Effect of American Ginseng (*Panax quinquefolius* L.) on Glycemic Control in Type 2 Diabetes

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A B S T R A C T

Since diabetes tends to progressively worsen over time, glycemic control often deteriorates in spite of taking regular therapy. Therefore, numerous research studies are by and large focused on finding more efficient therapy, both new medicines for treating type 2 diabetes mellitus, as well as supplements that could serve as an addition to conventional treatment modalities. A variety of herbal preparations have been shown to have modest short-term beneficial effects on glycemia, but of these, the best studied is American ginseng (AG). AG has been shown to be effective in improving glycemic control in type 2 diabetes through increasing post-prandial insulin levels and decreasing postprandial glycemic response. However, high variability in ginsenosides may result in just as high variability in antidiabetic efficacy of over-the--counter ginseng products. Therefore, the availability of standardized extracts of AG could assist greatly in advancing our knowledge on the role of this traditionally used herb and result in a wider application of ginseng product in diabetes management. The aim of this review is to outline the efficacy and safety of American ginseng for AG preparations on glycemic control in patients with type 2 diabetes as well as to increase awareness of the evidence supporting the use of these therapies in diabetes care.

Key words: *glycemic control, diabetes, ginseng, American ginseng*

Introduction

A growing worldwide epidemic of diabetes combined with the frequent failure of primary drug treatment in the majority of patients, make a compelling argument for better prevention and treatment strategies. Between 1995 and 2025 there will be a 35% increase in the worldwide prevalence of diabetes with a higher rise in developed than in developing countries[1]. The number of adults with diabetes in the world is estimated to increase by 122%, from 135 to 300 million[1]. Since glycemic control tends to worsen over time and additional medications are required to maintain the status quo, new, safe and effective treatments are of interest. Numerous research studies are by and large focused on finding more efficient therapy, both new medicines for treating type 2 diabetes mellitus, as well as supplements that could serve as an addition to conventional treatment modalities. Complementary and alternative medicine (CAM) use has increased at a considerable pace in recent years among the general public[2]. In 2007, almost 4 out of 10 adults in the U.S. had used CAM therapy in the past 12 months, with the most commonly used therapies being nonvitamin, nonmineral, natural products (17.7%) and deep breathing exercises (12.7%)[2]. One of the surveys that examined CAM use among those with diabetes reported that about one third of respondents use CAM to treat their condition[3], whereas another national survey in the US reported a lower incidence (8%) of diabetic patients using CAM[4]. Generally, data for the therapeutic effectiveness and safety of herbal products are lacking[5]. Nevertheless, herbal remedies or other dietary supplements taken by mouth are among the most prevalent CAM[3,4], and have been increasingly used in treatment of type 2 diabetes[5].

Received for publication June 15, 2012

Among 36 examined herbs the most promising supplements with purported hypoglycemic activity include Ivy gourd (*Coccinia indica*), American ginseng (*Panax spp.*), Bitter Melon (*Momordica charantia*), Gurmar (*Gymnema sylvestre*), Aloe vera, nopal, L-carnitine and vanadium[5]. American ginseng (*Panax quinquefolius L.*) along with Ivy gourd were found to have the best evidence from adequately designed randomized controlled trials (RCTs) to support clinical efficacy in diabetes[5]. A review by the American Diabetes Association in their 2002 Evidence Based Nutrition Recommendations has concluded that a variety of herbal preparations have been shown to have modest short-term beneficial effects on glycemia, but of these, the best studied is American ginseng[6]. The aim of this review is to outline the efficacy and safety of American ginseng preparations on glycemic control in patients with type 2 diabetes as well as to increase awareness of the evidence supporting the use of these therapies in diabetes care.

Ginseng – Background

Ginseng is a slow-growing herbaceous perennial belonging to the plant family Araliaceae and genus Panax indigenous both to Asia and North America. Thirteen distinct species of ginseng have been identified with numerous different cultivars[7]. These include Chinese or Korean ginseng (*Panax ginseng* C.A. Meyer), American ginseng (*P. quinquefolius* L.), Japanese ginseng (*P. japonicus*), Sanchi, and Vietnamese (*P. vietnamensis*). Two of the most common types are *Panax quinquefolius L.* and *Panax ginseng C.A. Meyer*, more commonly referred to as American ginseng and Asian ginseng[8]. Both have comparable compositions, but could be considered to be different in their effect. Asian ginseng and some of its fractions have been traditionally used as a sedative, tonic, anti-fatigue, anti-gastric ulcer drug, and also thought to have antitumor, memory increasing and immunostimulation activities[9]. Based on in vitro and animal research findings American ginseng, cultivated in United States and Canada, is thought to reduce stress, lower high blood sugar, increase sex drive, memory and learning abilities, decrease aging and adjust immunity[10].

