A Role for Ginseng in the Control of Postprandial Glycemia and Type 2 Diabetes

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Abstract

The use of herbals has increased considerably while their efficacy and safety remain untested. This unsupported surge in demand has prompted a call for their clinical evaluation. One area in which evaluations are emerging is ginseng and diabetes. Growing evidence is accumulating from in vitro and animal models indicating that various ginseng species, American (*Panax quinquefolius* L), Asian (*Panax ginseng* C.A. Meyer), Korean Red, San-chi (*Panax notoginseng* [Burk.] F.H. Chen), and the non-panax species Siberian (*Eleutherococcus senticossus*) ginsing, and their fractions, saponins (ginsenosides) and peptidoglycans (panaxans for panax species and eleutehrans for Siberian ginseng), might affect carbohydrate metabolism and related signaling molecules. Recent human studies from our laboratory have also shown a blood glucose lowering effect of American ginseng (AG) and some other ginseng spices postprandially after acute administration and chronically after administration for 8-weeks in people with type 2 diabetes. Although generally encouraging, these data only indicate a need for more evaluations of ginsengs safety and efficacy. Because of poor industry standardization, it is not known whether all ginsengs will affect blood glucose. In this regards some ginseng batches have demonstrated null effects while others have even raised postprandial glycemia. Clinical research should therefore focus on components involved in its glucose lowering effects.

Introduction

Diabetes control remains unsatisfactory. Despite numerous preventative strategies and an armamentarium of medications diabetes remains a major health problem. Its prevalence is increasing (1) and people with diabetes have benefited less from reductions in heart disease and all cause mortality (2). This insufficiency of treatment coincides with a surge in the demand for herbs. The general public has shown an increased interest in herbs, with a ~4-fold from 1990-1997 in the U.S (3).

One of the most widely used herbs is ginseng (4). It is an herb obtained from the root of several species of the plant family *Araliaceae* and the genus *Panax*. Popular commercial species include American (*Panax quinquefolius* L.), Asian (*Panax ginseng* C.A. Meyer), Korean red (steam treated *Panax ginseng* C.A. Meyer), Japanese (*Panax Japonicus* CA Meyer), San-chi (*Panax notoginseng* [Burk.] F.H. Chen), and the non-panax species Siberian (*Eleutherococcus senticossus*) ginsing. Many health benefits have been attributed to these various ginseng species. Recent therapeutic claims refer to improvements in immune function, cancer, cardiovascular health, mental capacity, fatigue, and athletic performance (5,6). Some consider belief in these claims a "triumph of mystique over medicine" (7). Most are based on animal studies, and uncontrolled non-randomized studies in humans that usually lead to a substantial overestimation of the effect. The reality is that the limited studies in humans do not support these claims. Based on data from 16 randomized controlled studies, the efficacy of ginseng has not been established beyond a reasonable doubt for any of its indications (6). The same is true for its safety. Some have cited side effects that include increased blood pressure, nausea, headache, insomnia, nervousness, diarrhea, and interaction with "blood thinning" agents (8). In contrast, the *World Health Organization* continues to endorse ginseng as an herb without known side effects (9).

There remains a deficiency of studies to resolve these controversies. This has prompted articles (10), editorials (11,12), and letters (13-16) calling for randomized controlled clinical trials to assess the safety and efficacy of herbs. In response, promising evidence at the basic and human level is beginning to accumulate for the therapeutic benefit of ginseng (5,17). This is especially true in the area of diabetes. Growing evidence from in vitro and animal models indicate that ginseng might affect glucose absorption, transport, and disposal (18). Recent human studies from both our laboratory and others also show a blood glucose lowering effect of ginseng (19-23), but these effects were not always consistent. This review will address both levels of evidence

describing the present state of the research, its implications, caveats, and avenues for future investigation.

