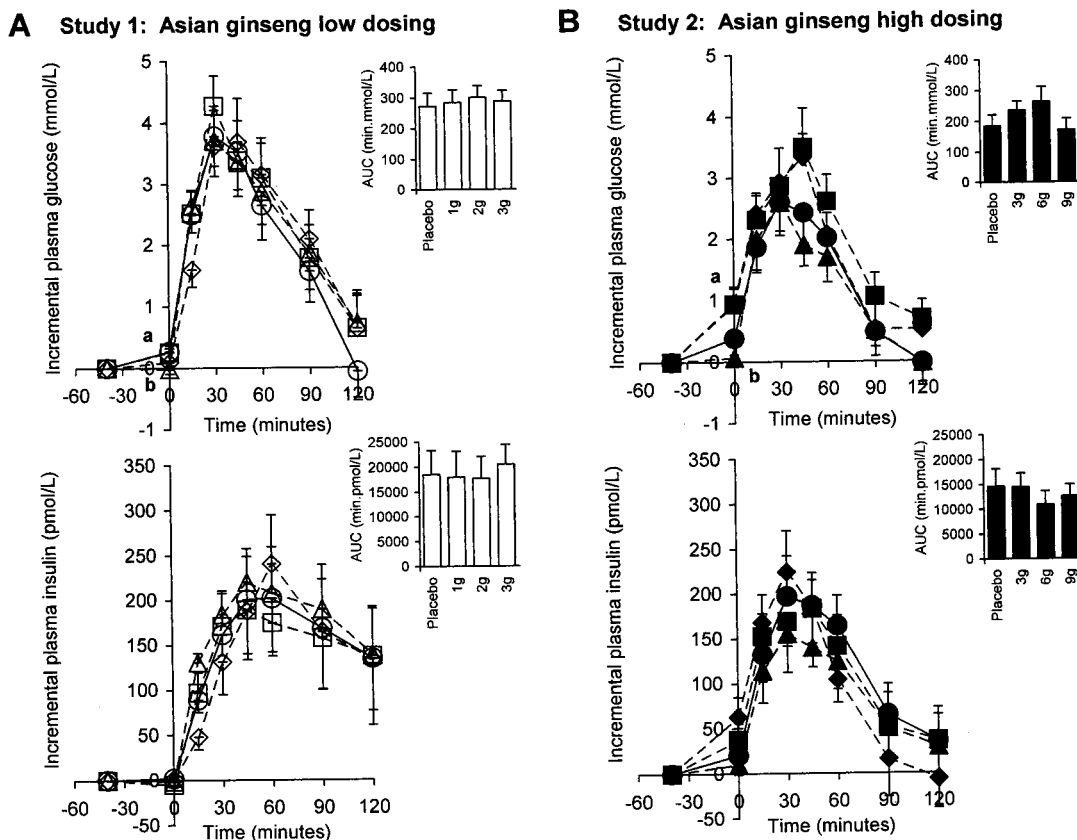


Fig. 2. Acute dose effects of Asian ginseng over a 1–9 g dose range on plasma glucose and insulin in two studies: (A) Study 1—the line plots and bars represent the incremental change and AUC for plasma glucose and insulin following placebo (○) or doses of 1 g (◇), 2 g (□), or 3 g (△) of Asian ginseng taken 40 minutes before a 75 g oral glucose tolerance test (75 g-OGTT) in 11 healthy, nondiabetic participants, in which each subject did all treatments in a single-blinded, randomized, multiple crossover design. (B) Study 2—the line plots and bars represent the incremental change and AUC for plasma glucose and insulin following placebo (●) or doses of 3 g (◆), 6 g (■), or 9 g (▲) of Asian ginseng taken 40 minutes before a 75 g oral glucose tolerance test (75 g-OGTT) in 11 healthy, nondiabetic participants, in which each subject did all treatments in a single-blinded, randomized, multiple crossover design. Data are mean ± SEM.

