



VIEWPOINT

Herbal remedies in the management of diabetes: Lessons learned from the study of ginseng

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Summary The only example of an approved antidiabetic drug that was developed from a herbal source with a long history of use for diabetes is the biguanide Metformin from French lilac (*Galega officinalis*). Clinical data are beginning to emerge that support antidiabetic indications for several other herbs. This viewpoint discusses the state of the evidence for their clinical antidiabetic efficacy. One of the most studied herbs, ginseng (*Panax* spp.), is used as a model to illustrate the challenges associated with achieving reproducible clinical efficacy. It is concluded that the best evidence for clinical efficacy in diabetes remains for ginseng. But overall insufficient evidence exists to claim a diabetes indication for herbs. The experience with ginseng suggests that although reproducible efficacy may be achieved using an acute postprandial clinical screening model to select an efficacious ginseng batch, dose, and time of administration, there is a need to develop a basis for standardization that ties the composition of herbs to efficacy. In the absence of such standardization, the use of herbs in diabetes must be approached cautiously.

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Introduction

Historical accounts of diabetes mellitus first appeared in the medical texts of several ancient

cultures over 2000 years ago. Symptoms that included polyuria and polydipsia were described in the Egyptian Ebers papyri, Greek Epidemics Book III of Hippocrates, and the Chinese Nei Ching [1,2]. Hindu writings in the Ayurvedic texts used these same symptoms and others including glucosuria and the smell of breath acetone to differentiate two main types of diabetes mellitus: one inherited and another acquired through obesity [1]. Recorded treatments for these disorders included largely

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diet- and plant-based remedies [1,2]. Ethnopharmacological investigations have since implicated thousands of plant-derived herbs in the treatment of diabetes. A comprehensive review of data for thousands of these herbs reported that >80% have demonstrated some antidiabetic activity in studies [3]. There is, nevertheless, only one example of an approved antidiabetic drug that was developed from an herb with a long history of use for diabetes: the biguanide metformin from French lilac (*Galega officinalis*) [4]. Numerous other herbs remain candidates for antidiabetic drug development. Clinical data are beginning to emerge, which support antidiabetic indications for several of these herbs. This viewpoint outlines the opportunity that exists for these herbs in the management of diabetes and the state of the evidence for their clinical antidiabetic efficacy. It then discusses of the clinical antidiabetic efficacy of one of the best-studied herbs, ginseng. An emphasis is placed on new data supporting its antihyperglycemic efficacy and related complementary metabolic effects. Finally, important caveats affecting the interpretation of data from clinical studies of herbs are discussed.

Opportunity for herbs in diabetes

Despite the numerous preventative strategies and armories of medication, the management of type 2 diabetes remains grossly unsatisfactory. Diabetes is emerging as a pandemic. Diabetes is predicted to increase by 27% in developed countries and 48% in developing countries from 1995 to 2025 [5]. In the U.S., the trends may already be outpacing the predictions. Diabetes increased by 61% from 1991 to 2001 [6]. The progression of the disease in those that have diabetes has been no better attenuated. Glycemic control targets for monotherapy continue to go unmet [7]. With increasing reliance on multiple patented pharmacological agents to meet targets, the cost of treatment has also become a real concern. The cost of metformin is 3- to 5-fold higher than that of the cheapest generic sulphonylureas. This spirals to 6-fold higher for repaglinide and 30-fold higher for thiazolidinediones [8]. The ability of developing countries to afford this level of treatment is dubious [9].

These concerns point to the need for more effective and cheaper management modalities. Complementary and alternative medicine (CAM) approaches that include herbs may hold promise in this regard. A compelling argument has been made that the random in vitro "high-throughput" screening for new drug therapies preferred by pharmaceutical companies has less practical merit

than an ethnopharmacological approach that involves ethnobotany and screening of traditional systems of medicine for candidate therapies [4]. This is especially true for diseases such as diabetes that are complex metabolic disorders, as certain metabolic targets of these approaches may be unrelated or secondary to effects on more proximal defects [4]. Herbal treatments not identified by conventional in vitro screening systems might therefore still be proven to have clinical efficacy and potential for development.

The public in their actions already endorse the use of herbs. Driven by the insufficiency of treatment and anecdotal evidence, paraherbalism and pseudoscience, the use of CAM increased by 68% from 1990 to 1997 in the U.S. [10]. The most recent estimates suggest that 75% of general medical patients in the U.S. are now using CAM therapies [11]. One of the strongest independent determinants of this behavior is the use of CAM to treat diabetes [12]. This increasingly high demand has occurred in the absence of safety and efficacy evidence, adequate regulatory standards, patient disclosures to physicians, and physician education. This has prompted a unified call from the medical community in the form of editorials, letters, and commentaries [13–21] for randomized controlled clinical trials (RCTs) to evaluate CAM treatments and provide a basis for legitimate health claims.