Ginseng and Glycemia - Basic Evidence:

Long term glycemia lowering effects of ginseng

Aqueous extracts of Asian ginseng root body and rootlets each administered orally at a dose of 500mg/kg/d body weight for 28d decreased fasting blood glucose by ~40% and ~37% with a concomitant decrease in insulin of ~76% and 52% in KKAy diabetic mice. Both results were comparable to reductions (37% for glucose and 67% for insulin) observed for the thiazolidinedione, rosiglitazone, administered at a dose of 0.33mg/kg (24). Asian ginseng fed at 1000mg/kg/d for 15-16d reduced fasting glycemia by ~35% in streptozocin-induced diabetic rats (25). Finally, Asian ginseng berry extract at 150mg/kg significantly improved body weight, fasting blood glucose, and glucose tolerance in db/db mice (26) and the same outcomes plus fasting insulin and insulin sensitivity in ob/ob mice after 12d (27).

Acute glycemia lowering effects of ginseng

Others have reported acute reductions with various ginsengs. A water extract of Asian ginseng injected intravenously at 100mg/kg with glucose decreased glycemia significantly compared with glucose alone in diabetic mice (28). An oral injection of a water extract of Asian ginseng decreased glycemia at doses of 200 and 400mg/kg by ~18 and 28% in normal mice and by ~23 and 36% in epinephrine induced hyperglycemic mice (29). Methanol extracts of Chinese, Korean red, Ontario grown American, and Sanchi ginsengs administered by stomach intubation decreased glycemia in resting mice from ~5-15% compared with placebo (30). And established extracts of Asian ginseng administered intraperintoneally reduced resting glycemia, epinephrine induced hyperglycemia, and intravenous glucose tolerance: *DPG-1* at 360 mg/kg (31), *DPG-3-2* from 3-100 mg/kg (32), *EPG-3-2* at 50mg/kg (33,34), and *Fraction 4* at 10mg (35). Taken together, the data suggest that ginseng possesses acute hypoglycemic effects.

Glycemia lowering effects of ginsenosides

Specific ginsenosides may play a role in the effects observed with whole ginseng and its extracts. Various ginsenosides and their classes have been shown to decrease glycemia directly.

For example, the most prevalent PPT ginsenoside, Rg_1, was shown to decrease glycemia in resting mice by 17% compared with placebo when administered by stomach intubation at 50mg/kg (30). Rb_2, a PPD, was also noticed to decrease glycemia in streptozotocin induced diabetic rats after 6d at 10mg/kg intraperintoneal injection (36). An Asian ginseng extract containing Rg and Re, a PPT ginsenoside high in the berries of Asian ginseng and root of American ginseng, significantly reduced glycemia in alloxan diabetic mice (31). Finally, Re decreased fasting glycemia in ob/ob mice after 12d at 20mg/kg of intraperintoneal injection (27).

Glycemia lowering effects of ginsenans/panaxans

Although oral administration of ginsenans and panaxans will, as suggested, likely result in their degradation, their role in the observed effects cannot be precluded. In this regard, when injected intraperitonealy most panaxans have shown an effect. Panaxans A-U from Asian ginseng (37-39) and quinquefolans A-C from AG (40) have all shown marked yet differential hypoglycemic effects when administered as intraperitoneal injections at doses from 10-300mg/kg in both normal and alloxan induced hyperglycemic mice (37-41). No studies of the effects of ginsenans on glycemia could be found in the literature.

Possible glycemia lowering mechanisms of ginseng:

How ginseng through its various fractions has its effect on glycemic regulation is not clear. Animal data support 3 possibilities: [1] modulation of glucose transport, [2] glucose disposal, or [3] insulin secretion (Figure 1).

Possible primary effects support the involvement of ginsenosides in these mechanisms. First, there is evidence of enhanced nitric oxide (NO) synthesis by total ginsenosides (55-60), PPT (56), Rg_1 (56,57), Re (57) Rg_3 (58), and Rc (58) in tissue including the nerves (61), aorta (56), brain (58) and kidney (59). This may affect insulin kinetics. Insulin stimulated glucose uptake in rat skeletal muscles and adipose tissue (62) and insulin secretion rat islets (63) appears NO dependent. Second, certain ginsenosides have shown effects consistent with cholinergic stimulation and adrenergic blockade. Rb_1, (64), Rg_1, Re (65) increased choline acetyltransferase mRNA, protein (64), and activity (65) in rat brains, suggesting possible enhancement of acetylcholine secretion. On the other hand, total ginsenosides, Rb_1, Rc, Re, Rf, Rg_1, (66), Rg_2 (67), Rg_3 (67,68), and Rh_2 (68), decreased catecholamine secretion (67,68) and Ca^{2+} current and membrane capacitance change, suggestive of a decrease in catecholamine secretion (66), in bovine adrenal chro-