Table 1. Ginsenoside Profiles

Ginsenosides	Content ¹		Δ (%)
	Present Asian ginseng	Original American ginseng	
Protopanaxadiols (PPD) (% wt/wt)			
Rb ₁	0.18	1.53	-88
Rb ₂	0.09	0.06	50
Rc	0.07	0.24	-71
Rd	0.02	0.44	-96
Protopanaxatriols (PPT) (% wt/wt)			
Rg ₁	0.16	0.1	60
Re	0.17	0.83	-80
Rf	0.12	0	-
Total (% wt/wt)	0.8	3.21	-75
Ratios (% wt/wt:% wt/wt)			
PPD:PPT	0.8	2.44	-67
Rb ₁ :Rg ₁	1.13	15.3	-93
Rb ₂ :Rc	1.3	0.25	420
Rg ₁ :Re	0.94	0.12	683

¹ Determined by HPLC-UV analyses [25]. The present Asian ginseng batch represents the Asian ginseng batch tested in the present study and the original American ginseng batch represents the American ginseng batch shown to be efficacious in our previous studies [12–16].

specific differences translated into marked differences between the two ginsengs. The present batch of Asian ginseng contained up to 96% lower and sevenfold higher quantities of various ginsenosides and their ratios than our previous efficacious batch of American ginseng.

DISCUSSION

The present dose-ranging studies demonstrate both null and opposing effects of a single batch of Asian ginseng on post-prandial indices of glucose and insulin regulation. Although the main effects of treatment and dose remained insignificant, glycemia was higher for the mean of all Asian ginseng doses at the diagnostically and therapeutically relevant [36] two-hour time point (2h-PG) compared with placebo. These findings are in direct contrast to the results observed with our original batch of American ginseng. We noticed that 6 g of our original batch of American ginseng lowered the PG response to a 75 g-OGTT significantly ($p < 0.05$) in 8 nondiabetic subjects [16,22]. This is in addition to the reductions we reported in an earlier series of dosing (1–9 g) and timing (120 minutes to 0 minutes before oral glucose) response studies in people with and without type 2 diabetes, following capillary glycemia protocols using a 25 g-OGTT [12–16].

An enticing explanation for the discrepancy in findings between the present Asian ginseng and our original efficacious batch of American ginseng are species-specific compositional

differences. Traditional systems of medicine have long considered the two species to be distinct: Asian ginseng is hot, replenishing the yang, while American ginseng is cool, replenishing the yin [37]. As diabetes represents principally a deficiency of the yin [38], our discrepant findings are predicted by this paradigm: Asian ginseng should aggravate while American ginseng should improve elevated glycemia. There is, however, no empirical evidence to suggest that the profile that defines Asian ginseng, the presence of Rf and ratios of Rg₁:Re and Rb₂:Rc > 1 [31–35], would produce differential results. In this regard, authentic Asian ginseng and its extracts have been shown to have numerous hypoglycemic effects in normal and hyperglycemic animal models [8–10].

Our discrepant findings may be related less to species-specific differences and more to differences arising from the recognized problem of high compositional variability among preparations [39]. There were marked differences between the present Asian ginseng and our original batch of American ginseng in ginsenosides whose quantities are not necessarily species-specific. As we noted previously for another batch of American ginseng that demonstrated null effects [22], it is possible that those shown previously to have hypoglycemic activity were below their efficacy range. Two of the three main PPD ginsenosides that were found to be in lower concentrations in the present Asian ginseng batch, Rb₁ and Rc, have been shown only to increase glucose transport at higher levels (> 1.0 μ M) in sheep erythrocytes [19]. It was also with a high dose of Re (20 mg/kg) that a significant decrease in glycemia in ob/ob mice was observed [20,21]. This dose is > 75 -fold higher than the Re equivalent dose range of 0.029–0.26 mg/kg for a 70 kg person that we fed in the present dosing studies. The suggestion is that these ginsenosides might have been present in insufficient quantities to have hypoglycemic effects. Lending support to this view is the tendency of the highest 9 g dose to lower glycemia relative to the 3 g and 6 g doses at two points in the second study. The stepwise increase in the insulin sensitivity index over the 3 g–9 g dose range was also approaching significance ($p = 0.088$). It is possible that doses > 9 g would have exhibited further lowering.