Clinical efficacy of herbs in diabetes

The call for more rigorous clinical assessments of CAMs is being answered by a segment of the literature. There is a growing database of clinical trials investigating the effects of several herbs in diabetes. The efficacy, safety, and mechanisms of these herbs in diabetes have been well described in a recent systematic review of 42 randomized and 16 nonrandomized clinical trials [22]. The reader is directed to this source for details. Briefly, the herbs with supporting clinical data in diabetes include ginseng (*Panax spp.*), ivy gourd (*Coccinia indica*), garlic (*Allium sativum* and *Allium cepa*), holy basil (*Ocimum sanctum*), fenugreek (*Trigonella foenum graecum*), prickly pear cactus or nopal (*Opuntia streptacantha*), milk thistle (*Silbum marianum*), fig leaf (*Ficus carica*), gurmar (*Gymnema sylvestri*), bitter melon (*Momordica charantia*), *Aloe vera*, *Ginkgo biloba*, and various herb combinations in Traditional Chinese Medicine, Native American Medicine, and Tibetan Medicine. Various hypoglycemic mechanisms have been suggested for these herbs from animal and in vitro models. These include delayed glucose

absorption in the gut (*A. vera*, prickly pear cactus), increased glucose uptake/disposal (fig leaf, ivy gourd), glucose stimulated insulin secretion (garlic, holy basil, and gurmar), the first two (fenugreek), the last two (bitter melon), or all three (ginseng) [22–24].

The antihyperglycemic efficacy remains inconclusive for the majority of these herbs. The conclusion of the systematic review was that although shown to be safe, there is insufficient evidence to make conclusions about their efficacy [22]. This was despite the direction of the evidence for a positive effect being strong: 76% of studies showed improved indices of glycemic control. The main limitation is that individual herbs have only a small number of clinical trials, the majority of which suffer from poor quality owing to under-powering or small sample size, lack of randomization, absence of blinding, and inadequate reporting of dropouts.

Compelling evidence is available to support the use of some herbs in diabetes. Ivy gourd and American ginseng (*Panax quinquefolius* L.) were concluded to have the best evidence for clinical antihyperglycemic efficacy from adequately designed RCTs [22]. The most recent nutrition recommendations from the American Diabetes Association agree with this conclusion as it relates to ginseng [25]. A detailed discussion of the evidence for ginseng follows.

Clinical efficacy of ginseng in diabetes

Before the year 2000, there were very limited data in humans to support the traditional use of ginseng in diabetes and confirm the hypoglycemic effect of ginseng observed in animal and in vitro models. Only a small group of flawed published studies were accessible. Sotaniemi and coworkers reported that 8 weeks of treatment with 100 and 200 mg/day of an unspecified ginseng improved fasting glycemia and long-term glycemic control, assessed by HbA1c, respectively, in 36 type 2 diabetic subjects [26]. But the results were ambiguous due to significant weight loss differences between the treatment groups and poorly described statistics. In another study, Tetsutani and coworkers reported that 24 months of treatment with a Korean red ginseng extract at doses from 3 to 4.5 g decreased HbA1c in 34 people with type 2 diabetes compared with controls [27]. But the subject selection, allocation to treatment, statistics, and follow-up of the study were very poorly described. Secondary sources also reported glyce-

[28]. But control groups were not reported and primary sources could not be retrieved for verification.

Acute antihyperglycemic effect of American ginseng

The need for good human data prompted us to initiate a clinical testing program to explore the acute and chronic effects of American ginseng in humans. We conducted a series of five randomized placebo-controlled acute clinical studies (Table 1) to evaluate the efficacy of American ginseng (Chai-Na-Ta Corp., BC) in lowering postprandial glycemia and its dosing and timing effects in subjects with and without diabetes using a 25-g OGTT protocol. The principal goal was to identify an efficacious dosing and timing schedule for a single batch of American ginseng for a long-term study. The main findings were 4-fold: (1) American ginseng reduced

Table 1 Energy, nutrient, and ginsenoside profile of the placebo and American ginseng (*Panax quinquefolius* L.) capsules used in five acute postprandial trials*

Constituent	Content	
	Placebo	American 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		
(20S)-Protopanaxadiols (PPD) (% w/w)		
Rb ₁	—	1.53
Rb ₂	—	0.06
Rc	—	0.24
Rd	—	0.44
PPD subtotal	—	2.27
(20S)-Protopanaxatriols (PPT) (% w/w)		
Rg ₁	—	0.1
Re	—	0.83
Rf	—	0
PPT subtotal	—	0.93
Total (% w/w)	—	3.21
Ratios (% w/w:% w/w)		
PPD:PPT	—	2.44
Rb ₁ :Rg ₁	—	15.3
Rb ₁ :Rc	—	0.25
Rg ₁ :Re	—	0.12

*Adapted with permission from authors.

postprandial glycemia from 9.1 to 38.5%; (2) doses from 1 to 9 g were equally efficacious; (3) time from 0 to 120 min before the glucose challenge was equally efficacious in diabetic subjects without interaction with their background antihyperglycemic therapy; and (4) only AG > 40 min before the OGTT reduced glycemia in nondiabetic subjects. We concluded that American ginseng was able to reduce acute postprandial glycemia [29–33].

