American ginseng (*Panax quinquefolius* L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals[1–3]

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ABSTRACT

Background: We previously showed that 3 g American ginseng administered 40 min before an oral glucose challenge significantly reduces postprandial glycemia in subjects without diabetes. Whether this effect can be replicated with doses <3 g and administration times closer to the oral glucose challenge is unclear.

Objective: Our objective was to study the dosing and timing effects of American ginseng on postprandial glycemia.

Design: In a random crossover design, 12 healthy individuals [$\bar{x}$ ± SEM age: 42 ± 7 y; body mass index (BMI; in kg/m^2): 24.1 ± 1.1] received 16 treatments: 0 (placebo), 1, 2, or 3 g American ginseng at 40, 20, 10, or 0 min before a 25-g oral glucose challenge. Capillary blood was collected before administration and at 0, 15, 30, 45, 60, and 90 min after the start of the glucose challenge.

Results: Two-way analysis of variance showed that the main effects of treatment and administration time were significant ($P < 0.05$). Glycemia was lower over the last 45 min of the test after doses of 1, 2, or 3 g ginseng than after placebo ($P < 0.05$); there were no significant differences between doses. The reductions in the areas under the curve for these 3 doses were 14.4 ± 6.5%, 10.6 ± 4.0%, and 9.1 ± 6%, respectively. Glycemia in the last hour of the test and area under the curve were significantly lower when ginseng was administered 40 min before the challenge than when it was administered 20, 10, or 0 min before the challenge ($P < 0.05$).

Conclusions: American ginseng reduced postprandial glycemia in subjects without diabetes. These reductions were time dependent but not dose dependent: an effect was seen only when the ginseng was administered 40 min before the challenge. Doses within the range of 1–3 g were equally effective. *Am J Clin Nutr* 2001;73:753–8.

KEY WORDS American ginseng, postprandial glycemia, dose, time, placebo, oral-glucose-tolerance test

INTRODUCTION

Despite numerous preventive strategies and armories of medication, the prevalence of diabetes is increasing (1, 2) and most people with diabetes die prematurely (3). A compelling case is made for more effective modalities to prevent and treat diabetes. To meet this need, an increasing number of people are turning to alternative therapies that include herbal remedies, such as ginseng (4). The response of the medical establishment has been a call for controlled clinical evaluations of the safety and efficacy of herbs (5–9).

Growing evidence from in vitro and animal models indicates that ginseng might have a viable use in diabetes. American ginseng (*Panax quinquefolius* L.) (10, 11), Chinese ginseng (*Panax ginseng* CA Meyer) (11, 12), Siberian ginseng (*Eleutherococcus senticosus*), Sanchi ginseng [*Panax notoginseng* (Burk) FH Chen], and Korean Red ginseng (steam-treated *P. ginseng* CA Meyer) (12) have significant hypoglycemic action in rodents. The same is true for some of the fractions of these ginsengs: saponins (ginsensoides), peptidoglycans (panaxans for the *Panax* species and eleutherans for *E. senticosus*), and the water-extracted (DPG-3-2) and methanol-extracted (EPG-3-2) fractions of Chinese ginseng (13).

Similar findings were noticed in 3 human studies (14–16). The first study found that supplementation for 8 wk with 200 mg/d of an unspecified type of ginseng extract resulted in an improvement in long-term glycemic control measured by glycated hemoglobin (Hb A_{1c}) (14). However, this observation was complicated by significant weight reduction. In the subsequent 2 studies, we investigated the efficacy of 3 g American ginseng at reducing postprandial glycemia in subjects with diabetes and in healthy subjects (15) and the effect of escalating the ginseng dose and time of administration on postprandial glycemia in subjects with diabetes (16). The conclusion from these studies was that American

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TABLE 1
Energy, nutrient, and ginsenoside profile of the American ginseng (*Panax quinquefolius* L.) and placebo capsules