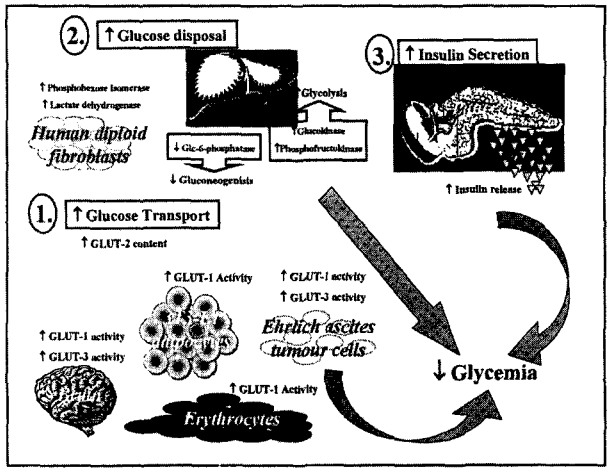

Fig. 1. Three possible hypoglycemic mechanisms of ginseng:

[1] modulation of glucose transport - A water extract of Chinese ginseng increased GLUT-2 protein in the livers of normal and hyperglycemic mice (29). PPT, (20R)-PPD, Rg_1, Rc, Rd, Re, Rf, Rg_2, Rh_1, Rb_1, and Rb_2 increased 2-Deoxy-D-[2-^{3}H]glucose (2-DG) uptake in isolated sheep erythrocytes by GLUT-1 in a dose dependent manner at doses from 0.01-10 mM (42). The standardized Asian ginseng extract G115®, which has a high ratio of PPD: PPT (43), increased 2-DG uptake in a dose dependent manner in rabbit brain at doses from 23-46mg/ml (44) and Ehrlich ascites tumour cells at doses from 0.5-10 mg/ml (45). Presumably these increases in uptake were mediated principally by GLUT-1 and/or GLUT3, as neither tissue expresses SGLT-1, GLUT-2 or GLUT-4 (46) and the GLUT-5 in brain has only low affinity for glucose (47). Finally, a water extract of Asian ginseng increased basal 2-DG uptake in 3T3-L1 adipocytes at a dose of 100 mg/ml (48).

[2] Modulation of glucose disposal - The saponin fraction from G115® at a dose of 200mg/ml increased the glycolytic enzyme, phosphohexose isomerase, and several isozymes of the pyruvate lactate shunt enzyme, lactate dehydrogenase, although no changes in intracellular or extracellular glucose concentrations or glucose uptake accompanied these changes (49). Oral administration of aqueous extracts of Asian ginseng root body and rootlets at a dose of 500 mg/kg for 28d decreased the activity of the rate limiting gluconeogenic enzyme glucose-6-phophatase (G6Pase) in liver preparations of KKAy diabetic mice by 46% and 20% (24). Finally, Rb_2 increased the activity of the rate limiting glycolytic enzymes phosphofructokinase and pyruvate kinase, while decreasing the activity of the rate limiting gluconeogenic enzyme G6Pase in liver from normal rats after a single 10mg intraperintoneal injection (50) and increased the activity of glucokinase while decreasing the activity of G6Pase in liver from streptozotocin diabetic rats after intraperintoneal injection at 10mg/d for 6d (51).