The part of American ginseng's profile that gave rise to these hypoglycemic effects was unclear. The principal reference components in ginseng, to which pharmacological effects have been attributed, are its ginsenosides (saponins with a steroidal glycoside structure; Fig. 1), although its peptidoglycan (quinquefolans for American ginseng, panaxans for Asian

ginseng, and eleutherans for Siberian ginseng) and glycan (ginsenos) components have also demonstrated pharmacological activity [34]. We measured the ginsenoside composition of the American ginseng used in all of the above acute studies (Table 2). It was noticed that it had a high proportion of PPD (Rb₁, Rb₂, Rc, and Rd) relative to PPT (Rg₁, Re, and Rf) ginsenosides, a ratio smaller than one for the ratios Rg₁/Re and Rb₂/Rc, and Rf was absent. All these features of its composition indicated that ginseng was of the genus and species selected [36–38]. Although it was tempting to suggest that these features might be responsible for its effects, without a basis for comparison we concluded that they were interpretable only for authentication [29–33]. Other unmeasured components could have played

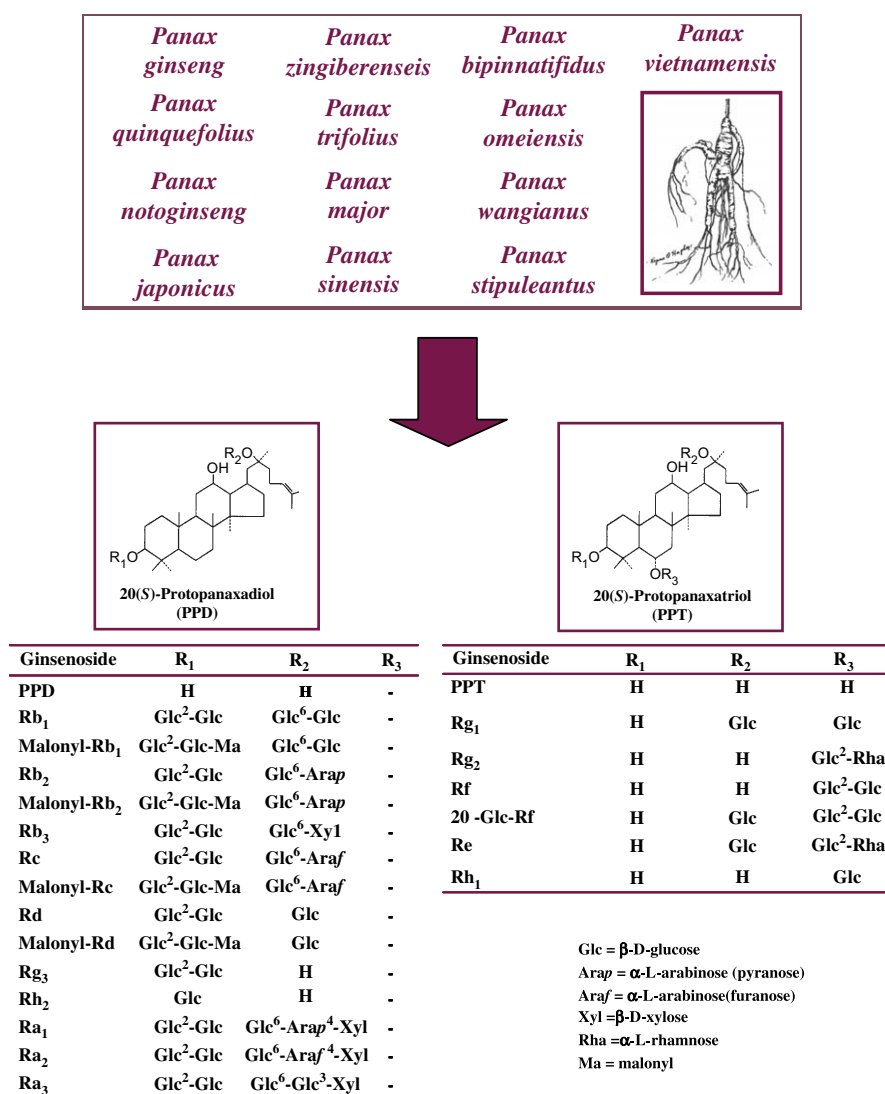


Figure 1 The 13 known species of ginseng and the structures of the two dammarane-type triterpene glycoside classes of ginsenosides derived from them with examples of the most common individual ginsenosides from each class [35].

Table 2 Summary of five acute studies assessing the dosing and timing effects of American ginseng (AG) on glycemia

Study description	Sample	OGTT (g)	AG dosing (g)	AG timing (min)	Percentage AUC reductions	<i>p</i> -value
Vuksan et al. [29,30]	10 NGT (age: 34 ± 2 years, BMI: 25.6 ± 1 kg/m ²)	25	3	−40	18 ↓ for 3 g AG at −40 min vs. placebo	<0.05
			3	0	No effect for 3 g AG at 0 min vs. placebo	NS
Vuksan et al. [29,30]	9 DM2 (age: 62 ± 2 years, BMI: 29 ± 1.7 kg/m ² , HbA1c: 7.6 ± 0.2%)	25	3	−40	22 ↓ for 3 g AG at −40 min vs. placebo	<0.05
			3	0	19 ↓ for 3 g AG at 0 min vs. placebo	<0.05
Vuksan et al. [31]	10 NGT (age: 41 ± 4 years, BMI: 24.8 ± 1.1 kg/m ²)	25	3, 6, 9	−120, −80, −40	26.6, 29.3, 38.5 ↓ for 3, 6, and 9 g vs. placebo No effect of timing	<0.05 NS
Vuksan et al. [32]	10 DM2 (age: 63 ± 2 years, BMI: 27.7 ± 1.5 kg/m ² , HbA1c: 7.3 ± 0.3%)	25	3, 6, 9	−120, −80, −40, 0	19.7, 15.3, 15.9 ↓ for 3, 6, and 9 g vs. placebo No effect of timing	<0.05 NS
Vuksan et al. [33]	12 NGT (age: 42 ± 7 years, BMI: 24.1 ± 1.1 kg/m ²)	25	1, 2, 3	−40, −20, −10, 0	14.4, 10.6, 9.1 ↓ for 1,2, and 3 g vs. placebo	<0.05
					14.1, 15.0, 9.2 ↓ for −40 min vs. −20, −10, and 0 min	<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.