Constituent (per g)	Placebo[1]	Ginseng[1]
Energy[2]		
(kJ)	14.68	14.39
(kcal)	3.51	3.44
Macronutrients[2]		
Carbohydrate (g)	0.73	0.57
Fat (g)	0.039	0.013
Protein (g)	0.069	0.26
Ginsenosides[3]		
(20*S*)-Protopanaxadiols (%)		
Rb_1	—	1.53
Rb_2	—	0.06
Rc	—	0.24
Rd	—	0.44
(20*S*)-Protopanaxatriols (%)		
Rg_1	—	0.100
Re	—	0.83
Rf	—	0
Total (%)	—	3.21

[1] To equate energy and macronutrient values to 1, 2, or 3 g American ginseng, multiply by 1, 2, or 3, respectively. To determine values for placebo, multiply by 2.
[2] Determined by the Association of Official Analytical Chemists methods for macronutrients (18).
[3] Determined by HPLC analyses (20).

ginseng significantly reduced the postprandial glycemic response to a 25-g oral glucose challenge in both groups. However, high doses of 3, 6, or 9 g were equally efficacious at reducing glycemia compared with placebo in subjects with diabetes. The same was true for times of administration of 120, 80, 40, or 0 min before the oral glucose challenge (16). In healthy subjects, only ginseng given 40 min before, not together with, the challenge reduced glycemia (15). Together, these human data suggest that ginseng may have an effect over a wide dosage range and that the timing of administration may be important in healthy subjects. However, whether there is a dose response with doses <3 g and a time response within the first 40 min before the glucose challenge is unknown. We therefore investigated the effect of administering 0 (placebo), 1, 2, or 3 g American ginseng at 40, 20, 10, or 0 min before a 25-g oral glucose challenge.

SUBJECTS AND METHODS

Subjects

Twelve subjects without diabetes [7 men and 5 women; $\bar{x}$ ± SEM age: 42 ± 2 y; body mass index (BMI; in kg/m^2): 24.1.6 ± 0.3] were recruited from the faculty and students of the University of Toronto and through hospital advertisements. All subjects gave informed, written consent to take part in the study, which was approved by the University of Toronto Human Subjects Review Committee.

Treatments

The study participants received a total of 16 treatments in a random multiple crossover design. To examine the effect of dose, 0 (placebo), 1, 2, or 3 g ginseng was administered in 500-mg capsules. The ginseng capsules contained 3-y-old Ontario dried and ground ginseng root (*P. quinquefolius* L.) provided by Chai-Na-Ta Corp, Langley, Canada. All processing and encapsulation was performed by the commercial provider using proprietary techniques. To ensure stability, the ginseng was stored in a cool, dry, dark location over the course of the study and used within 6 mo of production. The placebo, on the other hand, consisted of identical capsules containing corn flour. The energy and carbohydrate contents of the placebo capsules approximated the mean content of the middle dose (2 g) of ginseng (**Table 1**). Participants were blinded to the identity of the placebo and ginseng capsules by coding and by the indistinguishable nature of the capsules. To examine the effect of time of administration, the treatment doses were administered 0 (together with), 10, 20, or 40 min before a 25-g oral glucose challenge [100 mL of a 300-mL 75-g Glucodex solution (Technilab, Chambly, Canada) diluted with 200 mL tap water]. All ginseng and placebo capsules came from the same lot.

Protocol

The protocol followed the World Health Organization guidelines for the administration of the oral-glucose-tolerance test (17). Participants attended the Clinical Nutrition and Risk Factor Modification Centre at St Michael's hospital on 16 separate mornings after a 10–12-h overnight fast. A minimum of 3 d separated each visit to minimize carryover effects. Each participant was instructed to maintain the same dietary and exercise patterns the evening before each test and to consume ≥150 g carbohydrate each day for 3 d before the test. To ensure that these instructions were followed, participants completed a questionnaire that detailed presession information about their diet and lifestyle patterns and were provided with examples of what constituted 150 g carbohydrate.