Chemical Composition – Ginsenoside

It is believed that the primary active components of ginseng to which pharmacological effects have been attributed are a group of >30 different triterpene saponins, also refered to as ginsenosides, which vary in content and relative proportions among different species of ginseng[9,11]. Its other components that have also demonstrated pharmacological activity to some extent include polysaccharide (ginsenans)[12,13] and peptide (panaxans/quinquefolans/eleutherans) fractions[11].

Differences in ginsenoside content have been observed between wild kinds and its cultivated counterpart[14], ginseng harvested from different locations, within the same plant[15], among root parts[16], and according to its age (largest increases coming between 4th and 6th years of growth)[17]. Both these interspecies and intraspecies differences contribute to a high degree of variability of ginsenosides implying that the effects of ginseng could be equally highly variable in its pharmacological effect which is often reflected in commercial ginseng products[18]. Poor standardization of ginsenosides remains a major barrier to its efficacy and safety[18,19].

Mechanism of Hypoglycemic Activity of Ginseng

Mechanisms of action of different ginseng sources and components through which glycemic control is achieved are not fully clear. Studies have shown that ginseng and its components could influence hyperglycemia through enhancing pancreatic β-cell function and through reducing insulin resistance. Four possible mecahnisms of action that have been proposed include glucose absorption, insulin secretion and binding, glucose transport, and/or glucose disposal. Indirect evidence suggest that different sources of ginseng may affect the rate of digestion which results in decreasing rate of carbohydrate absorption into portal hepatic circulation[20]. Various ginseng extracts, ginsenosides and panaxan B increase insulin secretion and binding, as seen in many studies[21–23] by stimulating insulin biosynthesis[21], increasing glucose[22] and nonglucose stimulated insulin secretion, and increasing insulin binding[23]. Glucose transport in various cell lines may also be increased by increasing proteins responsible for transport in a dose dependent manner[24]. It has been found that glucose disposal may be increased by different ginseng extracts and ginsenosides through increasing activity of several enzymes[25] or decreasing activity of the rate limiting gluconeogenic enzyme glucose-6-phosphatase[26]. American ginseng has been shown to be effective in improving glycemic control in type 2 diabetes through increasing post-prandial insulin levels, achieved via altering cell metabolism, increasing insulin production and reducing apoptosis in a dosage dependent manner[27]. The action of AG could be compared to sulphonylurea, which has an insulinotropic effect on pancreatic β-cells. The difference between ginseng and sulphonylurea, however, is that ginseng only stimulates insulin release in response to a meal (i.e. a glucose-stimulated insulin secretion)[10]. The advantage of taking AG is thus a reduced risk of hypoglycemic episodes in the case of postponed or missed meals, a common issue for patients on sulphonylurea treatment. This was also demonstrated in an 8-week study where no hypoglycaemic episodes were recorded despite having added American ginseng to current treatments[28].

Hypoglycemic Activity – Preclinical and Clinical Evidence

Though recent systematic reviews[5,8] remarked on the lack of sound proof to make conclusions about the efficacy of ginseng, numerous reports that have emphasized anti-hyperglycemic effect of ginseng have begun emerg-