an independent interactive role. These include >25 different ginsenosides, >10 peptidoglycans (quinquefolans for American ginseng), various ginsenosides, numerous peptides and fatty acids, and countless other organic compounds. It was reasoned that replication of the findings with an American ginseng designed to have a similar profile would offer evidence for the efficacy of this ginsenoside profile. This approach was taken as the next step.

Chronic antihyperglycemic efficacy of American ginseng

Our acute observations suggested that American ginseng with a ginsenoside profile similar to our efficacious batches might have long-term therapeutic value. To investigate this possibility, we studied the long-term effects of an extract (China-Ta Corp., Langley, BC) that we designed to have a ginsenoside profile similar to that of the American ginseng used in the five acute studies [29–33]: 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 1 g of ginseng extract or placebo taken 40 min before each meal (3 g/day) on glycemic control in 24 type 2 diabetic subjects [38]. Fasting glucose and HbA1c were decreased following the extract compared with placebo after 8 weeks. There was also an observable but insignificant increase in insulin suggesting a possible improvement in β -cell function. These benefits occurred without increasing adverse events or altering hepatic, renal, haemostatic, or blood pressure function. Taken together, the data represented proof of two concepts. First, standardization of key features of the ginsenoside profile may lead to reproducible effects. Nevertheless, whether it is the standardized ginsenoside component that is driving this reproducibility is unclear. It is possible that these ginsenosides may only be acting as a proxy for other non-measured ginsenosides or nonsaponin components such as the peptidoglycan fraction (quinquefolans). Second, our acute postprandial testing model used to select the most efficacious batch, dose, and time of administration of ginseng successfully predicted long-term safety and efficacy of a batch of American

ginseng. The ~15–20% glycemic lowering efficacy seen acutely [29–33] was sustained in this long-term investigation.

Acute antihyperglycemic efficacy of Korean red ginseng

To test whether the batch, dosing, and timing of another species of ginseng could be selected to have long-term efficacy using the same acute postprandial testing program, a similar approach was applied to Korean red ginseng (steam treated *Panax ginseng* C.A. Meyer) [39]. We conducted a batch-finding study of different Korean red ginseng (KRG) root fractions followed by a dose-finding study of the most efficacious fraction. Double-blind, randomized, within-subject designs were used in both studies. In the batch-finding study, 7 healthy subjects received 6 g placebo and KRG-rootlets, -body, and -H₂O extract 40 min before a 50-g OGTT. In the dose-finding study, 12 healthy subjects received 0 g (placebo), 2, 4, and 6 g of the most efficacious root fraction following the same protocol. The studies were successful in identifying efficacious batch and dose of Korean red ginseng. In the batch-finding study, a wide variation in the ginsenoside profiles was achieved across the three root fractions. This variation coincided with differential effects, although the PPD:PPT ratio was unrelated. KRG-rootlets decreased AUC by 29% compared with placebo, while neither KRG-H₂O extract nor KRG-body affected glycemia. In the dose-finding study, the KRG-rootlets were tested as the most efficacious fraction. A significant effect of KRG-rootlets treatment (mean of three doses) but not dose was found. The mean of three doses decreased AUC by 17% compared with placebo. Taken together the studies indicated that 2 g KRG-rootlets was sufficient to achieve reproducible reductions in postprandial glycemia. This was indicated for long-term study [40,41].

Chronic antihyperglycemic efficacy of Korean red ginseng

The data from the acute data were applied to the long-term study [39]. The efficacious batch (Korean red ginseng rootlets) and dose (2 g) selected from the sequential acute batch- and dose-finding studies were subjected to long-term testing. A double-blind, randomized, placebo-controlled, crossover trial was conducted. Nineteen type 2 diabetic subjects received 2 g placebo

or Korean red ginseng rootlets 40 min before each meal (6 g/day) for 12 weeks, while maintained on their conventional diabetes treatment. Fasting plasma insulin and 75-g OGTT derived AUC plasma insulin were significantly decreased on the selected KRG treatment compared with placebo. This occurred while fasting plasma glucose was unchanged and 75-g OGTT derived AUC plasma glucose was significantly decreased. The combination was reflected in an identical 33% increase in both the homeostasis model assessment (HOMA) and the 75-g OGTT derived insulin sensitivity indices on the selected Korean red ginseng rootlets treatment compared with placebo. These benefits occurred without increasing adverse events or altering hepatic, renal, haemostatic, or blood pressure function. We concluded that our acute testing program identified a Korean red ginseng batch and dose that improved long-term glucose and insulin regulation safely beyond conventional treatment in type 2 diabetes [42].

