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Antidiabetic Effects of Ginseng in Humans and Rodents

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Abstract

Ginseng, one of the most commonly used herbs worldwide, has known anti-hyperglycemic effects. Twenty-eight (28) studies on diabetic mice and rats from 7 research centers (in 6 different nations) indicate that both Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are effective anti-hyperglycemic supplements, putatively acting via improvements in insulin secretion, insulin sensitivity, islet protection, obesity reduction, anti-oxidation, energy expenditure, and fat absorption. Investigations in clonal beta-cells (MIN6, RINmF, INS-1, HIT-T15) and non-beta-cells (3T3-L1, C1C12, HepG2) further confirm that ginseng may protect against pancreatic beta-cell apoptosis and promote insulin secretion and glucose uptake. Among 18 human trials from 4 independent groups, 15 are single dose trials; whereas, 4 are long-term trials, with treatment periods lasting longer than 4 weeks. Eleven of the single dose trials observed anti-diabetic effects, while 4 observed no improvements. In the long-term studies, two-thirds of the studies on type 2 diabetic (T2D) patients observed anti-hyperglycemic effects. Based upon the sound evidence from cell lines and animal models, along with the improvements from the majority of human subject trials, ginseng appears to be a potent anti-diabetic supplement. Regardless, more long-term trials on T2D patients are required before ginseng can be safely recommended as a broadly-used anti-diabetic agent.

Keywords: MDA; Ginseng; Ginsenoside; Diabetes

Introduction

Type 2 diabetes (T2D) is a worldwide epidemic disease. Because commonly prescribed anti-diabetic drugs are riddled with safety concerns and/or have limited efficacy, management of T2D can be challenging. Therefore, alternative medicines, derived from natural products which have very little to no side-effects, offer exciting possibilities for the development of successful anti-diabetic therapies.

Originally used as a stress-reducing tonic for several thousand years in Asia, Ginseng is one of the most popular herbal supplements in the world [1]. In support of ancient Asian wisdom, a number of contemporary researchers have suggested that pharmacological doses of ginseng positively affect the cardiovascular, immune, and central nervous systems [2,3]. The primary active components of ginseng are the ginsenosides (ginseng saponins) that comprise 3-6% of ginseng. Based on their structure, the ginsensosides can be classified into 3 groups: the panaxadiol group (Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2); the panaxatriol group (Re, Rf, Rg1, Rg2, Rh1); and the oleanolic group (Ro) [2,4]. In China, herbs are routinely used in combination with conventional anti-diabetic therapies to improve hyperglycemia. For single-herb prescriptions, ginseng is the most commonly-used herb: for example, ginseng is one of the top 10 most frequently-prescribed herbs, among the 30 anti-diabetic formulas currently approved by the Chinese government [5]. Intriguing results from basic research have demonstrated that ginseng improves diabetes by enhancing insulin sensitivity, stimulating insulin secretion, protecting pancreatic islets and inhibiting intestinal absorption of carbohydrates [6]. In addition to reliable *in vitro* and *in vivo* evidence (Table 1), the majority of reports in human trials also indicate that ginseng administration does indeed have anti-diabetic effects [7-20], though some controversy does exist [16,21,22]. In this review, we focus on the anti-diabetic effects of ginseng from both animal and randomized, controlled human studies, discuss possible reasons for the discrepancies among human trials and provide topics for future investigations.

Animal Studies

Mice

A number of independent research groups have shown that ginseng has hypoglycemic effects. The majority of the reports are from the Kimura group (Japan), Chung group (South Korea), Yuan group (USA), and Cheng group (Taiwan).

Early in the 1980s, Kimura et al. [23] revealed that ginseng radix (root) extract (10-50 mg/kg) decreased blood glucose and increased blood insulin concentrations in alloxan-induced diabetic mice. Insulin antisera injections abolished these effects, indicating that ginseng-stimulated insulin release is critical for the observed anti-hyperglycemic effects [23]. A 3-h treatment of ginseng extract (0.5 mg/ml) stimulated insulin biosynthesis in islets from KK-CAy mice [24]. The Kimura group further observed that the anti-hyperglycemic effect of ginseng was diminished in diabetic KK-CAy and alloxan-induced diabetic mice, if ginseng was combined with anemarrhena or licorice (two additional herbs commonly used in traditional Asian medicine) [25], indicating potential interaction of ginseng with other drugs.

Investigations from Chung and colleagues from South Korea also demonstrated that ginseng has anti-diabetic effects that synergize with the anti-diabetic drug, metformin. Oral administration of white ginseng radix and rootlet for 4 weeks in KKAy mice significantly reduced fasting blood glucose levels, presumably by blocking intestinal glucose absorption [26]. In high fat (HF) diet-fed ICR mice, the Chung group showed that wild ginseng ethanol extract (WGEE, 250 and 500 mg/kg) significantly inhibited body weight gain, fasting blood glucose, triglyceride and free fatty acid levels in a dose-dependent manner. WGEE also improved the insulin resistance index (>55%) and decreased white and brown adipocyte diameter (>46%) compared to HF-fed controls [27]. A vinegar-processed, as well as non-processed, form of ginseng radix (500 mg/kg/day for 8 weeks) both have significant anti-metabolic