ing in human as well as animal studies. Animal studies have demonstrated significant anti-hyperglycemic action by a variety of ginsengs (e.g. American, Chinese, Siberian and Korean Red) using either the root or a particular extract of the root[29]. In one animal study, methanol fraction extract of AG, ferulic acid, and cinnamic acid yielded antihyperglycemic effects in a type 2 diabetic mouse model[30]. In addition, the glycogen and high density lipoprotein (HDL) contents were significantly increased while levels of plasma cholesterol and low density lipoprotein (LDL) concentration were significantly decreased in the AG treated group[30]. Intraperitoneal injections of TGCG (total ginsenosides in Chinese ginseng) or oral administration for 12 days significantly lowered the fasting blood glucose levels in diabetic ob/ob mouse model which indicated TGCG was endowed with significant anti-hyperglycemic properties[31]. Ginsenoside Re reduced blood glucose levels, improved levels of cholesterol and triglycerides as well as reduced oxidative stress in diabetic rats[29]. Based on animal studies, it has been suggested that ginseng increases insulin secretion, insulin sensitivity and may slow gastric emptying. Ginseng might mediate the insulin stimulated glucose uptake in rat skeletal muscles and adipose tissue[32] as well as glucose dependent secretion of insulin in rat islet cells[33].

Clinical studies have also reported that American ginseng has the ability to lower blood glucose in diabetic patients. To select batches and treatment protocols (dosing, timing, and modes of administration) of American ginseng (Chai-Na-Ta Corp., BC, Canada) that achieve reproducible and sustainable efficacy, a series of five acute, randomized, single-blind, placebo-controlled clinical studies were conducted in subjects with and without diabetes using a 25 g OGTT protocol. It was found that American ginseng reduced postprandial glycemia from 9.1–38.5% when administered either 30–40 min before, or together, with an oral glucose challenge in subjects with diabetes, and only when given 30–40 min before the challenge in normal subjects[10]. Doses from 1–9 g were equally efficacious and time from 0–120 min before the glucose challenge was equally efficacious in diabetic subjects without interaction with their background antihyperglycemic therapy[10,34,35]. It was also found that administration of 6g of AG increased the insulin secretion twofold in the first 45 min after a 25 g oral glucose challenge[19]. As the first 60 min of a 25 g oral glucose challenge is considered to be representative of the early phase of insulin secretion, these data suggest that AG may be able to affect this phase, the loss of which is a primary defect in type 2 diabetes. Although it was tempting to suggest that its ginsenoside composition was responsible for these effects, other unmeasured components, such as unmeasured ginsenosides, peptidoglycans, various ginsenans, peptides, fatty acids and other organic compounds could have played an independent or interactive role. It was concluded that the ginsenoside profile was interpretable only for authentication[10,34,35], and replication of the findings with an American ginseng selected or designed to have a similar profile was considered the most reasonable approach.

Until recently, there was a limited amount of long-term clinical studies that could support the use of ginseng in treatment of diabetic patients. Sotaniemi and coworkers reported that 8 weeks of treatment with 100 mg or 200 mg/day of an unspecified ginseng extract improved fasting glycemia and long-term glycemic control, assessed by HbA1c[36]. However, due to significant weight loss differences between the treatment groups and weakly described statistics results were equivocal. Another study, that investigated the long-term therapeutic value of American ginseng, used an American ginseng extract with a ginsenoside profile similar to the one used in the series of 5 acute studies[10,34,35]. In an 8-week double-blind, placebo-controlled crossover trial, in which the American ginseng extract (Chai-Na-Ta Corp., BC, Canada) or corn starch placebo at a dose of 1 g was taken 40 min before each meal (3 g/day), it was found that fasting glucose and HbA1c were decreased compared with placebo after 8 weeks[28]. 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.

Due to a lack of clear distinction between various ginseng species, remarks made about its alleged hypoglycemic effect and evidence from sound clinical trials did not support the use of ginseng in alleviating hyperglycemia[8]. This limitation is particularly true for ginseng, and the fact that these prominent species (*Panax ginseng* and *Panax quinquefolium*) distinguish themselves significantly in terms of their complex mixture of numerous potentially bioactive constituents (e.g. ginsenosides). Most of ginseng's components have not yet had their effects reproduced, while in some other cases effects have been both hypoglycemic and hyperglycemic for the same component between different studies[23,37] which could be attributed to the differences in models studied.