[3] Modulation of insulin secretion: DPG-3-2 stimulated insulin biosynthesis in mice islets and rat pancreas at concentrations from 0.5-1.0 mg/ml (34,52). EPG-3-2 increased glucose stimulated insulin secretion in alloxan diabetic mice at doses from 10-50 mg/kg after intraperintoneal injection (52). TotaL ginsenosides from Asian ginseng increased glucose and nonglucose stimulated insulin release from rat islets in a dose dependent manner at doses from 0.10-0.25 mg/ml (53). Finally, Rg_1 increased insulin binding with a ~2-fold increase in the total number of binding sites in rat liver and brain 3d and 5d after 3 consecutive days of intraperintoneal injections at 10 mg/kg (54).

mafin cells. Such changes in either system will increase glucose uptake (69,70) and glucose stimulated insulin secretion in rat islet cells (71,72). Third, an effect on the peroxisome prolifera-

tor activated receptor-γ (PPARγ), the target of the thiazolidinediones, has been observed. The aqueous extract of Asian ginseng rootlets increased PPARg protein comparably with rosiglitazone in KKAy mice (24). Finally, effects on intracellular metabolites involved in insulin signaling have been observed. Rh_1 and Rh_2 decreased protein kinase C (PKC) activity at concentrations from 10-100 μM, via a concomitant decrease in its allosteric activator diacylglycerol (DAG), in NIH 3T3 fibroblasts (73). In another study, Rb_1, Rb_2, and Rc decreased TNFa in human macrophages at concentrations from 10-100 μM (74). Such changes have been related to improvements in insulin sensitivity (75,76).

Opposing glycemic effects of ginseng and specific ginsenosides:

Opposing glycemic effects of specific fractions and ginsenosides have also been observed. A water extract of Asian ginseng, expected to have a low ratio of PPD:PPT, significantly inhibited insulin stimulated 2-DG uptake compared with control in a dose related manner (48). PPTs inhibited [^{14}C]-α-mean glucose uptake via the glucose transporter SGLT-1 at doses from 10-100 μg in cultured rabbit renal proximal tubular cells (77). Finally, an extract containing Rb and Rc increased glycemia at 100 mg/kg (31). These opposing effects might explain differences between different ginsengs.

Ginseng and Glycemia: Human Evidence

Longterm efficacy of ginseng in diabetes:

Very limited clinical evidence is available to confirm the hypoglycemic effect of ginseng observed in animal models in humans. Only 2 studies could be found. In the first study, 8 wks of treatment with 100 and 200 mg/day of an unspecified ginseng improved fasting glycemia and longterm glycemic control, assessed by HbA_{1c}, respectively in type 2 diabetic subjects (78). But the results were also ambiguous due to significant weight loss differences between the treatment groups. In the second study, 24mos of treatment with a Korean red ginseng extract at doses from 3-4.5 g decreased HbA_{1c} in 34 people with type 2 diabetes compared with controls (79). Secondary sources also report glycemic benefits of Korean red ginseng in diabetes (80). But control groups were not reported and primary sources could not be retrieved for verification.

Table 1. Summary of 5 acute studies assessing the dosing and timing effects of American ginseng (AG) on glycemia

Study Description	Sample	OGTT	AG Dosing	AG Timing	% AUC Reductions	P value
Arch Intern Med (115)	10 NGT (Age: 34±2years, BMI: 25.6±1kg/m^2)	25g	3g 3g	-40min 0min	18% ↓ for 3g AG @ -40min vs. placebo No effect for 3g AG @ 0min vs. placebo	P<0.05 P=NS
Arch Intern Med (115)	9 DM2 (Age: 62±2years, BMI: 29±1.7kg/m^2, HbA_{1c}: 7.6±0.2%)	25g	3g 3g	-40min 0min	22% ↓ for 3g AG @ -40min vs. placebo 19% ↓ for 3g AG @ 0min vs. placebo	P<0.05 P<0.05
J Am Coll Nutr (116)	10 NGT (Age: 41±4years, BMI: 24.8±1.1kg/m^2)	25g	3, 6, 9g	-120, -80, -40min	26.6, 29.3, 38.5% ↓ for 3,6, and 9g vs. placebo No effect of timing	P<0.05 P=NS
Diabetes Care (117)	10 DM2 (Age: 63±2years, BMI: 27.7±1.5kg/m^2, HbA_1c: 7.3±0.3%)	25g	3, 6, 9g	-120, -80, -40, 0min	19.7, 15.3, 15.9 % ↓ for 3,6, and 9g vs. placebo No effect of timing	P<0.05 P=NS
Am J Clin Nutr (118)	12NGT (Age: 42±7 years, BMI: 24.1±1.1 kg/m^2)	25g	1, 2, 3g	-40, -20, -10, 0min	14.4, 10.6, 9.1 % ↓ for 1,2, and 3g vs. placebo 14.1, 15.0, 9.2 % ↓ for -40min vs -20, -10, and 0min	P<0.05 P<0.05