At the start of the test, an ≈250-μL fasting finger-prick capillary blood sample was collected by using a Monoejector Lancet device (Owen Mumford Ltd, Woodstock, England). One of the 16 treatments was then administered. When the placebo or 1, 2, or 3 g ginseng was given before the oral glucose challenge, the subjects took either set of capsules with 250 mL tap water. After the time required by the treatment had passed (10, 20, or 40 min), the subjects provided another blood sample (0 min) and consumed the 25-g oral glucose challenge over exactly 5 min. Additional finger-prick blood samples were obtained 15, 30, 45, 60, and 90 min after the start of the challenge. When the placebo or ginseng was taken together with the challenge (0 min), the same protocol applied, with the exception that there was no waiting period and the capsules were taken simultaneously without additional water.

Blood glucose analysis

All samples were collected in tubes containing fluoride oxalate, frozen immediately at −20°C pending analysis, and analyzed within 3 d of collection. The glucose concentration of each was determined by the glucose oxidase method with use of a YSI 2300 Stat glucose/L-lactate analyzer (model 115; Yellow Springs Instruments, Yellow Springs, OH). The interassay CVs of this method for 2 sample pools were 3.3% (3.99 ± 0.13 mmol/L; n = 91) and 1.8% (14.35 ± 0.26 mmol/L; n = 89).

Ginseng analyses

Energy, nutrient, and ginsenoside profiles of the American ginseng and placebo used on the present study were measured by

using standard techniques. Energy, fat, protein, and carbohydrate contents were measured by Chai-Na-Ta corporation with use of the Association of Official Analytical Chemists methods for macronutrients (18). The content of various ginsenosides was also assessed (Table 1). Ginsenosides are dammarane saponins with either (20*S*)-protopanaxadiol or (20*S*)-protopanaxatriol as the aglycone. Ginsenoside Ro, an oleanolic acid-type saponin, is the one exception (19). Four of the protopanaxadiol (Rb_1, Rb_2, Rc, and Rd) and 3 of the protopanaxatriol (Rg_1, Re, and Rf) ginsenosides were analyzed by using a Beckman HPLC system with a reversed-phase Beckman ultrasphere C_{18}, 5-μm octadecylsilane, 250 × 4.6 mm column (Beckman Coulter Inc, Fullerton, CA), following HPLC techniques developed for the American Botanical Council Ginseng Evaluation Program (20). The ginsenoside standards used for comparison were provided by 2 sources; Rg_1 and Re were provided by H Fong, University of Illinois, and Rf, Rb_1, Rc, Rb_2, and Rd were provided by Indofine Chemical Co, Somerville, NJ.

Statistical analyses

Blood glucose curves were plotted as the incremental change in blood glucose from time 0, and the positive incremental area under the curve (AUC) was calculated geometrically for each participant, ignoring areas below the fasting blood glucose value (21). Incremental blood glucose concentrations were used to control for baseline (fasting) differences between the treatments. Statistical analyses were then performed with use of NUMBER CRUNCHER STATISTICAL SYSTEM 2000 (NCSS, Kaysville, UT). Repeated-measures three-way analysis of variance (ANOVA) assessed the interactive and independent effects of treatment dose (0, 1, 2, or 3 g), adminstration time (40, 20, 10, or 0 min before the challenge), and sampling time [fasting (−40, −20, −10, or 0 min), 15, 30, 45, 60, or 90 min] on incremental blood glucose. Repeated-measures two-way ANOVA assessed the interactive and independent effects of each pairing of each of these 3 factors: treatment dose × adminstration time, treatment dose × sampling time, and administration time × sampling time. If the interaction term was significant between the last 2 pairings, then further 2-way ANOVAs assessed the interactive and independent effects of treatment dose and administration time on incremental glycemia at each postprandial sampling point (15, 30, 45, 60, 90 min) and on the AUCs. Adjustment with the Tukey-Kramer test was done for contrasting means among both the treatment doses and the adminstration times to control for multiple comparisons. Repeated-measures one-way ANOVA, with the same adjustment, assessed differences in absolute fasting blood glucose among the treatment doses and adminstration times. Finally, this same statistic also assessed differences in absolute blood glucose between the points before ginseng administration (−40, −20, or −10 min) and the 0-min point. All results are expressed as means ± SEMs and were considered statistically significant at $P < 0.05$.

