American Ginseng (*Panax quinquefolius* L) Reduces Postprandial Glycemia in Nondiabetic Subjects and Subjects With Type 2 Diabetes Mellitus

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Background: Despite a lack of medical evidence to support its therapeutic efficacy, the use of herbal medicine has increased considerably. Ginseng, one of the most widely used herbs, is hypothesized to play a role in carbohydrate metabolism and diabetes mellitus. We therefore undertook a preliminary short-term clinical study to assess whether American ginseng (*Panax quinquefolius* L) affects postprandial glycemia in humans.

Design: On 4 separate occasions, 10 nondiabetic subjects (mean [±SD] age, 34±7 years; mean [±SD] body mass index [BMI], 25.6 ± 3 kg/m^2) and 9 subjects with type 2 diabetes mellitus (mean [±SD] age, 62 ± 7 years; mean [±SD] BMI, 29 ± 5 kg/m^2; mean [±SD] glycosylated hemoglobin A_{1c}, 0.08±0.005) were randomized to receive 3-g ginseng or placebo capsules, either 40 minutes before or together with a 25-g oral glucose challenge. The placebo capsules contained corn flour, in which the quantity of carbohydrate and appearance matched the ginseng capsules. A capillary blood sample was taken fasting and then at 15, 30, 45, 60, 90, and 120 (only for subjects with type 2 diabetes mellitus) minutes after the glucose challenge.

Results: In nondiabetic subjects, no differences were found in postprandial glycemia between placebo and ginseng when administered together with the glucose challenge. When ginseng was taken 40 minutes before the glucose challenge, significant reductions were observed ($P<.05$). In subjects with type 2 diabetes mellitus, the same was true whether capsules were taken before or together with the glucose challenge ($P<.05$). Reductions in area under the glycemic curve were 18%±31% for nondiabetic subjects and 19±22% and 22±17% for subjects with type 2 diabetes mellitus administered before or together with the glucose challenge, respectively.

Conclusions: American ginseng attenuated postprandial glycemia in both study groups. For nondiabetic subjects, to prevent unintended hypoglycemia it may be important that the American ginseng be taken with the meal.

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THE USE of herbal medicine as an unconventional health treatment is gaining considerable recognition and popularity worldwide.[1] Despite skepticism and a lack of medical evidence to support its therapeutic efficacy,[2] use of herbal remedies has increased approximately 380% during the last 7 years in the United States.[3] Belief in the superiority of herbs is based mainly on anecdotal evidence, paraherbalism, and pseudoscience.[4] It is only recently that guidelines for their investigation have been developed and a few herbs have been clinically studied.[5]

One of the most widely used herbs is ginseng. According to Chinese tradition, it is used as a tonic with prophylactic, restorative, and aphrodisiac properties.[4] The herb is obtained from a man-shaped root of several species of the genus *Panax* of the family Araliceae indigenous both to Asia and North America. Two of the most common types are Asian ginseng (*Panax ginseng* CA Meyer) and American ginseng (*Panax quinquefolius* L).

Both have comparable compositions, but are believed to be somewhat different in their effect. In vitro and animal research findings for both are reported in more than 300 original papers in Chinese and English.[6] Based on these studies, Asian ginseng and some of its fractions have been noticed to affect blood flow and have antistress, memory increasing, and antifatigue activities.[6] Other pharmacological properties include immunostimulation,[7] liver-protective activities,[8] and athletic endurance enhancement in the rat.[9] By comparison, its American counterpart is thought to increase sex drive,[10] memory, and learning[11]; decrease aging[12]; and possess both digestion-regulating[13] and liver-protective activi-

PARTICIPANTS AND METHODS

PARTICIPANTS

Ten nondiabetic subjects (6 male and 4 female subjects; mean [±SD] age, 34 ± 7 years; mean[±SD] body mass index [BMI], 25.6 ± 3 kg/m^2; mean [±SD] weight,73±7 kg) and 9 subjects with type 2 diabetes mellitus (5 male and 4 female subjects; mean [±SD] age, 62 ± 7 years; mean [±SD] BMI, 29 ± 5 kg/m^2; mean [±SD] weight, 81±9 kg) were recruited from faculty and students at the University of Toronto, Toronto, Ontario, and through hospital advertisements. The 2 groups did not differ significantly in their weight (P = .6, t test). All 19 subjects were outpatients and gave informed written consent to take part in the study, approved by the University of Toronto Human Subjects Review Committee. The subjects with type 2 diabetes mellitus were reasonably well controlled (mean [±SD] glycosylated hemoglobin A_{1c} [HbA_{1c}], 0.08±0.005; reference range, 0.06-0.08; reference range for well-controlled type 2 diabetes mellitus, 0.065-0.075), with an average (±SD) duration of 11.2 ± 2.3 years (duration range, 2-24 years). Current treatments for this group included diet (n = 3), sulfonylurea (n = 3), and a combination of sulfonylurea and metformin (n = 3). The treatments were maintained constant throughout the study.