NGT, DM2, OGTT, and AUC denote normal glucose tolerance, type 2 diabetes mellitus, oral glucose tolerance test, and area under the curve respectively. P-values are for comparisons between absolute values using repeated measures ANOVA adjusted with the Newman Keuls procedure. Data are mean±SEM.

Acute efficacy of American ginseng in lowering glycemia:

The need for human data led us to conduct a series of 5 randomized placebo controlled acute clinical studies to evaluate the efficacy of a single batch of AG (*Chai-Na-Ta Corp.*, BC, Canada) in lowering postprandial glycemia and its dosing and timing effects in subjects with and without diabetes using a 25 g-OGTT protocol (Table 1). The main findings were 4-fold: [1] AG reduced postprandial glycemia from 9.1-38.5%; [2] Doses from 1-9g were equally efficacious; [3] Times from 0-120min before the glucose challenge were equally efficacious in diabetic subjects; and [4] only AG >40 min before the OGTT reduced glycemia in nondiabetic subjects. Using a 75g-OGTT protocol, we also saw that 6g of the same AG reduced glycemia (Figure 2A). This was achieved with a tendency for higher first release insulin and nitric oxide (81), supporting one the mechanisms described above. We concluded that AG is able to reduce acute postprandial glycemia.

Differential effects of different ginseng species

Although Asian, Korean red, American, Sanchi, and Siberian ginsengs and their components

have all shown glycemic effects in rodent models, the magnitude and direction of their effects can be quite variable. The question remains whether other ginseng types are able to replicate the glycemia lowering we observed previously with AG. To investigate this possibility, we assessed the effect of 8 popular ginseng types (Sanchi; the nonpanax species, Siberian; American; Asian; Korean red; Japanese; Wild American; and Vietnamese), on glycemic indices following a 75g-OGTT, using a double-blind, randomized, double-placebo controlled, within-subject design in 12 healthy subjects. Comparisons showed that a 2nd batch of AG lowered glycemia, while Asian and Siberian ginseng raised it, compared with the mean of 2 placebos (Data not presented). These comparisons also showed that Asian ginseng significantly increased preprandial insulin at 0 min

