Similar Postprandial Glycemic Reductions With Escalation of Dose and Administration Time of American Ginseng in Type 2 Diabetes

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OBJECTIVE — We previously demonstrated that 3 g American ginseng (AG) reduced postprandial glycemia (PPG) in type 2 diabetic individuals. We investigated whether further reductions can be achieved with escalation of dose and time of AG administration.

RESEARCH DESIGN AND METHODS — Ten type 2 diabetic patients (6 men, 4 women; age 63 ± 2 years; BMI 27.7 ± 1.5 kg/m^2; HbA_{1c} 7.3 ± 0.3%) were randomly administered 0 g (placebo) or 3, 6, or 9 g ground AG root in capsules at 120, 80, 40, or 0 min before a 25-g oral glucose challenge. Capillary blood glucose was measured before ingestion of AG or placebo and at 0, 15, 30, 45, 60, 90, and 120 min from the start of the glucose challenge.

RESULTS — Two-way analysis of variance (ANOVA) demonstrated that treatment (0, 3, 6, and 9 g AG) but not time of administration (120, 80, 40, or 0 min before the challenge) significantly affected PPG ($P < 0.05$), with significant ($P = 0.037$) interaction for area under the curve (AUC). Pairwise comparisons showed that compared with 0 g (placebo), 3, 6, or 9 g significantly ($P < 0.05$) reduced AUC (19.7, 15.3, and 15.9%, respectively) and incremental glycemia at 30 min (16.3, 18.4, and 18.4%, respectively), 45 min (12.5, 14.3, and 14.3%, respectively), and 120 min (59.1, 40.9, and 45.5%, respectively). However, pairwise comparisons showed no differences between the 3-, 6-, or 9-g doses and any of the times of administration.

CONCLUSIONS — AG reduced PPG irrespective of dose and time of administration. No more than 3 g AG was required at any time in relation to the challenge to achieve reductions. Because these reductions included glycemia at the 2-h diagnostic end point, there may be implications for diabetes diagnosis and treatment.

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Reductions in both fasting blood glucose and prolonged elevation of postprandial glycemia (PPG) are of paramount importance in diabetic glycemic control and the prevention of diabetic complications (1,2). A proper diet, physical activity, and pharmacotherapy are instrumental to achieve these therapeutic goals (3,4). An increasing number of patients are also using herbs to improve treatment outcomes, often without advice from their physicians (5). The medical establishment has questioned the safety and efficacy of this practice, urging for more randomized placebo-controlled clinical studies to provide evidence for the health benefits of herbs (6–9).

One of the most commonly used herbs is ginseng (7). It is traditionally considered a tonic and is often used as a cure-all or panacea (10). A number of health claims have been made for ginseng; however, in the most recent review of randomized control studies with this herb, it was reported that the evidence for its claimed indications is unconvincing (7).

Still, an intriguing property of ginseng is its hypoglycemic effect, which is supported by several animal studies (11–13). Additionally, 2 studies in humans have confirmed ginseng's glucose-lowering ability (14,15). A study of type 2 diabetic individuals demonstrated that administration of 200 mg ginseng per day for 8 weeks reduced HbA_{1c} levels (14). This result was equivocal, however, because those receiving ginseng treatment also experienced a reduction in body weight.

In a more recent randomized placebo-controlled study, we observed that 3 g American ginseng (AG; *Panax quinquefolius* L.) taken with or 40 min before a 25-g oral glucose challenge reduced PPG in type 2 diabetic individuals (15). To extend from these findings, we hypothesize in the current study that further reductions in PPG will be achieved with escalation of AG dose (3, 6, and 9 g) and time of administration (0, 40, 80, and 120 min) before a 25-g oral glucose challenge in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants

Ten type 2 diabetic patients (6 men, 4 women; age 63 ± 2 years; BMI 27.7 ± 1.5 kg/m^2; HbA_{1c} 7.3 ± 2.8% [range 5.5–8.4]) were recruited from hospital advertise-