RESULTS

All participants were able to follow the study protocol without difficulty. No adverse effects from the ginseng or placebo or from the timing of their administration were reported by the subjects during or after the testing sessions. In addition, differences in fasting values between the doses and times of administration were not significant and no preprandial hypoglycemic effect of ginseng was observed between the time of ginseng administration (−40, −20, −10 min) and the 0-min blood sample.

Repeated-measures three-way ANOVA showed that the effects of dose ($P < 0.001$), administration time ($P < 0.001$), and sampling time ($P < 0.001$) on incremental glycemia were all significant, with a significant 3-way interaction ($P = 0.028$). The repeated-measures two-way ANOVAs further showed significant interactions between each pairing of the 3 factors: treatment dose × administration time ($P < 0.001$), treatment dose × sampling time ($P = 0.0053$), and administration time × sampling time ($P < 0.001$). Because the interaction terms for the last 2 pairings were significant, the effects of treatment dose and administration time were assessed at each postprandial sampling time point (15, 30, 45, 60, and 90 min) and for the AUCs.

Effect of treatment dose

The effect of the 4 treatment doses of ginseng (0, 1, 2, or 3 g) independent of time of administration on the glycemic response to a 25-g oral glucose challenge at 15, 30, 45, 60, and 90 min and on the AUC is compared in **Figure 1**. Glycemic values for each dose represent the mean of the 4 times of administration (−40, −20, −10, and 0 min). Repeated-measures two-way ANOVA applied to these data showed that the effect of treatment on incremental glycemia was significant at 60 ($P < 0.001$) and 90 ($P = 0.026$) min and approached significance at 45 min ($P = 0.051$). This was reflected in a significant effect of treatment on the AUC ($P < 0.001$). Pairwise comparisons using the Tukey-Kramer test showed that, compared with placebo, the glycemic response to the oral glucose challenge was significantly lower after 2 g ginseng at 45 min; after 1, 2, or 3 g ginseng at 60 min; and after 1 g ginseng at 90 min and the AUC was significantly lower after 1, 2, or 3 g ginseng. Expressed as a percentage of placebo, the reductions in the AUC after 1, 2, and 3 g ginseng were 14.4 ± 6.5%, 10.6 ± 4.0%, and 9.1 ± 6%, respectively ($P < 0.05$). No significant differences were observed between the 1-, 2-, and 3-g doses.

Effect of administration time

The effect of the 4 times of administration (−40, −20, −10, and 0 min) independent of dose on the glycemic response to a 25-g oral glucose challenge at 15, 30, 45, 60, and 90 min and on the AUC is compared in **Figure 2**. Glycemic values for each time of administration represent the mean of the 4 doses (0, 1, 2, and 3 g). Repeated-measures two-way AVOVA applied to these data showed that the effect of time of administration on incremental glycemia was significant at 30 ($P < 0.001$), 45 ($P = 0.0011$), 60 ($P < 0.001$), and 90 ($P = 0.0033$) min after the glucose load. This was reflected in a significant effect on the AUC ($P < 0.001$). Pairwise comparisons showed that when the time of administration was 40 min before the challenge the glycemic response to the oral glucose challenge was significantly ($P < 0.05$) lower at 30 and 45 min than when administration was >40 min before the challenge; significantly lower at 60 min than when administration was 10 or 0 min before the challenge; and significantly lower at 90 min than when administration was 20 or 0 min before the challenge. The AUC was significantly lower when the time of administration was 40 min before the challenge than when it was >40 min before the challenge. The reductions in the AUC were 14.1 ± 5.6%, 15.0 ± 6.7%, and 9.2 ± 12.0% ($P < 0.05$) when administration was 40 min before the challenge compared with 20, 10, or 0 min before the challenge, respectively.