Complementary metabolic efficacy of ginseng

In addition to improving long-term glycemic control, complementary metabolic effects of ginseng have been observed on several features of the metabolic syndrome. First, body weight improvements have been reported following ginseng supplementation. In the clinical diabetes trial of Sotaniemi and coworkers, 100 and 200 mg/day of the unspecified ginseng decreased body weight after 8 weeks of treatment compared with baseline [26].

Second, lipid and lipoproteinemia improving effects have been observed. Korean red ginseng at a dose of 4.5 g/day (1.5 g before each meal TID) improved dyslipidemia, decreasing triglycerides and increasing HDL-cholesterol after 7 days in an uncontrolled pilot study of 5 normal and 6 hyperlipidemic men [43]. In our long-term randomized, double-blind, crossover study with the American ginseng extract, total-cholesterol, LDL-cholesterol, and the total-/HDL-cholesterol ratio were reduced compared with placebo, with an observable but insignificant increase in HDL-cholesterol [44].

Third, antihypertensive effects have been observed. Different ginseng preparations improved various indices of blood pressure function. Korean red ginseng at a dose of 4.5 g/day (1.5 g before each meal TID) decreased 24 h mean systolic blood pressure compared with placebo after 8 weeks in

26 subjects with essential hypertension in a non-randomized, unblinded, crossover study with a shortened placebo phase (4 vs. 8 weeks) [45]. The Asian ginseng (*P. ginseng* C.A. Meyer) extract *Ginsana G115* (Pharmaton, Ridgefield, CT, USA) significantly decreased acute blood pressure 2 h after ingestion compared with baseline [46]. Korean red ginseng significantly increased forearm blood flow responses, consistent with mediation by nitric oxide, in 7 hypertensive test subjects compared with 10 untreated hypertensive control subjects [47]. In our long-term study with the American ginseng extract, both systolic and diastolic blood pressures were significantly reduced compared with placebo [48].

Finally, improvements in haemostatic parameters have been observed with ginseng. In our long-term study with the American ginseng extract, a significant reduction in plasminogen activator inhibitor-1 (PAI-1) was observed from baseline. But the comparison with placebo was only approaching significance [49].

Taken together, these additional metabolic benefits described in humans support the primary effects of American and Korean red ginsengs on glycemia. Because the efficacy was demonstrated across different ginseng-types, doses, related disease models and investigator groups, these data can be considered robust.

Caveats

Variability in composition

This evidence for antidiabetic efficacy of herbs comes with serious limitations. Ginseng serves as an example. To quantify the extent of the variability in ginsenosides in ginseng, we undertook a meta-analysis of the coefficient-of-variation (CV) in ginsenosides across ginseng-type (batch, preparation, variety, and species), assay-technique, and ginsenoside-type. Thirty-two articles met the inclusion criteria. Together these articles reported ginsenoside concentrations for 317 batches of ginseng that included 10 levels of different ginseng-types, 6 levels of different assay-techniques, and 21 levels of different ginsenoside-types. The CV in ginsenosides were found to be from 26 to 103% for ginseng-type, 31 to 81% for assay-technique, and 36 to 112% for ginsenoside-type (Fig. 2) with the differences in ginseng-type dependent on the assay-technique used. This analysis demonstrated that the ginsenoside composition of ginseng is

highly variable across different ginseng source parameters [50].

Variability in efficacy

There is evidence that this high variability in composition may contribute to equally high variability in efficacy. Variable pharmacological effects appear secondary to differences in composition. Our experience with ginseng is again instructive. We conducted a series of acute, blinded, placebo-controlled clinical studies to assess the effect of increasing ginsenoside variability across similar ginseng source parameters of progressively greater ginsenoside variability (batch, preparation, variety, and species) on postprandial glycemia. A 75-g oral-glucose-tolerance-test (75-g OGTT) protocol was followed with ginseng administered 40 min before the start of each test. The ginsenoside variability we were able to achieve experimentally across the ginseng source parameters was equal to the actual variability seen across similar parameters in the meta-analysis. This coincided with highly variable glycemic effects. In the first study, while our original efficacious batch of American ginseng again demonstrated acute postprandial glycemic lowering efficacy, a second batch with a depressed ginsenoside profile including a low PPD:PPT ratio was ineffective [51]. In the next two studies, another species, Asian ginseng, with marked inversions in its ginsenoside profile (PPD:PPT < 1) had null and opposing effects on plasma glucose indices [52]. Finally, in the most recent study, in which 8 of the most common ginseng-types with distinct ginsenoside profiles were compared head-to-head, decreasing, null, and increasing effects were observed. A third batch of American ginseng lowered plasma glucose, while Japanese-rhizome (*Panax japonicus* C.A. Meyer), Sanchi (*Panax notoginseng*), Vietnamese-wild (*Panax vietnamensis*), and Korean red ginsengs had null effects and Asian, Siberian (*Eleutherococcus senticosus*), and American-wild ginsengs significantly raised acute postprandial plasma glucose (Fig. 3). The PPD:PPT ratio was implicated as the sole independent predictor of 4 of 7 plasma glucose and insulin outcomes in this study. But the variance explained by this ginsenoside ratio was <7% (Fig. 4), bringing into question its utility as a marker for standardization [53]. Again other unmeasured saponin or nonsaponin components could have played independent or interactive roles. Taken together, the high variability in acute postprandial glycemia appeared secondary