Cardioprotective Effects of American Ginseng

Various sources of AG showed differential effects on different metabolic disorders related to diabetes in various human cohorts, such as dyslipidemia, hypertension, obesity and impaired fibrinoloysis. In a longterm, randomized, double-blind, crossover study the selected AG extract given at a dose of 1 g as an oral agent – 40 min preprandially TID (3 g/day), decreased total-cholesterol, LDL-cholesterol, and the Total-/HDL-cholesterol ratio compared with placebo, with an observable but insignificant increase in HDL cholesterol in subjects with type 2 diabetes[38]. Similar results were reported in a longterm, randomized, double-blind, crossover study investigating the efficacy and safety of the combination of the selected batch of AG plus viscous soluble-fiber blend containing Konjac mannan, where after 12-weeks of therapy combination treatment reduced total cholesterol by 7%, LDL cholesterol by 10%, and apolipoprotein B100 (apoB100)

by 9.9% compared to placebo in 30 subjects with well-controlled type 2 diabetes[39].

Compared to other ginseng species (e.g. Korean red ginseng), AG has shown less consistent effects on blood pressure. Eight weeks of supplementation with the selected AG extract given at a dose of 1g as an oral agent – 40 min preprandially TID (6g/day) significantly reduced systolic and diastolic blood pressures compared with placebo in 24 subjects with type 2 diabetes[40]. In contrast, two follow up studies showed neutral acute and long-term effects of 6 batches of AG[41,42]. Moreover, it was concluded that long-term ginseng use had a neutral effect on renal function in hypertensive individuals[42]. Based on this, it can be said that American ginseng is safe for use by individuals who have hypertension.

In addition, systematic review of the effects of ginseng on cardiovascular risk factors yielded incosistent results[43]. They found that ginseng slightly decreased blood pressure compared with placebo (range 0–4%), with 5 of 9 studies showing improvement in one or more lipid parameters compared with baseline (range 7–44%)[43]. No changes in weight were reported with the selected AG extract in any of the afore mentioned studies[19,28,39,42]. Improvements in haemostatic parameters have been observed with an AG extract where a significant reduction in plasminogen activator inhihibitor-1 (PAI-1) was observed from week 0 to week 12 in 24 type 2 diabetic subjects[44].

Furthermore, effects of North American ginseng, reported to reduce cardiac hypertrophy, were investigated on RhoA/ROCK (Ras homolog gene family, member A/Rho-associated, coiled-coil containing protein kinase) and mitogen-activated protein kinase (MAPK) activation in ventricular cardiomyocytes exposed to leptin (50 ng/mL) and the possible role of p115RhoGEF and p63RhoGEF in these responses[45]. Results of the study demonstrated a potent inhibitory effect of ginseng against leptin-induced cardiac hypertrophy, an effect associated with prevention of p115RhoGEF-RhoA/ROCK-dependent p38 MAPK activation[45]. The effects of AG and heat-processed AG (H-AG) on diabetic renal damage using streptozotocin (STZ)-induced diabetic rats were investigated[46]. The study found that AG and H-AG inhibit advanced glycation endproduct (AGE) acumulation in diabetic rat kidney by their hypoglycemic and renal function ameliorating effects, and this effect was stronger in the H-AG-administered group than in the AG-administered group. These findings indicate that H-AG may have beneficial effect on pathological conditions associated with diabetic nephropathy[46].

Recent studies have revealed that ginseng, including AG, exerts antioxidant effects in the cardiovascular system; however, the underlying mechanisms are not fully understood[47]. One of the proposed mechanisms was that AG suppresses oxidative stress and oxidative stress-induced cell death in cardiomyocytes through activating the Nrf2 pathway, thereby providing cardioprotection against pathological cardiac remodeling[47]. Another study suggested that ginsenoside Rb1 (gRb1) conferred cardioprotection that was mediated via attenuating reactive oxygen species (ROS) and suppressing ROS-induced JNK activation[48].

These data suggest that American ginseng might play complementary roles in reducing diabetes and cardiovascular disease risk in humans. However, despite some evidence showing beneficial effects on cardiovascular risk factors, well-designed, randomized, controlled trials evaluating its effects are lacking.

Safety

Although ginseng employment has not been associated with reports related to its toxicity, various side-effects have been associated to its use[49]. Several adverse effects include insomnia, diarrhea, vaginal bleeding, mastalgia, severe headache, schizophrenia, and the Stevens-Johnson syndrome[8]. However, their incidence seems to be low. When taken at doses much higer than the recommended dose, up to 15 g per day, for a 2 year period, around 10% of patients in an observational study reported hypertension, gastrointestinal disturbances, insomnia and nervousness. The validity of these side-effects is questionable due to a lack of placebo treatment in the study and the fact that subjects were not controlled for other bioactive substance intake (e.g. caffeine)[50]. Only a few cases of ginseng toxicity or side-effects were reported when taken at the recommended dosages.