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Abbreviations: AG, American ginseng; ANOVA, analysis of variance; AUC, area under the curve; HPLC, high-performance liquid chromatography; PPG, postprandial glycemia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Energy, nutrient, and ginsenoside profile of AG and placebo capsules*

Constituent	Amount (per g)*	
	Placebo	Ginseng
Energy (kcal)†	3.51	3.44
Macronutrients†		
Carbohydrate (g)	0.73	0.57
Fat (g)	0.039	0.013
Protein (g)	0.069	0.26
Ginsenosides‡		
Total (%)	0	3.21
Rb_1 (%)	0	1.53
Rg_1 (%)	0	0.10
Rb_1/Rg_1	0	15.3

*To equate energy and macronutrient values to 3, 6, or 9 g of AG, multiply by 3, 6, and 9, respectively. To determine values for placebo, multiply by 6. †Determined by the Official Analytical Chemists' methods for macronutrients (19). ‡Determined by HPLC analyses (20).

ments. Five were receiving treatment for their diabetes with sulfonylureas, 2 with a combination of sulfonylureas and metformin, and 3 with diet alone. Their median duration of diabetes was 6.5 years (range 2–12). All patients gave informed written consent to take part in the study, approved by the University of Toronto Human Subjects Review Committee.

Treatments

Ontario-grown ground root of AG (Chai-Na-Ta Corp., British Columbia, Canada) was encapsulated and used for study at doses of 3, 6, and 9 g. The placebo was a 500-mg capsule of corn flour that was identical in appearance to and closely approximated the caloric and carbohydrate content of the AG capsules. It was given at a dose equivalent to the middle dose (6 g) of ginseng. Energy, macronutrient, and ginsenoside profiles are provided for both the AG capsules and the placebo in Table 1. All AG and placebo capsules came from the same lot.

To elucidate the combined effect of AG dose and time of administration on postprandial glycemia, all participants received each dose at every time point in a randomized order. Accordingly, the participants received 0 g (placebo) or 3, 6, or 9 g AG at 120, 80, 40, or 0 min before a 25-g oral glucose challenge (100 ml of a 300-ml 75-g Glucodex solution [Technilab, Quebec, Canada] diluted with 200 ml tap water).

Protocol

The protocol followed the World Health Organization guidelines for the administration of an oral glucose tolerance test (16), using a single-blind design in which subjects were blinded to the identity of the AG and placebo treatments. Participants attended the Clinical Nutrition and Risk Factor Modification Centre at St. Michael's Hospital on 16 separate mornings, each after a 10- to 12-h overnight fast. Each participant was instructed to maintain the same dietary and lifestyle patterns before each test. To ensure that these instructions were followed, participants completed glycemic testing questionnaires that provided information about their presession fasting and activity patterns. A minimum of 3 days separated each visit to minimize carryover effects. This washout was shortened compared with our earlier study (1 week) (15) because AG appears to have a half-life of less than 8 h (17) with a time course of effects not lasting beyond 24 h (18). There was also a concern that a longer washout would have contributed to confounding from diabetes deterioration resulting from an excessively long study period.

At the start of the test, patients receiving pharmacological treatment for their diabetes took their regular medications. Each participant then provided a fasting finger-prick capillary blood sample (~250 µl) using a Monoejector Lancet device (Owen Mumford, Oxon, U.K.), after which 1 of the 16 treatments was administered in random order. Randomization was done using a random number table. When the placebo or AG (3, 6, or 9 g) was given before the oral glucose challenge, subjects consumed either set of capsules with 300 ml tap water. After the specified time had passed (40, 80, or 120 min), the participants gave another blood sample (0 min) and consumed the glucose challenge over exactly 5 min. Additional finger-prick blood samples were obtained 15, 30, 45, 60, 90, and 120 min after the start of the glucose challenge. The participants remained sedentary throughout the test. When the placebo or AG was taken together with the challenge (0 min), the same protocol was 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 days of collection. The glucose concentration of each was determined by the glucose oxidase method using a YSI 2300 Stat glucose/L-lactate analyzer, model 115 (Yellow Springs Instruments, Yellow Springs, OH).