TREATMENTS

Participants received a total of 4 treatments in random order: 2 test and 2 control. The test treatments consisted of gelatin capsules containing 3 g of American, Ontario-grown ginseng (Chai-Na-Ta Corp, Langley, British Columbia) given either 40 minutes prior to a 300-mL, 25-g oral glucose challenge (100 mL of a 300-mL, 75-g Glucodex solution; Rougier Inc, Chambly, Quebec, diluted with 200 mL of tap water) or together with the same oral glucose challenge. The control treatments were identical except placebo capsules containing corn flour were substituted for the ginseng. The carbohydrate and protein content, as well as appearance were matched. All ginseng and placebo capsules came from the same manufacturer lot.

PROTOCOL

Participants attended the Clinical Nutrition and Risk Factor Modification Centre at St Michael's Hospital, Toronto, on 4 separate mornings following a 10- to 12-hour overnight fast. A minimum of 1 week separated each visit to minimize carryover effects. Participants were 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 3 days prior to the test. To ensure that these instructions were followed, participants completed a questionnaire detailing presession information about their diet and lifestyle patterns. Before the beginning of each test, subjects were weighed and subjects with type 2 diabetes mellitus took their regular medications. After 30 minutes, the test was commenced. Each gave an approximately 250-µL fasting finger-prick capillary blood sample, using a lancet (Monoejector Lancet; Owen Mumford Ltd, Woodstock, England). One of the 4 treatments was then administered. When the placebo or ginseng were given before the oral glucose challenge, subjects took either set of capsules with 250 mL of tap water. After 40 minutes, they gave another blood sample and consumed the glucose challenge over exactly 5 minutes. Additional finger-prick blood samples were obtained at 15, 30, 45, 60, and 90 minutes after the start of the meal for nondiabetic subjects. The same was true for subjects with type 2 diabetes mellitus with the addition of a finger-prick blood sample at 120 minutes. When the placebo or ginseng were taken together with the glucose challenge, the same protocol applied with the exception that there was no waiting period and the capsules were taken simultaneously without additional water. In either case, all blood samples were collected in tubes containing fluoride oxalate and immediately frozen at -20°C pending analysis.

BLOOD GLUCOSE ANALYSIS

All blood samples were analyzed within 3 days of collection. The glucose concentration of each was determined by the glucose oxidase method using a glucose/L-lactate analyzer (model 115; YSI 2300 Stat glucose/L-lactate analyzer, Yellow Springs, Ohio). Measurements were expressed in millimoles per liter. To convert from millimoles per liter to milligrams per deciliter multiply by 18. The interassay coefficient of variation of this method for 2 sample pools was 3.3% (n = 91, 3.99±0.13 mmol/L, mean±SD) and 1.8% (n = 89, 14.35±0.26 mmol/L, mean±SD).

STATISTICAL ANALYSES

Blood glucose curves were plotted as the incremental change in blood glucose levels over time and the positive incremental area under the curve (AUC) was calculated geometrically for each participant, ignoring areas below the fasting blood glucose value.[22] 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 Statistical Software, Kaysville, Utah). Repeated measures 2-way analysis of variance (ANOVA) assessed interactive and independent effects of treatment (placebo vs ginseng) and administration (together vs 40 minutes before) on AUC. Pairwise differences in AUC and incremental glycemia at each time point (15, 30, 45, 60, 90, and 120 minutes) between the treatments were assessed by repeated measures 1-way ANOVA adjusted for multiple comparisons with the Newman-Keuls procedure. Both of these analyses were done separately for nondiabetic subjects and subjects with type 2 diabetes mellitus. All results were expressed as mean + SD and considered statistically significant if $P<.05$.

ties[14] in the rat. Supporting clinical studies using Asian ginseng are few and inconclusive: some show an effect[15] while others do not.[16,17] No clinical studies using American ginseng could be found in the literature.