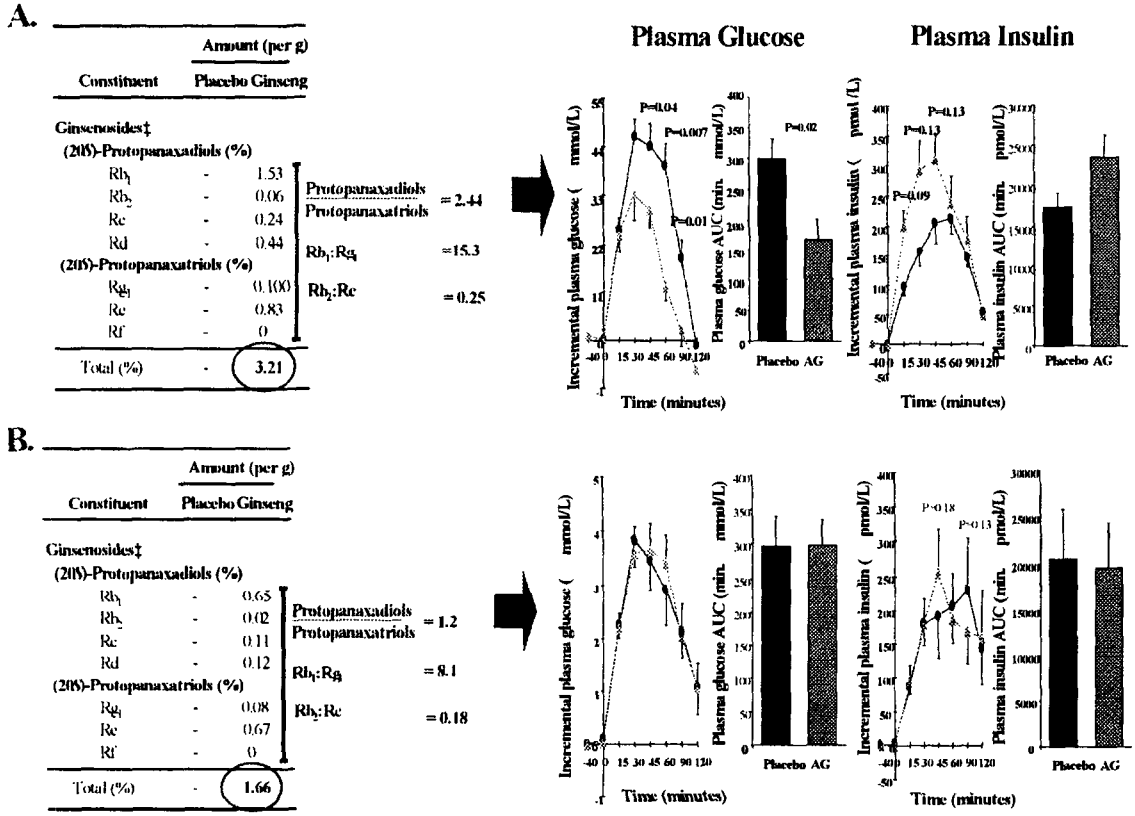

Fig. 2. Differential effects of American ginseng (AG) batches with different compositions.**Panel** A is for the ginseno-side profile and glycemic effects for the original batch of AG used in our 5 previous studies (49-52). Panel B is for the ginsenoside profile and glycemic effects for a new batch of AG. The line plots and bars represent the incrementa change and AUC for plasma glucose and insulin following control (•) or 6g AG (▲) taken 40 min before a 75 g-OGTT in 12 nondiabetic subjects. P values are for repeated measures ANOVA. Ginsenosides were assessed by HPLC/UV. Data are mean±SEM.

(P=0.04). A subsequent dose response study confirmed these glycemia and insulinemia raising effects of Asian ginseng (82).

American ginsengs ginsenoside composition and acute efficacy

The fraction of AGs profile that gives rise to the hypoglycemic effects observed is unclear. To begin to understand whether the ginsenoside profile contributed to effects, we compared the first efficacious AG from our acute studies (Figure 2A) with a 3rd batch of AG from the same supplier (Figure 2B) with ~70% less total ginsenosides and a ratio of PPDs:PPTs and Rb_1:Rg_1 ~50% smaller, at the expense of PPDs and Rb_1. Neither postprandial glucose nor insulin was affected by this batch. In keeping with the findings above, we concluded that the decrement in PPDs might explain its lack of effect (83).

Standardized American ginseng and long term efficacy of type 2 diabetes

Taken together, our observations suggested that AG with a profile similar to our efficacious batches might have long-term therapeutic value. To investigate this possibility, we studied the long term effects of a proprietary extract, *CNT 2000* (*Chai-Na-Ta Corp.,* Langley, BC), designed to have a ginsenoside profile similar to that of the AG used on the 5 acute studies (83-87): total ginsenosides of 3.54 and a PPD:PPT ratio of 2.4. An 8-week double-blind, placebo-controlled crossover trial was undertaken to investigate the effects of 1g of *CNT 2000* or placebo taken 40min before each meal TID on glycemic control in 24 type 2 diabetic subjects (88). Fasting glucose and HbA_{1c} were decreased following CNT2000 compared with placebo after 8-weeks. There was also an observable but insignificant increase in insulin suggesting a possible improvement in b-cell function.