AG analyses

Energy, nutrient, and ginsenoside profiles of the AG and placebo used in the present study were measured using standard techniques. Chai-Na-Ta Corporation measured the energy, fat, protein, and carbohydrate content using Official Analytical Chemists' methods for macronutrients (19). Total ginsenoisides (ginseng dammarane saponins), the 20(S)-protopanaxadiol ginsenoside, Rb_1, and the 20(S)-protopanaxatriol ginsenoside, Rg_1, in the AG were measured by Dr. John T. Arnason in the Department of Biology, Faculty of Science, University of Ottawa, Ontario, Canada using high-performance liquid chromatography (HPLC) analyses, developed for the American Botanical Council Ginseng Evaluation Program (20). This assay used a Beckham HPLC system with a reverse-phase Beckham ultrasphere C-18, 5-µm octadecylsilane 250 × 4.6 mm column. The ginsenoside standards for Rg_1 and Rb_1 were provided by Dr. H. Fong, University of Illinois and Indofine Chemical, Somerville, New Jersey, respectively.

Statistical analyses

Blood glucose curves were plotted as the incremental change in blood glucose from baseline (time 0 min) at each time point (−120, −80, −40, 0, 15, 30, 45, 60, 90, and 120 min). The positive incremental area under the curve (AUC) was calculated geometrically for each participant, and areas below the fasting baseline value were ignored (21). Incremental blood glucose concentrations were used to control for baseline/fasting differences between the treatments. Statistical analyses were then performed using the Number Cruncher Statistical System (NCSS) 2000 software (NCSS, Kaysville, UT). Repeated-measures 2-way analysis of variance assessed interactive and independent effects of treatment (0, 3, 6, or 9 g AG) and time of administration (120, 80, 40, or 0 min before the challenge) on incremental blood glucose level at each time point (15, 30, 45, 60, 90, and 120 min), adjusted for multiple pairwise comparisons with the Newman-Keuls procedure. This same statistic also assessed interactive and independent effects of treatment (0, 3, 6, or 9 g) and timing (120, 80, 40, or 0 min before the challenge) on AUC. All