There is also a suggestion that both types of ginseng may influence carbohydrate metabolism and diabetes mellitus. Numerous animal studies indicate that *P ginseng* CA Meyer[6,18] and *P quinquefolius* L[19,20] have sig-

nificant hypoglycemic action. Very limited clinical evidence is available to confirm these findings. In the only study to date, Sotaniemi et al[21] demonstrated a reduction in the levels of fasting blood glucose and glycosylated hemoglobin A_{1c} (HbA_{1c}) in persons with type 2 diabetes mellitus treated with ginseng relative to placebo.[21] The type of the ginseng used in this study, however, was not specified, and the results were ambiguous due to significant weight differences between the treatment groups. It remains unclear whether American ginseng will affect glucose metabolism in humans. We therefore studied its action on postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus.

RESULTS

All subjects completed all treatments without difficulty. Questionnaires revealed that subjects ate a minimum of 150 g of carbohydrate each of the 3 days before the 4 treatment sessions and that evening activities, amount of sleep, reported feelings of health and well-being, mode of transportation to the clinic, and weight did not differ between the treatment sessions for each subject. No complaints were reported about the nature of the placebo or ginseng capsules or side effects from the consumption of either during the test or within the 24 hours following the test. The only exception was some mild insomnia reported by 1 of the subjects with type 2 diabetes mellitus on 1 occasion after receiving ginseng.

NONDIABETIC SUBJECTS

Figure 1 shows incremental changes in glycemia and AUC following the administration of ginseng or placebo either before or together with a 25-g oral glucose challenge in 10 nondiabetic subjects. Two-way ANOVA indicated that differences in the effect of treatment (placebo vs ginseng) on AUC were statistically insignificant ($P = .06$), while differences in the effect of administration (together vs before) were significant ($P = .02$) with no interaction ($P = .07$). The results of pairwise comparisons shown in the figure indicated that ginseng did not significantly lower incremental glycemia at any time point following the oral glucose challenge when administration was together. In contrast, when administration was 40 minutes prior to the glucose challenge, ginseng significantly lowered incremental glycemia at 45 (1.7±1.2 mmol/L vs 2.8±1.0 mmol/L, $P<.05$) and 60 minutes (0.1±0.8 mmol/L vs 0.8±1.1 mmol/L, $P<.05$) compared with placebo. These results were reflected in the AUCs. When ginseng was administered together with the oral glucose challenge, it was unaffected; however, when administration was 40 minutes before the glucose challenge, AUC was significantly lower for ginseng than placebo (122±39 mmol/L vs 93±31 mmol/L, $P<.05$). This difference represented an 18%±31% reduction.

SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Figure 2 shows incremental changes in glycemia and AUC following the administration of ginseng or placebo

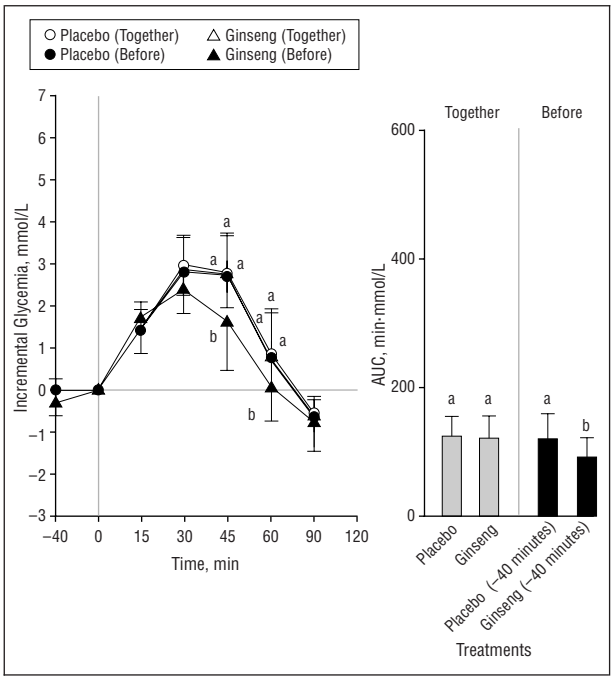

Figure 1. *Comparison of incremental changes in glycemia and area under the blood glucose curve (AUC) between American ginseng (*Panax quinquefolius *L) and a matched corn flour placebo administered either 40 minutes before (–40 minutes) or together with a 25-g oral glucose challenge in nondiabetic subjects (n = 10). Incremental glycemia at individual time points (A) and bars (B) with different lowercase letters are significantly different (repeated measures 1-way analysis of variance adjusted for multiple comparisons by the Newman-Keuls procedure,* P<.05*).*