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Groups	Nation	Cell	Ginseng type	Outcome
Luo	USA	INS	American Ginseng	Protect apoptosis[66]
Chung	Korea	HIT-T15	Compound K*	Increase GSIS[29]
		HIT-T15	RG3	Increase GSIS[31]
		RINmF	Fermented ginseng	Protect apoptosis/Increase GSIS[67]
		MIN6	Rb1, Rg1	Protect apoptosis/Increase GSIS[68]
Kim	Korea	MIN6	Ginseng extract	Protect apoptosis[69]
Yuan	USA	MIN6	Ginseng extract	Protect apoptosis/Increase GSIS[70]
Shang	China	3T3-L1	Rb1	Increase glucose uptake[71]
		3T3-L1 /C2C12	Rb1	Increase glucose uptake[72]
Zhang	China	3T3-L1	Re	Activate insulin signaling[73]
Jun	Korea	3T3-L1	Rb1,Rg1	Increase glucose uptake[68]
Lee	Korea	3T3-L1	Rg3,Re	Increase glucose uptake[74]
Kwon	Korea	C2C12	Rc	Increase glucose uptake[75]
Chung	Korea	HepG2	Compound K*	Lipid metabolism[76]
		HepG2	Rg1	Inhibited liver glucose production[77]
Yuan	USA	C2C12	IH-901*	Stimulation of glucose uptake[78]

*: intestine metabolites of ginsenoside

Table 1: Summary of Cell Studies.

syndrome effects in HF-fed ICR mice, with >81% decrease in insulin resistance, >67% reduction in white adipocytes and a marked inhibition of weight gain (approx. >53%), compared to the HF-fed control animals [28]. Further, in male db/db mice treated for 8 weeks, Compound K (CK), a major intestinal ginsenoside metabolite from the ginseng radix, also exhibited an anti-hyperglycemic effect through increases in insulin secretion, similar to that of sulfonylureas, potent insulin secretagogues. Importantly, the CK (10 mg/kg) + metformin (150 mg/kg) group had the lowest insulin resistance index indicating synergistic effects of the drug combination [29]. In a long-term study using C57BL/KsJ db/ db mice, CK improves oral glucose tolerance, increases insulin release and protects against the destruction of pancreatic islets. CK shifted hepatic glucose metabolism from production to utilization and improved insulin sensitivity by elevating plasma adiponectin levels and up-regulating genes for the glucose transporter and adipogenesis in the adipose tissue [30]. In ICR mice, ginsenoside Rg3 suppressed blood glucose levels by enhancing insulin secretion [31]. In the same ICR mice model, ginseng extract (IH-901 at 25 mg/kg) lowered plasma glucose, triglyceride, cholesterol and free fatty acid levels approximately 20.7-41.6%. Plasma insulin levels were significantly increased between 2.2 and 3.4-fold. Furthermore, histological observation show preserved architecture of the pancreatic islet.

Interesting work from the Yuan group (United States) validated that ginseng berries and leaves are also effective anti-diabetic supplements; juice prepared from the ginseng berry or a water extract of American ginseng can also achieve this goal. Daily intraperitoneal injections of *Panax ginseng* berry extract (150 mg/kg) in db/db mice for 5 consecutive days significantly decreased fasting blood glucose (FBG) levels (180.5 ± 10.2 mg/dl vs. control 226.0 ± 15.3 mg/dl). After 12 days of treatment, the db/db mice returned to fasting normoglycemia (134.3 ± 7.3 mg/dl), while FBG concentrations in vehicle-treated mice remained high (254.8 ± 24.1 mg/dl). Ginseng-treated mice also lost a significant amount of weight between days 5 and 12. Lean littermates treated with the same dose of ginseng berry extract also lost weight but did not have comparable reductions in FBG [32]. Similar to the db/db mouse study, obese-diabetic ob/ob mice treated with the ginseng berry extract presented with significant weight loss, reductions in both food intake and plasma cholesterol and increases in energy expenditure and body temperature, compared to lean littermate controls. The ginsenoside Re plays an important role in the anti-hyperglycemic action of ginseng [33,34]. The same dose of ginseng berry extract (150 mg/kg) exhibits more potent anti-hyperglycemic activity, compared to ginseng root extract and only ginseng berry shows marked anti-obesity effects in ob/ob mice [35]. As a more convenient, safe, and practical means of delivery, the Yuan group prepared ginseng berry juice that can be provided orally. Ob/ob mice given ginseng berry juice preparation (0.6 ml/kg) for 10 consecutive days had significantly lower FBG levels and notable improvements in both glucose tolerance and body weight, which all persisted for at least 10 d following cessation of the treatment [36]. Daily intraperitoneal injections of extracts from the American ginseng leaf (50 or150 mg/kg) in diabetic ob/ob adult mice significantly increased glucose disposal, decreased body weight, and increased body temperature by day 12 of treatment [37]. In ob/ob mice, daily intraperitoneal injections for 12 days of American ginseng root extract (300 mg/kg), prepared by a simple water extraction procedure, significantly improves FBG levels and glucose tolerance, while simultaneously reducing body weight [38]. A research group from Taiwan reported that the hypoglycemic effect of ginseng was only produced in pentobarbital-anesthetized BALB/c and C57BL/6 mice; however, in conscious mice this effect could be achieved only if guanethidine was provided at a sufficient dose to block sympathetic tone [39].