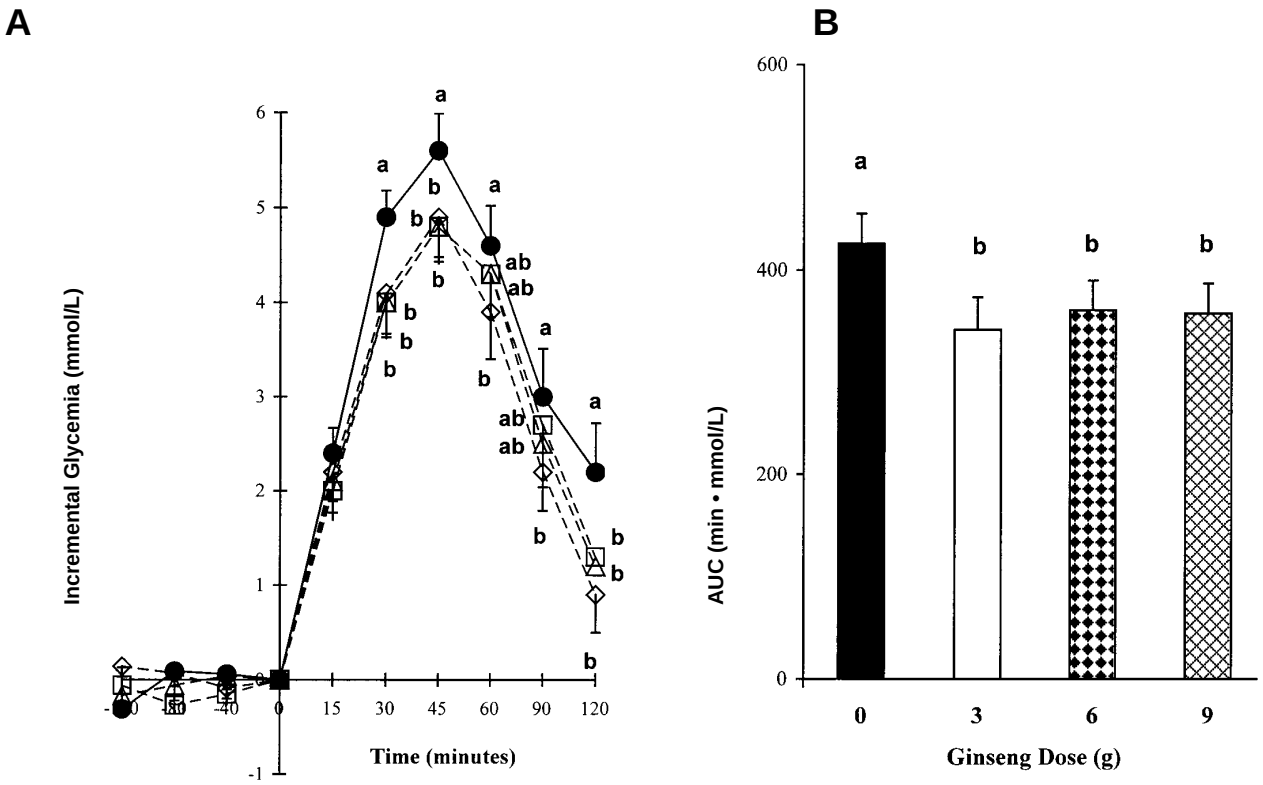

Figure 1—*Effect of dose (placebo or 3, 6, or 9 g) of AG (*Panax quinquefolius *L.) independent of time of administration on incremental changes in glycemia at selected time intervals (15, 30, 45, 60, 90, and 120 min) (A); and glycemic AUC (B) after a 25-g oral glucose challenge in 10 type 2 diabetic individuals. Points at the same time interval and bars with different letters are significantly different (*P *< 0.05; repeated-measures 2-way analysis of variance adjusted for multiple pairwise comparisons with the Newman-Keuls procedure). Data are means ± SEM. —●—, 0 g ginseng (placebo); ---△---, 3 g ginseng; ---□---, 6 g ginseng; ---△---, 9 g ginseng.*

results were expressed as means ± SEM and considered statistically significant at $P < 0.05$.

RESULTS — All participants followed the study protocol without difficulty and reported no side effects from the doses and administration times of AG or placebo during or after the testing sessions. Two of the participants requested an additional 150 ml water with all tests except for the first test (3 g at −80 min and 6 g at −120 min, respectively).

Effect of dose

Figure 1 shows the effect of different AG doses (0, 3, 6, or 9 g) on *1)* incremental changes in pre- and postprandial glycemia and *2)* blood glucose AUC in type 2 diabetic individuals after a 25-g oral glucose tolerance test (independent of administration time). Glycemic values at each time interval (Fig. 1*A*) and for AUC (Fig. 1*B*) represent the mean of the 4 administration times (−120, −80, −40, and 0 min) for the individual AG doses.

Repeated-measures 2-way ANOVA performed on the data in Fig. 1*A* demonstrated a significant effect of treatment on incremental glycemia at 30, 45, 60, 90, and 120 min ($P < 0.05$). This was reflected in reductions in AUC (Fig. 1*B*) by the 3 AG doses: 19.7% with 3 g, 15.3% with 6 g, and 15.9% with 9 g ($P < 0.05$). Pairwise comparisons showed that compared with 0 g (placebo), any given dose of AG (3, 6, or 9 g) lowered incremental glycemia at 30 min (16.3, 18.4, and 18.4%, respectively), 45 min (12.5, 14.3, and 14.3%, respectively), and 120 min (59.1, 40.9, and 45.5%, respectively) ($P < 0.05$). Additionally, 3 g AG lowered incremental glycemia at 60 min (30.3%) and 90 min (26.6%) ($P < 0.05$). There were, however, no differences in AUC or incremental glycemia at any time point between the 3-, 6-, or 9-g doses.