either before or together with a 25-g oral glucose challenge in 9 subjects with type 2 diabetes mellitus. Two-way ANOVA indicated that differences in the effect of treatment on AUC were significant ($P = .008$), while differences in the effect of administration (together vs before) were insignificant ($P = .2$) with no interaction ($P = .6$). The results from pairwise comparisons shown in the figure indicated that when administered together with the glucose challenge, ginseng significantly lowered incremental glycemia following the oral glucose challenge at 45 minutes (4.2±1.3 mmol/L vs 5.3±1.3 mmol/L, $P<.05$) and 60 minutes (3.6±1.4 mmol/L vs 4.9±1.5 mmol/L, $P<.05$) compared with placebo. When it was given 40 minutes before the glucose challenge, the same was found at 30 minutes (3.8±1.2 mmol/L vs 4.8±0.9 mmol/L, $P<.05$) and 45 minutes (4.5±1.1 mmol/L vs 5.3±1.2 mmol/L, $P<.05$). These findings carried over to AUCs. Whether given together (319±112 min·mmol/L vs 407±107 min · mmol/L, $P<.05$) or 40 minutes before (303±97 min · mmol/L vs 377±102 min · mmol/L, $P<.05$) the 25-g glucose challenge, AUC was significantly lower for ginseng than placebo. These differences represented 22%±17% and 19%±22% reductions, respectively.

COMMENT

This study, although small both in size and scope, represents a trial in which a phytomedicine has been challenged by rigorous scientific evaluation. The lack of such trials has been characterized as a major deficiency in the assessment of alternative therapies.[23] Using a placebo-

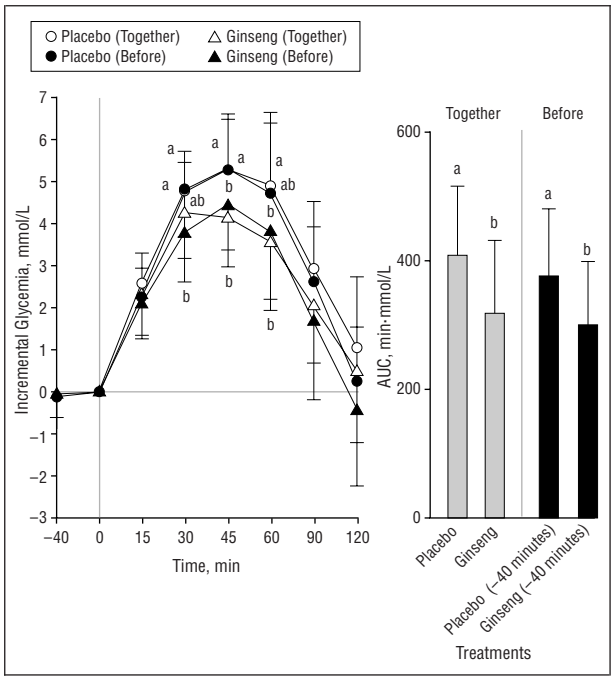

Figure 2. *Comparison of incremental changes in glycemia and area under the blood glucose curve (AUC) between American ginseng (*Panax quinquefolius *L) and a matched corn flour placebo administered either 40 minutes before (–40 minutes) or together with a 25-g oral glucose challenge in subjects with type 2 diabetes mellitus (n = 9). Incremental glycemia at individual time points (A) and bars (B) with different lowercase letters are significantly different (repeated measures 1-way analysis of variance adjusted for multiple comparisons by the Newman-Keuls procedure,* $P<.05$*).*

controlled, short-term clinical trial, to our knowledge, we are the first to demonstrate an effect of American ginseng on postprandial glycemia in humans. We noticed significant blood glucose–lowering action both in nondiabetic subjects and subjects with type 2 diabetes mellitus when ginseng was given 40 minutes prior to the test meal. When given together with the meal, this effect did not persist in nondiabetic subjects. To avoid an unintended hypoglycemic reaction, these findings suggest that it might be important for persons with type 2 diabetes mellitus to take ginseng with meals.

There are differences between our study and those of others that complicate comparisons to the literature. In our study, we noticed our effect with a high dose (3 g) relative to that given by others studying various types of ginseng in humans. A review of clinical studies shows the quantity administered is typically 1.5 g or less.[15-17,24] In research specific to diabetes, Sotaniemi et al[21] observed an improvement in glycemic control as measured by HbA_{1c} and an improvement in fasting glucose levels with a small 200-mg and 100-mg dose, respectively. Our rationale for using a higher dose was based on traditional medical practices. In Asian medicine, herbs are treated much like diluted drugs, as a result the minimum daily dose for individual nontoxic medicinal herbs is 3 g.[25] Unlike others, we also investigated giving ginseng 40 minutes before the oral glucose challenge, as well as together with the oral glucose challenge. Traditional practices again offer justification. According to Asian medicine, ginseng is usually taken fasting or between meals,[26] not simultaneously. Another contrast is that we investigated American ginseng.