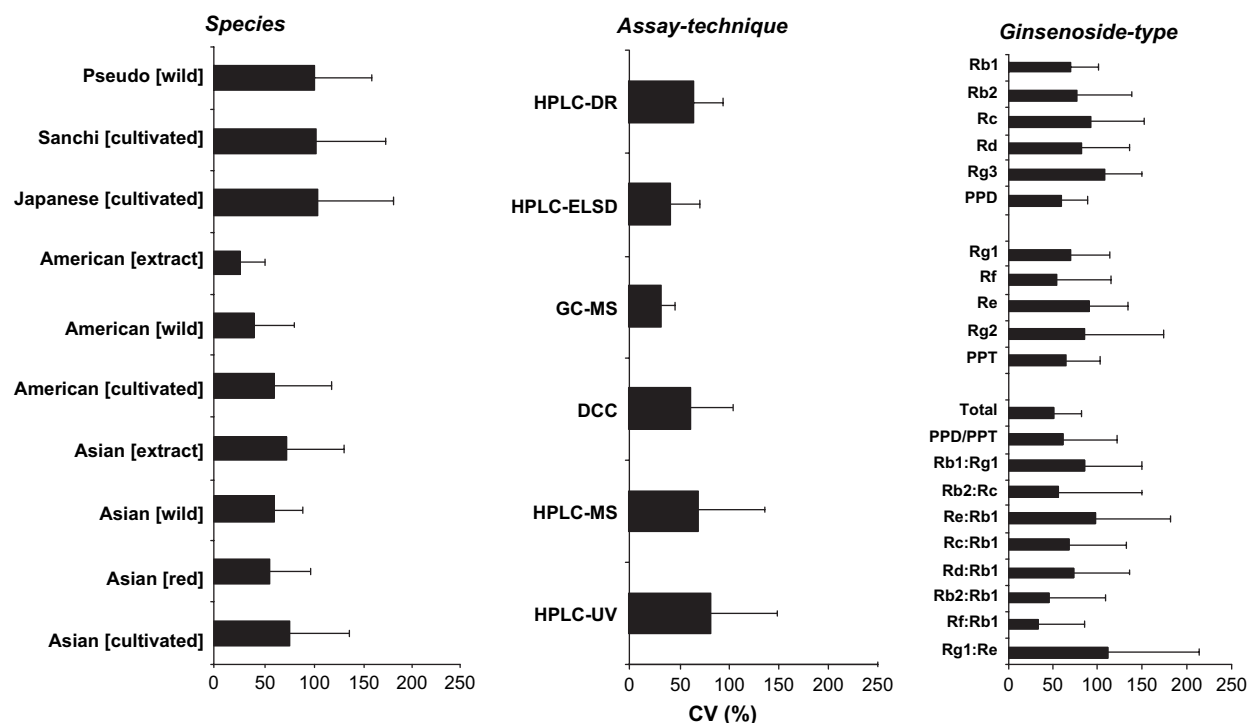


Figure 2 Three-factor analysis of the coefficient-of-variation (CV) of ginsenoside concentrations for the main effects of species, assay-technique, and ginsenoside-type. CV of ginsenoside concentrations were calculated as $CV = SD/mean \times 100\%$ in a factorial block design. A blocking principle was applied to the data such that each level of each factor (10 levels of species, 6 levels of assay-technique, and 2 levels of ginsenoside-type) was crossed with each level of the other factors for the calculation of CV. Species comprised 10 levels of *Panax* species, their preparations, and their varieties derived from ginsenoside concentrations reported for 121 Asian (cultivated) (*Panax ginseng* C.A. Meyer [cultivated]), 36 Asian (red) (*P. ginseng* C.A. Meyer [red]), 3 Asian (wild) (*P. ginseng* C.A. Meyer [wild]), 35 Asian (extract) (*P. ginseng* C.A. Meyer [extract]), 74 American (cultivated) (*Panax quinquefolius* L. [cultivated]), 4 American (wild) (*P. quinquefolius* L. [wild]), 7 American (extract) (*P. quinquefolius* L. [extract]), 12 Japanese [*Panax japonicus* C.A. Meyer], 10 Pseudo [*Panax pseudoginseng* WALL.], and 10 Sanchi [*Panax notoginseng* [Burk.] F.H. Chen] ginseng batches. Assay-technique comprised 6 levels of different assay-techniques derived from (213 HPLC–UV, 43 GC–MS, 33 HPLC–MS, 12 DCC, 9 HPLC–differential refractometry [DR], and 4 HPLC–ELSD). Ginsenoside-type comprised 21 levels of ginsenoside indices, the protopanaxadiol (PPD) ginsenosides (207 Rb₁, 197 Rb₂, 199 Rc, 202 Rd, and 34 Rg₃), protopanaxatriol (PPT) ginsenosides (202 Rg₁, 230 Rf, 208 Re, and 105 Rg₂) their sums (228 PPD, 229 PPT, and 252 Total) and ratios (239 PPD:PPT, 255 Rb₁:Rg₁, 197 Rb₂:Rc, 261 Re:Rb₁, 262 Rc:Rb₁, 258 Rd:Rb₁, 259 Rb₂:Rb₁, 254 Rf:Rb₁, and 207 Rg₁:Re). The CV data calculated for each possible combination were pooled and meaned for each level of each factor. As a result, CV data are mean \pm SD.

to the variability in the ginseng source (batch, preparation, variety, and species) and its composition, as represented by the measured ginsenoside profile, specifically the PPD:PPT ratio.