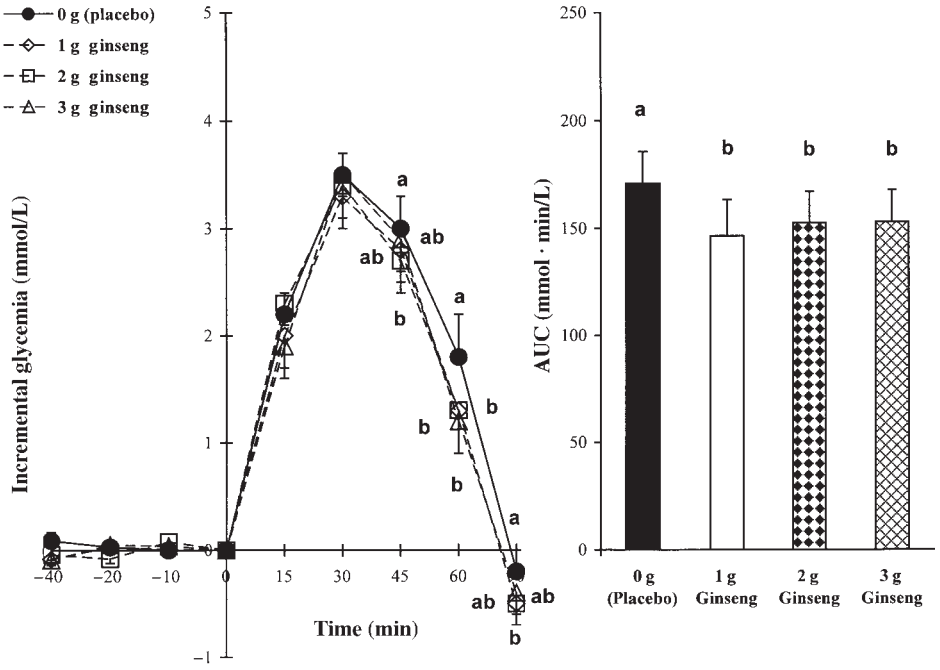

FIGURE 1. Effect of treatment dose [0 (placebo), 1, 2, or 3 g] of American ginseng (*Panax quinquefolius* L.) independent of time of administration on incremental changes in glycemia at selected time intervals (15, 30, 45, 60, and 90 min) and on glycemic area under the curve after a 25-g oral glucose challenge in 12 subjects without diabetes. Glycemic values for each dose represent the mean of the 4 times of administration (−40, −20, −10, and 0 min before the oral glucose challenge). Because the interaction term between treatment dose and sampling time was significant ($P = 0.0053$), repeated-measures two-way analysis of variance, adjusted for multiple pairwise comparisons with the Tukey-Kramer test, was applied to these data to assess differences at each time interval. Points at the same time interval and bars with different letters are significantly different, $P < 0.05$. Data are means ± SEMs.

Interaction: treatment dose × adminstration time

There was significant interaction between treatment dose and time of administration at each point of significance in the above analyses. Repeated-measures two-way ANOVA showed significant interaction at 30 ($P = 0.0034$), 45 ($P = 0.0056$), 60 ($P < 0.001$), and 90 ($P = 0.035$) min. It also showed significant interaction between treatment dose and administration time for the AUC ($P < 0.001$).

DISCUSSION

Our present findings indicate that, in healthy subjects, American ginseng (*P. quinquefolius* L.) significantly lowers the postprandial glycemic response to a 25-g oral glucose challenge from 9% to 15%, with no effect on fasting blood glucose. This postprandial effect appears to occur in a manner dependent on the time of administration. Only when administration was 40 min before the challenge were differences in glycemia observed. Decreases in glycemia did not, however, appear to occur in a dose-dependent fashion. Although 1, 2, and 3 g ginseng all decreased glycemia significantly compared with 0 g (placebo), there were no significant differences among the doses. That is, doses within the range of 1–3 g appeared to be equally effective. Together, these data suggest that 2 variables must be in place for American ginseng to be effective: a dose between 1 and 3 g and administration 40 min before the meal.