Results of a randomized, double-blind, placebo-controlled study of efficacy and safety revealed that ginseng use did not appear to compromise safety[51]. Overall, study showed no differences between the intervention and the control groups in frequency and severity of adverse events[28]. To support what was previously stated, results of a 2002 systematic review of 146 clinical trials with ginseng reported that the incidence of adverse events in intervention and control groups was similar[52]. Ginseng use was found to be well tolerated and its effects mild and reversible. Though ginseng has been proclaimed as without contraindications and serious adverse effects[53], use of CAM in general has not been approved in the treatment of diabetes on the basis of inadequate evidence for its safety and efficacy.

Recommendations

A 2003 systematic review of 42 randomized and 16 nonrandomized clinical trials showed that AG along with Ivy gourd have the best evidence from adequately designed RCTs to support clinical efficacy in diabetes[7]. A review by the American Diabetes Association in their 2002 evidence based nutrition recommendations drew the same conclusion related to AG[10].

Conclusion

Diabetes is possibly the world's fastest growing metabolic disorder, and as the awareness of the need for tighter glycemic control increases, so does the need for

more appropriate therapies[54–57]. Both clinical and animal studies have indicated that ginseng root has the ability to improve glycemic control, and that it might serve as a simple dietary adjunct to existing therapies. Despite having the best evidence for efficacy in diabetes among herbs, the evidence remains inconclusive for ginseng. This owes both to the insufficiency in data quantity and quality, and a lack of reproducibility of its safety and efficacy. Furthermore, high variability in ginsenosides may result in just as high variability in antidiabetic efficacy and safety of different batches, and as such, may not be generalizable to over-the-counter ginseng products. Poor standardization of ginseng calls for a more direct and systematic clinical approach to identify active components what would generate reproducible and sustainable clinical evidence and result in a wider ginseng product use. Nevertheless, since AG has been shown to be effective in improving glycemic control in type 2 diabetes (through increasing post-prandial insulin levels), if further research reaffirms its safety and efficacy this new therapy could provide a useful addition to conventional treatments. Therefore, the availability of standardized extracts of American ginseng will assist greatly in advancing our knowledge on the role of this traditionally used herb and move industry toward a better understanding of which processing method to use in order to preserve the efficacy of AG.

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UTJECAJ AMERIČKOG GINSENGA (*Panax quinquefolius* L.) NA KONTROLU GLIKEMIJE U ŠEĆERNOJ BOLESTI TIPA 2

S A Ž E T A K

S obzirom na progresivni tijek šećerne bolesti, regulacija glikemije se usprkos redovitom uzimanju terapije često pogoršava. Stoga su brojna istraživanja usmjerena na pronalaženje učinkovitije terapije, i to kako na nove lijekove za liječenje šećerne bolesti tako i na primjenu dodataka u prehrani koji bi mogli biti korisna dopuna konvencionalnoj terapiji. Različiti biljni pripravci pokazali su umjerene i kratkotrajne povoljne učinke na glikemiju, ali od svih je najviše istraživan američki ginseng (AG). AG se pokazao djelotvornim u poboljšanju regulacije glikemije kod šećerne bolesti tipa 2 kroz povećanje post-prandijalne razine inzulina i smanjenje post-prandijalnog glikemijskog odgovora. Međutim, visoka varijabilnost ginsenozida mogla bi rezultirati jednako visokom varijabilnošću antidijabetičkog učinka over-the-counter (OTC) pripravaka ginsenga. Stoga bi raspoloživost standardiziranih ekstrakata AG-a mogla uvelike pomoći u unaprjeđenju našeg znanja o ulozi ove tradicionalno korištene biljke, te rezultirati širim korištenjem pripravaka ginsenga u terapiji šećerne bolesti. Cilj ovog pregleda je istaknuti učinkovitost i sigurnost preparata AG-a u regulaciji glikemije kod pacijenata s tipom 2 šećerne bolesti, kao i podići svijest o dokazima koji podupiru upotrebu dopune konvencionalnoj terapiji u skrbi dijabetesa.