Effect of time of administration

The time of AG administration (−120, −80, −40, or 0 min) did not affect incremental glycemia or blood glucose AUC (Fig. 2*A* and *B*). However, there was a significant interaction between dose and time of administration for blood glucose AUC ($P = 0.037$). No other data showed a significant interaction.

CONCLUSIONS — Consistent with our previous study (15), the present findings demonstrated the efficacy of AG in reducing PPG in type 2 diabetes. The reductions, however, occurred independent of the AG dose used. Increasing the dose of AG from 3 to 6 to 9 g did not yield further reductions in AUC and PPG at 30 and 45 min compared with placebo. The same was true at the diagnostically important 2-h end point, at which 3, 6, and 9 g AG reduced glycemia by 59.1, 40.9, and 45.5%, respectively, compared with placebo. This effect was seen irrespective of the time of AG administration, such that AG taken with or up to 120 min before the glucose challenge was equally efficacious in lowering PPG. Taken together, these data indicate that 3 g administered within 2 h of the test may be sufficient to achieve reductions in PPG in type 2 diabetic individuals.

The lowest acute testing dose (3 g) of ginseng in the current study was considerably higher than that used in most other clinical studies (7). In these studies, the amount of ginseng consumed per day ranged from 100 mg to 1.5 g. We, however,