Consistent observations after a similar dosage and schedule were made in our previous study (15). We likewise observed that 3 g American ginseng had a glycemia-attenuating effect only when it was administered 40 min before a 25-g oral glucose challenge in subjects without diabetes. When administered together (at 0 min) with the challenge, the effect was lost. The percent reduction in postprandial AUC observed was also similar. Compared with placebo, administration of ginseng 40 min before the challenge significantly reduced glycemia by 18% in our previous study. This is comparable with the 9–15% reduction we observed in the present study when ginseng was administered 40 min compared with 20, 10, or 0 min before the challenge. The uniformity supports the notion that ginseng must be administered 40 min before a challenge to lower postprandial glycemia in persons without diabetes.

The reason we did not observe a dose response between 1 and 3 g may be that the dose range studied was too high. Although in traditional Chinese medicine the minimum daily dose for individual nontoxic medicinal herbs is 3 g (22), most clinical ginseng studies in the literature administered <1.5 g (23–26). For example, Sotaniemi et al (14) observed an improvement in Hb A_{1c} and fasting glucose with 200 and 100 mg/d, respectively, of an unspecified ginseng. Therefore, a postprandial dose-response effect of ginseng may plateau beyond 1 g, lying closer to 100 mg.

In the absence of an observed dose response between 1 and 3 g, mechanisms that may explain ginseng's hypoglycemic effect are likely still similar to those proposed previously (15, 16). Animal data support 4 possibilities: modulation of digestion (27, 28), insulin secretion (29), insulin sensitivity (12, 30), or a combination of these. Budgetary constraint did not allow us to measure insulin, precluding us from addressing an effect of American ginseng on insulin secretion or sensitivity more