Despite these differences, we believe our findings in humans support the hypoglycemic activities of ginseng previously observed in animal models. These include decreasing glucose tolerance curves in diabetic mice,[19] and decreasing the level of fasting blood glucose both in mice and rats. The latter having been accomplished by several types of ginseng and their isolates: American,[19,20] Asian,[6,18] Korean red, Shiu-Chi, Eleutherrococcus, Aralia, Canadian white,[19] and fraction DPG-3-2.[20] Also included are the benefits observed in humans by Sotaniemi et al.[21] Specifically, the long-term improvements in HbA_{1c} they observed may be explained partially by the benefit we observed to postprandial glycemia in our study. The ability of a diet to raise blood glucose levels has been found to be a factor of glycemic control. We demonstrated previously that the consumption of diets with a low glycemic index (GI) improve HbA_{1c} relative to high GI diets in subjects with type 2 diabetes mellitus.[27] If ginseng can lower the glycemic response to glucose, then it may be possible to use it as a means for lowering the GI of the whole diet, thereby improving glycemic control.

The mechanism by which ginseng lowers the blood glucose concentration is unknown. There are several plausible hypotheses that may work independently or in concert. First, a modulating effect of ginseng on digestion may be involved. An inhibition of neuronal discharge frequency from the gastric compartment of the brainstem in rats by American ginseng has been observed.[28] Inhibition of gastric secretion by Asian ginseng has also been observed in rats.[29] The result of both may be to slow the digestion of food, decreasing the rate of carbohydrate absorption into portal hepatic circulation.

Second, an effect on glucose transport may be involved. Asian ginseng has been shown both to increase glucose transporter-2 protein in the livers of normal and hyperglycemic mice[18] and glucose uptake into sheep erythrocytes in a dose-dependent manner.[30] This effect may be mediated by nitric oxide (NO). It was recently shown that insulin-stimulated glucose uptake in rat skeletal muscles and adipose tissue is NO dependent.[31] Evidence suggests that an increase in NO capable of eliciting this response might be accomplished by ginseng. Enhanced NO synthesis by ginseng in endothelium of lung, heart, and kidney and in the corpus cavernosum has been noticed.[32]

Last, ginseng may exert its effect through modulation of insulin secretion. Some ginseng fractions have been noticed to increase the blood insulin level and glucose-stimulated insulin secretion in alloxan diabetic mice.[33] This effect may also be mediated by NO. It was recently shown that NO stimulates glucose-dependent secretion of insulin in rat islet cells.[34]

These last 2 mechanisms offer a possible explanation why we only saw an effect of ginseng when it was given 40 minutes before the glucose challenge in nondiabetic subjects. Research done on sildenafil (Viagra), which is hypothesized to amplify the NO-signaling cascade, indicates that it should be administered 1 hour before intercourse to allow sufficient time to develop its ef-

fect.[35] The possible reason it worked in both cases for the subjects with type 2 diabetes mellitus may be due to its ability to interact with or potentiate the action of various drugs[36]: 7 of the 9 subjects with type 2 diabetes mellitus were treated with oral hypoglycemic medications. Alternatively, its proposed adaptogenic qualities may offer an explanation.[37]

Implications of our preliminary findings are promising. Two recent epidemiological cohort studies observed that a reduction in GI of the diet between the highest and lowest quintiles decreased the risk of developing diabetes in women[38] and men.[39] The observed difference in GI between these quintiles (17% for women and 18% for men) was very similar to the 18%±10% reduction for nondiabetic subjects and the 19%±7% and 22%±6% reductions for subjects with type 2 diabetes mellitus seen after ginseng was administered before or together with oral glucose, respectively. It is tempting to suggest that in healthy persons, this may indicate a potential use of ginseng in prevention. In people who already have established type 2 diabetes mellitus, an improvement in glycemic control with oral hypoglycemics and insulin was shown to decrease the development and progression of microvascular complications.[40] If this improvement in control could again be accomplished by a decrease in the GI of the diet affected by ginseng, then it may prove a useful adjunct to the conventional treatment of diabetes mellitus. In short, either use may offer a new way to use an old medicine.

Whether these results will prove clinically relevant, however, is debatable. Before American ginseng's therapeutic benefit in these areas can be realized, studies of the efficacy of long-term administration using HbA_{1c} as a surrogate end point and dose response are required. Mechanistic investigations, including those that explore a ginseng-NO link, are also warranted.

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