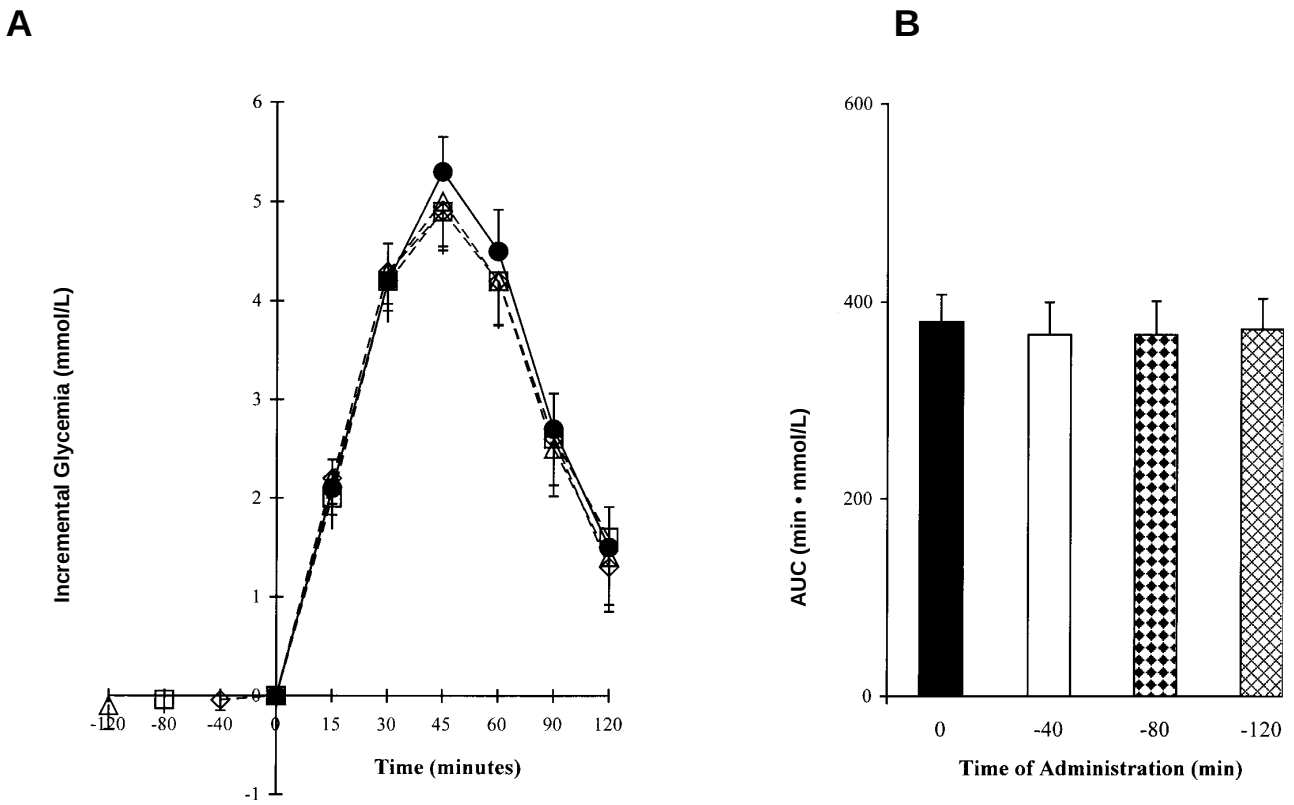

Figure 2—*Effect of time of administration (−120, −80, −40, and 0 min) of AG (*Panax quinquefolius *L.) independent of dose on incremental changes in glycemia at selected time intervals (15, 30, 40, 60, 90, and 120 min) (A) and glycemic AUC (B) after a 25-g oral glucose challenge in 10 type 2 diabetic individuals. No points were significantly different (*$P < 0.05$*; repeated-measures 2-way analysis of variance adjusted for multiple pairwise comparisons with the Newman-Keuls procedure). Data are means ± SEM. —●—, 0 Min; ---◇---, –40 min; ----□---, –80 min; ----△---, –120 min.*

used higher doses of AG to follow traditional Oriental medicine, which considers herbs to be diluted drugs and recommends a daily dose of ~10 g, with 3 g being the lowest daily dose (22). Therefore, in keeping with these recommendations, we administered a minimum dose of 3 g and escalated it by 2 and 3 times for the other doses. The maximum dose chosen was 9 g; a higher amount was avoided to prevent possible side effects previously reported with excessive ginseng intake (23,24). In an early study, Siegel (23) reported the "ginseng abuse syndrome," which is a group of symptoms arising from prolonged and excessive ginseng intake. He indicated that individuals consuming 15 g ginseng per day experienced depersonalization and confusion (23). It should be noted, however, that in Siegel's report no control group existed and no analysis of the ginseng types that the subjects were ingesting was made. In another report, explosive headache, nausea, vomiting, and cerebral arteritis were experienced by a woman who consumed 25 g ethanol-extracted ginseng (24). Nonetheless, Chandler (25) indicated that prolonged or excessive ginseng consumption involves very low risk to the user.

Other side effects have been reported at lower doses. These have included nausea, headache and dizziness, insomnia, nervousness, and hypertension (26). Isolated cases of diarrhea and fatigue also have been reported (7). Not all of these attributed side effects, however, have been observed with all types of ginseng. None except for mild insomnia by a patient in our previous acute study (15) were, for example, reported after administration of AG. We also did not observe any side effects with AG in the present study. Additional side effects may result from concurrent use of ginseng with drugs. Interactions with blood-thinning agents such as warfarin, heparin, aspirin, and other nonsteroidal anti-inflammatory drugs are an unconfirmed possibility because of antiplatelet components found in ginseng (26). Interference with drug metabolism, however, seems unlikely. It was reported that selected ginsenosides from panax ginseng and elutherosides, peptidoglycans from Siberian ginseng (*Eleutherococcus senticosus*), did not inhibit the metabolism of coadministered substrates by various isoforms of cytochrome P450, although 2 ginsenosides stimulated activity (27). In addition, no adverse interactions were observed between AG and the oral hypoglycemic agents that 7 of 10 study participants took before each session in our study.

Positive interaction with oral antidiabetic agents might nevertheless be a possibility. Because reductions in PPG after AG were seen beyond placebo with medications, AG might have potentiated the blood glucose–lowering effect of the medications. The suggestion is that concurrent use of AG with oral hypoglycemic agents prescribed to control mealtime glycemia may improve outcomes. This practice, however, may create undesired postprandial hypoglycemia. Either way, practitioners may wish to make themselves aware of their patients' use of ginseng as a preemptive measure.