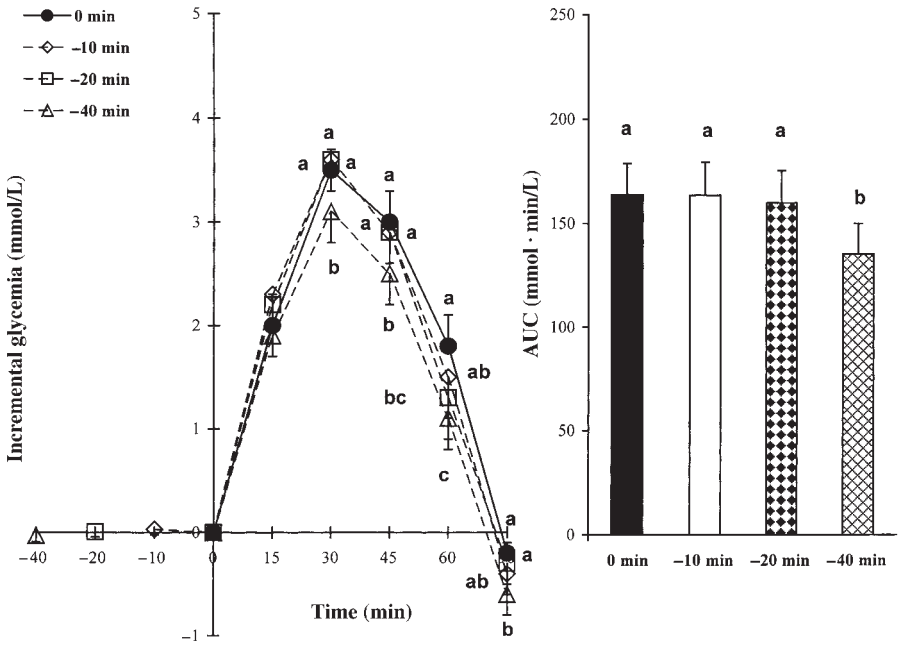

FIGURE 2. Effect of time of administration (−40, −20, −10, and 0 min) of American ginseng (*Panax quinquefolius* L.) independent of dose on incremental changes in glycemia at selected time intervals (15, 30, 45, 60, and 90 min) and on glycemic area under the curve after a 25-g oral glucose challenge in 12 subjects without diabetes. Glycemic values for each time of administration represent the mean of the 4 doses (0, 1, 2, and 3 g). Because the interaction term between administration time and sampling time was significant ($P < 0.001$), repeated-measures two-way analysis of variance, adjusted for multiple pairwise comparisons with the Tukey-Kramer test, was applied to these data to assess differences at each time interval. Points at the same time interval and bars with different letters are significantly different, $P < 0.05$. Data are means ± SEMs.

directly. Nevertheless, our blood glucose data seem to offer stronger support for an enhancement of insulin secretion or sensitivity than a slowing of digestion. Consistent with the results of our previous studies (15, 16), the reductions in glycemia were observed only in the final 45 min of the test. If American ginseng were able to slow digestion, then, as seen with soluble dietary fiber (31) and acarbose (32, 33), we also would have expected lower values in the first 30 min.

Involvement of ginsenosides may play an important mechanistic role (19). Total ginsenosides were shown to modulate nitric oxide synthesis (34). The most common protopanaxadiol saponin, Rb_1, and protopanaxatriol saponin, Rg_1, both of which were measured in the present study, were shown to affect the cholinergic (35), dopaminergic (36), and adrenergic (37) systems. Additional regulatory effects on these and other systems were shown by the 4 other ginsenosides measured in the present study: Rc, Rd, Re (38), and Rf (37). Some of these effects may explain possible secondary effects on carbohydrate metabolism (39, 40). For example, the protopanaxadiol Rb1 increased glucose uptake into sheep erythrocytes in a dose-dependent manner (30). Another protopanaxadiol, Rb_2, was also shown to increase the activity of the rate-limiting glycolytic enzymes glucokinase and phosphofructokinase while decreasing the activity of the rate limiting gluconeogenic enzyme glucose-6-phophatase in rat liver preparations (41, 42). When the data are taken together, the implication is that the ginsenosides measured in the present study might be responsible for the observed reductions in postprandial glycemia; however, there remains insufficient evidence to make this extrapolation. Neither studies that investigated the effect of isolated ginsenosides on carbohydrate metabolism in humans nor direct investigations of the hypoglycemic activities of the >20 other ginsenosides can be found in the literature.

The ginsenoside profile observed in the present study is nevertheless useful for purposes of authentication. A high proportion of protopanaxadiols (Rb_1, Rb_2, Rc, and Rd in the present study) relative to protopanaxatriols (Rg_1, Re, and Rf in the present study) was shown to be indicative of *P. quinquefolius* L. (43, 44). A ratio smaller than one of the ginsenoside ratios (Rg_1:Re or Rb_2:Rc) is also a indicative of *P. quinquefolius* L. (44, 45). Another more powerful marker is the absence of Rf, a ginsenoside found in Chinese ginseng but not American ginseng (45). All 3 conditions were met in the present study. The suggestion is that the ginseng used in the present study was of this genus and species.

In conclusion, the American ginseng used in the present study reduced postprandial glycemia in healthy subjects without diabetes in a manner that was dependent on the time of administration but not the dose. An effect was seen only when administration was 40 min before the challenge, and doses within the range of 1–3 g were equally effective. This lack of a dose response suggests that the next step should be to study lower doses. Feeding of isolated ginsenosides and comparison between different ginseng types with different profiles would also be a worthwhile avenue of investigation for exploring ginseng's mechanism of action. Other research should investigate American ginseng's long-term efficacy, safety, and adverse events as a monotherapy in impaired glucose tolerance and drug-naive type 2 diabetes and as part of multiple therapy in type 2 diabetes treated by oral agents.

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