The limitation of this argument is that although the relative proportion of ginsenosides was less in the present batch of Asian ginseng, the dose administered was up to ninefold greater than the lowest dose found to be efficacious with our original batch of American ginseng [12–16]. The implication is that for even those ginsenosides such as Rb₁, Rc, and Re that were $> 70\%$ lower, the quantity administered would be roughly equivalent. If this is true, then counter-regulatory effects of specific ginsenosides present in higher relative proportions must be considered. Total PPT ginsenosides are a possible candidate. Total PPTs were observed to inhibit [¹⁴C]- α -mean glucose uptake in a dose dependent manner at doses from 10–100 μ g in cultured rabbit renal proximal tubular cells [40]. As the PPD:PPT ratio was lower through a marked increase in the relative proportion of PPT in the present Asian ginseng

batch studied, this might have opposed glucose transport mechanisms.

Insufficient quantities and/or opposing effects of other components might also have contributed to the differences between the present Asian ginseng and our original efficacious American ginseng batch. For example, the peptidoglycans (panaxans) have shown hypoglycemic effects [41–43] when administered as intraperitoneal injections in both normal and alloxan induced hyperglycemic mice. Despite the argument that these components would be degraded by human and microfloral digestive processes and impermeable across the enterocytes when consumed orally, some absorption and subsequent action is a possibility [44]. Their capacity to produce independent and interactive glyceamic effects cannot be precluded.

Identification of the ginsenosides, panaxans, and/or other principles involved in ginseng's variable effects becomes important for reasons of safety. Null and opposing effects of certain batches of ginseng, such as that seen with the present Asian ginseng, may contribute to unintended hyperglycemic episodes. This might be of significance in people who are using it in lieu of or as an adjunct to proven conventional treatment strategies without their physician's knowledge, as >60% of CAM users do [45].

These concerns assume that the effects seen with ginseng are secondary to its composition. An alternative explanation is that the effects may be more related to its timing. A longer treatment period with Asian ginseng may be required to replicate the hypoglycemic effects seen acutely with single doses of our original efficacious American ginseng batch. For example, the Finnish study [11] observed benefits in fasting glycemia and the longterm marker of glyceamic control, HbA_{1c}, with only once daily administration of an unspecified ginseng without regard to mealtime. The animal literature, nevertheless, does not support this hypothesis. There are nearly as many studies that have shown hypoglycemic effects of Asian ginseng following acute (from –6 h to 0 h) single dosing [9–10,18,46–48] as have shown hypoglycemic effects of Asian ginseng following longterm (from 2 days to 28 days) multiple dosing [19–21,49–52]. Our reason for not pursuing a multiple *versus* single dosing regimen in the present study was the ability to make comparisons with our past work. As meal stimulated effects were seen acutely when it was given in single-doses ≥ 40 minutes before the oral glucose load in healthy participants [14–16], we regarded our original batch of American ginseng as a prandial agent. Proof of the concept came from observing longterm improvements in glyceamic control with American ginseng when we applied the same prandial dosing and timing schedule in a randomized controlled trial in people with type 2 diabetes [16].

In conclusion, as suggested in traditional systems of Chinese medicine, not all ginseng species may be equal in their effects. While we have repeatedly demonstrated the acute glyceamic-lowering efficacy of a batch of American ginseng, null

to opposite effects were observed with the present Asian species. These contradictory effects however cannot be interpreted as representative for all Asian ginseng species. The high variability in composition compromises the generalizability of our findings, highlighting the need for greater experimental research. The effect of intra- and inter-species variation in components on safety and efficacy must be explored further. Whether the dose range of Asian ginseng studied was below the efficacy threshold and increasing doses will result in reductions needs also to be resolved. The ultimate goal of future research should be to identify candidate components to provide a basis for standardization that allows for the development of profile-specific indications and contraindications. In the absence of standardization, practitioners should warn their patients about the potentially variable effects of ginseng.

ACKNOWLEDGEMENT

The funding for the two studies was provided by a Grant for Applied Research and Education from the Canadian Diabetes Association. Findings from the two studies were presented in two separate posters, one at the Federation of American Societies for Experimental Biology (FASEB) conference, Orlando, FL, March 31–April 04, 2001 [53], and the other at the American Diabetes Association (ADA) conference, San Francisco, CA, June 14–18, 2002 [54]. J.L.S. was in receipt of an Ontario Graduate Scholarship during the conduct of this work.

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Received October 15, 2002; revision accepted April 4, 2003