The implication of this high variability in composition coupled to high variability in efficacy is that the evidence for efficacy and safety reported for specific herbal products may not be generalizable to other over-the-counter batches, preparations, varieties, and species of the herb. Although this concern makes a compelling argument for better regulatory standards, there are mitigating factors. One limitation is that no basis for standardization exists. It is not clear which of the > 30

ginsenosides and their ratios should be standardized. The independent and interactive roles of other principles such as panaxans (peptidoglycans) and ginsenans (polysaccharides) are also unknown [34]. The implication is that even with ginsenoside-standardized products, uncertainty remains. Another important limitation is the assay. No universal assay exists for most compositional factors. In the case of ginsenoside measurements, the observed interaction between species and assay may produce biases in comparisons. Together these limitations indicate the need to tie reference components to efficacy and establish specific assay criteria. Steps in this direction are being

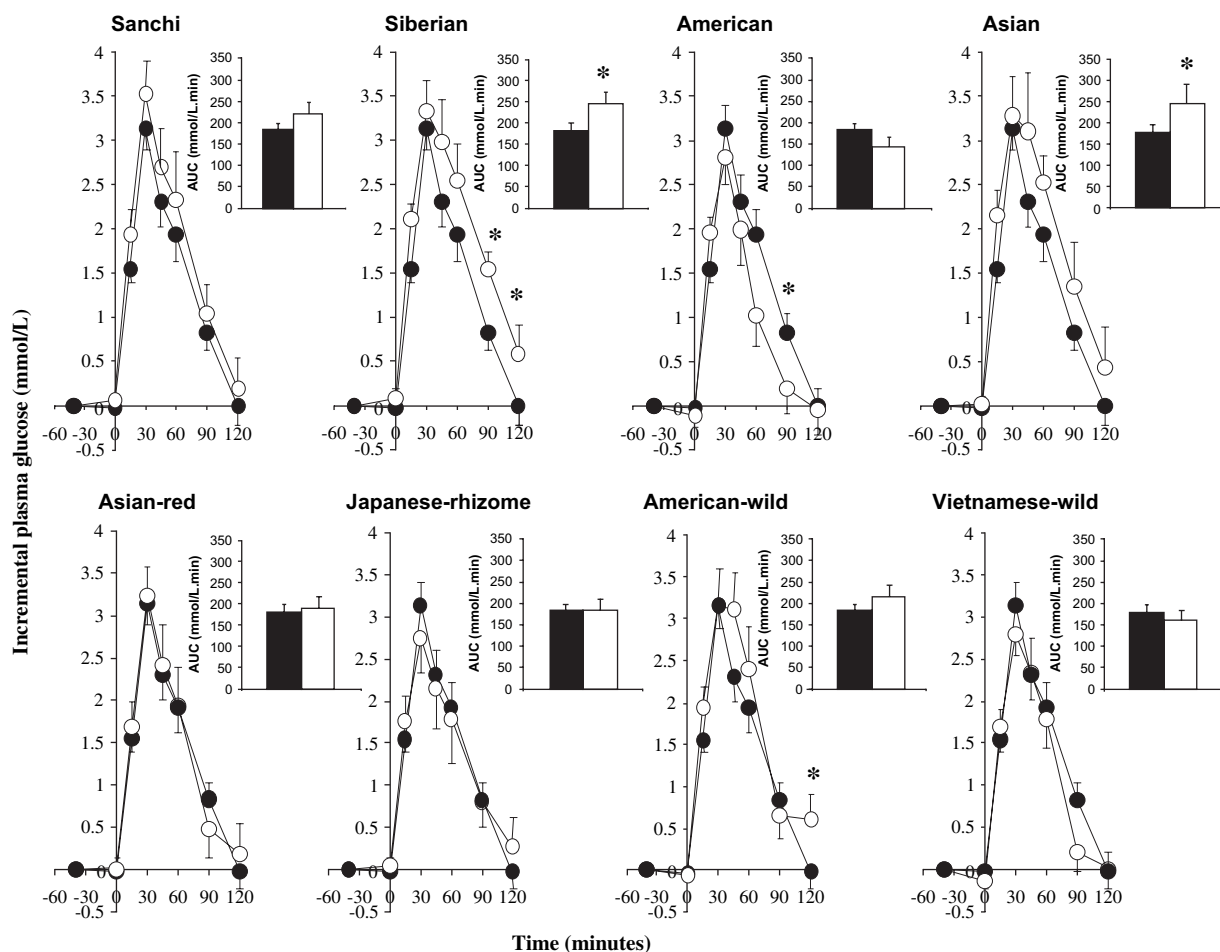


Figure 3 Differential effects of eight types of ginseng on postprandial plasma glucose. The line plots and bars in the array represent the incremental change and area under the curve (AUC) for the mean of two identical placebos (●) or one of eight of the most popular ginseng-types, Sanchi, Siberian, American, Asian, Asian-red, Japanese, American-wild, or Vietnamese-wild ginsengs, (○) administered at a dose of 3 g 40 min before a 75-g OGTT in 12 nondiabetic subjects (sex: 6 m and 6 f, age: 34 ± 3 years, BMI: 25.8 ± 1.2 kg/m²). Asterisks indicate that points or bars for ginseng are significantly different from placebo ($p < 0.05$, one-way repeated measures ANOVA with non-orthogonal contrasts). Data are mean \pm SEM. Adapted with permission from Sievenpiper et al. [53].