In addition to determining the optimal dose of AG, the current study showed a reduction in PPG with AG in type 2 diabetic individuals at all administration times

tested. This finding is of practical importance; type 2 diabetic individuals can be advised to consume AG at their convenience (i.e., together with a meal or any time up to 2 h before a meal) to achieve comparable reductions in PPG. Furthermore, it is important to stress that AG did not reduce glycemia at time 0, after AG ingestion (40, 80, or 120 min), or before consumption of glucose (0 min), indicating that AG alone will not cause undesired hypoglycemia. Overall, these results indicate that AG exerts its glucose-lowering effect only postprandially or when stimulated by glucose ingestion.

Such reductions in PPG by AG may be due to one or a combination of different mechanisms, including modulation of digestion, insulin sensitivity, or insulin secretion. The glycemic profiles in the present study do not seem to support the first mechanism. Although ginseng has been shown to inhibit gastric secretion in rats (28) and decrease glucose and maltose absorption in isolated rat and human duodenal samples (29), if AG was slowing digestion, then we would have expected lower values during the first 15 min of our study. This observation is typical with soluble dietary fiber (30) and acarbose (31,32), both of which operate through delaying or inhibiting the absorption of carbohydrates in the gut. Stronger support is therefore offered for a ginseng-modulating effect on insulin sensitization and secretion. An effect on insulin sensitivity has been shown twice in mice and cell lines. Chinese ginseng preparations were observed to increase GLUT2 protein in the livers of normal and hyperglycemic mice (12) and glucose uptake into sheep erythrocytes in a dose-dependent manner (33). DPG-3-2, a water extract of ginseng, was also shown to stimulate insulin secretion directly, increasing biosynthesis in different preparations of mice islets and rat pancreases (34).

Active components of ginseng that may play an important mediating role in these postulated processes include its polysaccharide (ginsenans), peptidoglycan (panaxans), and ginsenoside profiles. Most pharmacological actions of ginseng, however, are attributed to the involvement of ginsenosides, of which there are 3 classes: 20(S)-protopanaxadiols, 20(S)-protopanaxatriols, and oleanic acid–ginsenoside (10). Recent studies have shown that total ginsenosides and the most common protopanaxadiol, Rb_1, and protopanaxatriol, Rg_1, all of which were measured in the present study, affect the cholinergic, dopaminergic, and adrenergic systems in rodents (35–37). Total ginsenosides have also been shown to modulate nitric oxide synthesis, the enhancement of which has been linked to ginseng's effects (38). The former 3 systems affect glucose metabolism in vivo (39), and nitric oxide has been noticed to increase insulin-stimulated glucose uptake in rat skeletal muscles and adipose tissue (40) and to stimulate glucose-dependent secretion of insulin in rat islet cells (41). It is therefore possible that these ginsenosides contributed to the postprandial hypoglycemic effects we observed. In this regard, several ginsenosides, particularly Rb_1 (33) and Rb_2 (18,42), have been shown to induce hypoglycemic activity when isolated. Nevertheless, there is insufficient evidence to suggest that that the measured levels of total ginsenosides, Rb_1, Rg_1, or their ratios contributed to the observed effects. To our knowledge, neither studies that have investigated isolated ginsenosides in humans nor reliable data on the ginsenoside content of AG (43,44) exist. A high Rb_1-to-Rg_1 ratio is however thought to be a rough indicator of *Panax quinquefolius* L. (43), suggesting that the ginseng used in the present study was indeed of this genus and species.

Overall, the current study confirms our previous findings that AG administered to type 2 diabetic individuals can acutely reduce PPG (15). Furthermore, this study demonstrated that 3 g AG is sufficiently high to yield desirable PPG reductions, and this effect is independent of the time when AG is taken (up to 2 h before the meal). Additionally, because elevated glycemia 2 h after a glucose challenge is a hallmark of diabetes, and normalization of PPG at this time point is one of the primary goals of treatment (1), the AG-induced reduction of glycemia at the 2-h time point shows important clinical relevance.

Future studies should determine whether AG doses <3 g, given closer than 40 min before a meal, can yield reductions in PPG. If this is the case, then the safety and practicality of AG as an antidiabetic agent will be improved. But before AG can be suggested to patients and considered for clinical use, longitutidinal studies with varying clinical measurements must be performed.

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