We observed modest yet significant between treatment decreases in FPG and HbA_{1c} after CNT2000 compared with placebo: 12.8% (p=0.026) and 4.5% (p=0.016) respectively. These effects were accompanied by an observable but insignificant increase in FPI (23%, P=0.15). NOx was also significantly increased following CNT2000 compared with placebo (P=0.03) and this increase correlated significantly with the improvement observed in HbA_{1c} (r=-0.42, P=0.043) (89). None of the safety parameters, including blood pressure, liver and kidney function and blood pressure were safety measures were adversely affected. It was concluded that 2g/day of CNT2000 extract added to the conventional treatment of diabetes improved blood glucose control beyond conventional treatment alone in type 2 diabetes, again without apparent side effects.

Possible Implications

Our preliminary clinical findings, demonstrating a blood glucose lowering effect of ginseng, postprandially after acute administration and chronically after longterm administration, are encouraging. Prospective cohort studies have shown that lowering the postprandial blood glucose load of the diet may be important in the prevention of type 2 diabetes (90,91). Although it is the position of *American Diabetes Association* (*ADA*) that there is no evidence that supports preferential targeting of postprandial blood glucose in the management of diabetes (92), therapy with this focus might also be an important strategy (93). Numerous pharmacological agents for diabetes reduce HbA_{1c} through targeting postprandial blood glucose. These include alpha-glucosidase inhibitors, rapid acting oral insulin secretagogues, and rapid acting insulin analogues (92). A recent investigation further demonstrated that targeting postprandial blood glucose with a combination of insulin lispro and glyburide improved HbA_{1c} significantly more than targeting FPG with bedtime NPH insulin and glyburide or targeting preprandial blood glucose with metformin and glyburide (94). These data raise the possibility that AG, which was also administered in a way that targets postprandial blood glucose in both our acute and longterm studies, might have similar benefits to conventional approaches in diabetes prevention and management.

Caveats

There are several caveats that should be considered when interpreting these possible benefits. First, ginseng may not have its effects solely through a postprandial mechanism. Sotaneimi and coworkers observed benefits in HbA_{1c} with only once daily administration of ginseng that was without regard to mealtime. They also did not observe differences between OGTTs done at the beginning and end of the ginseng treatments (95). Second, interactions with other oral hypoglycemic agents remain an unconfirmed possibility. In those subjects with type 2 diabetes who were taking their oral agents concurrently with the treatments during our acute and longterm testing, AG plus oral agents reduced glucose beyond oral agents alone (oral agents plus placebo). Although the postprandial efficacy of American ginseng was not found to be affected when glucose lowering was compared between those taking oral American ginsengents and those who were not in our acute (96) and long-term studies, this finding suggests that American ginseng might derive benefit or precipitate undesired effects through augmentation of oral agents. Practi-

tioners may wish to keep themselves informed of their patients use of American ginseng and other ginsengs. Finally, because of the poor standardization of ginseng, it is also not known whether the observed glucose lowering effects would apply to other ginseng species or even whether other American ginseng products or another batch of the same American ginseng would produce the same results. Ginsenoside concentrations in commercial ginseng products have been shown to vary as much as 15-fold in capsules and 36-fold in liquid preparations (97). There have also been reports that 32% of Chinese patent medicines contain undeclared pharmaceuticals and potentially toxic levels of heavy metals (98). In this regard, a recent advisory by the Federal Drug Administration (FDA) reported that a ginseng preparation, marketed as a diabetes remedy, contained a sulfonylurea (99). Generalizing these data to ginsengs with unknown composition should, therefore, be avoided.

Future Research

Before ginseng can be recommended as a novel prandial glucose regulator, and for long term diabetes control, more questions need to be answered. Specifically, are the effects observed reproducible in a greater number of people? Are the effects reproducible in people with different categories of glucose regulation or diabetes control? Will the results hold over a longer period of time? Will ginsengs of a different origin, composition, or species elicit similar responses? And which components are responsible for its effects? Studies that attempt to answer some of these questions are currently underway in our laboratory.

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