made for ginseng. A growing database of rigorously conducted animal studies is pointing to different ginsenosides for antihyperglycemic indications. Some of the most promising isolated components for which there are consistent data across different models, species, doses, and investigator groups include Re [54,55], Rb₂ [55–57], and panaxan B [58,59]. The American Botanical Council has also initiated the largest ginseng evaluation program with the development of a common HPLC–UV assay [60].

Conclusions

In conclusion, although traditional systems of medicine demonstrate a strong history of use and

clinical evidence is mounting to support a diabetes indication for herbs, the reproducibility of their safety and efficacy remains questionable. Ginseng is a model example. Although we have twice shown that a ginseng batch, dose, and time of administration can be selected using an acute postprandial screening model to have long-term efficacy and safety in people with type 2 diabetes, the effects of randomly selected ginseng can be erratic. Highly variable acute glycemic effects are observed secondary to the ginsenoside profile as it varies across ginseng batch, preparation, variety, and species. With the variability in ginsenoside profiles found to be alarmingly high across these same parameters of ginseng source, the implication is that its efficacy and safety may be equally highly variable. This situation necessitates that compositional markers of its antihyperglycemic effects

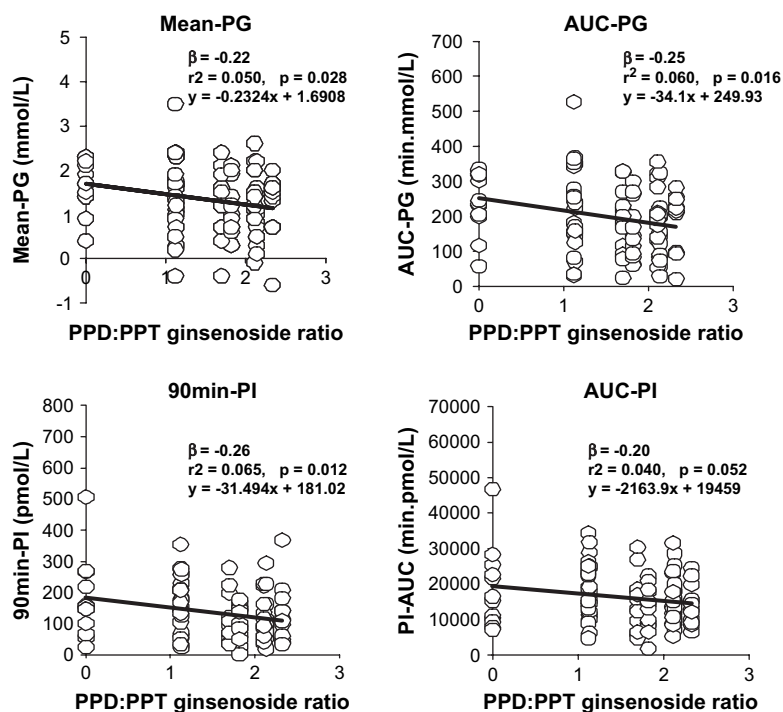


Figure 4 Scatter plots with regression lines for the sole independent ginsenoside predictors of mean-plasma glucose (Mean-PG), area under the curve-PG (AUC-PG), 90 min-plasma insulin (90 min-PI), and AUC-PI in 12 nondiabetic subjects. PPD:PPT denotes protopanaxadiol:protopanaxatriol. Trend lines and equations are for linear trend. β -Coefficients, p -values, and partial- r^2 values are for separate stepwise-multiple regression models. Only the data for the PPD:PPT ginsenoside ratio is shown for each of the 4 models, as it was the only independent variable selected by the stepwise regression. The 4 of the 7 models that were significant are presented.

be identified. This includes other unmeasured saponin and nonsaponin compositional factors must also be considered. Without these data the consumer cannot be assured of the safety and efficacy of ginseng products and the call from the medical community for randomized controlled trials and standardization of ginseng are moot. Although some leads have emerged from the literature, it remains unclear which batches, preparations, varieties, and species of ginseng have antihyperglycemic efficacy and which saponin or nonsaponin components confer this efficacy. The implication is that a basis for standardization for ginseng or other less well-studied herbs is premature. One alternative may be to conduct batch-to-batch efficacy screening to identify efficacious batches using the same stepwise acute postprandial clinical screening model we have developed. But this alternative seems practically and financially untenable. Future research directed at the identification of active components becomes the only viable means of supporting efficacy claims for all herbs. In the absence of such standardization, health practitioners and consumers alike should remain optimistic but wary.

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