Ginseng also has an inhibitory effect on the absorption of dietary fat in male Balb/c mice [40]. Aerobic exercise plus ginseng appears to lower serum lipid, regulate lipid metabolism, promote anti-oxidation, and enhance immune activity in a mouse model of hyperlipidemia through feeding of a high cholesterol diet [41]. However, *in vivo* administration of ginseng extract and ginsenosides may cause significant impairment of PPAR α-dependent activation of genes involved in the fatty-acid β-oxidation, suggesting that the use of ginseng be limited under certain pathophysiological conditions, such as hypercholesterolemia [42].

Rats

Using the rat as research model, a number of independent groups have demonstrated that ginseng has obvious hypoglycemic effects; in a 40-week study ginseng treatment delayed the development of diabetes. Studies with rats are primarily from four independent groups in Korea, one group from the United States, one from Japan and the Cheng group from Taiwan.

An early report from a Japanese group showed that Ginseng radix fraction (10-50mg/kg) increased liver glycogen content, inhibited epinephrine-induced transient hyperglycemia and reduced free fatty acid release from rat epididymal fat pad [43]. Later four independent Korean groups demonstrate that ginseng has anti-obesity effects, which may have beneficial effects on the pathobiology of diabetes. Kim et al. [44] showed that administration of crude saponin from Korean red ginseng (200 mg/kg, ip) for 3 weeks in obese, male Sprague-Dawley rats (HF diet-induced) significantly reduced body weight, food intake and fat content to levels comparable to that of normal weight, chow-fed rats. The hypothalamic NPY expression and serum leptin levels were also reduced in the ginseng-treated HF-fed rats [44]. The results further implicate that the anti-obesity effects of ginseng may result from energy expenditure and normalizing hypothalamic neuropeptides and serum biochemicals related to the control of obesity [45]. Another group from Korea observed that ginseng attenuated the development of overt diabetes. Oral administration of Korean red ginseng (KRG) (200 mg/kg/d) in Otsuka Long-Evans Tokushima Fatty (OLETF) rats for 40 weeks reduced weight gain and visceral fat mass (without altering food intake), improved insulin sensitivity and significantly preserved

glucose tolerance comparable to control animals for up to 50 weeks of age. KRG promoted fatty acid oxidation in skeletal muscle and cultured C2C12 muscle cells by the AMPK medicated up-regulation of PPAR-gamma coactivator-1 alpha, nuclear respiratory factor-1, and glucose transporter 4 (GLUT4) [46]. More recent research from the Chung group in Korea further confirmed ginseng's anti-diabetic effect: ginseng provided via an oral or injection route lowers hyperglycemia induced by streptozotocin (STZ) in Sprague Dawley rats. Oral administration of 250 or 500 mg/kg of fermented ginseng for 20 days (starting one week before STZ injection) reduces plasma glucose level and elevates plasma insulin levels by 266% and 334%, respectively. STZ-induced destruction of pancreatic islets was hindered, through mechanisms involving reductions of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [47].

Research completed by Liu et al. [48] from Taiwan indicates that ginseng may reverse the development of insulin resistance. In rats with insulin resistance induced by the consumption of a high fructose diet, oral administration of *Panax ginseng* root (125.0 mg/kg, thrice daily for 3 days) reduced the elevated glucose-insulin index. The plasma glucose concentrations were significantly lower than those of the vehicle-treated group. Importantly, the plasma glucose-lowering response of tolbutamide was markedly prolonged in *Panax ginseng* root treatment group, suggesting that oral administration of *Panax ginseng* could be a suitable adjuvant therapy for those with insulin resistance [48]. Liu et al. also showed that in high-fat fed Wistar rats plasma glucose is decreased and plasma insulin and C-peptide levels are increased by 60 min following an intravenous injection of ginsenoside Rh2 (0.1-1.0 mg/kg). Rh2 also enhanced insulin secretion mediated by the pancreatic nerve [49]. Intravenous infusion of Rh2 over 120 min in STZ-diabetic rats decreased plasma glucose in a dose-dependent manner, while also increasing gene expression of GLUT 4 in soleus muscle [50]. Single intravenous injections of ginsenoside Rh2 in rats with high-fructose diet-induced insulin resistance decreased plasma glucose concentrations, ultimately improving insulin sensitivity [51].

Researchers from the United States recently observed that either acute or chronic administration of ginsenoside Rb1 is safe and effective in rats. Acute intraperitoneal injections of Rb1 dose-dependently (>5 mg/kg) suppressed food intake mediated by central mechanisms (without eliciting signs of toxicity). Additionally, 4-week administration of ginsenoside Rb1 (10 mg/kg) significantly reduced food intake, body weight gain, and body fat content and increased energy expenditure in HFD-induced obese rats. Rb1 also significantly decreased fasting blood glucose and improved glucose tolerance. These effects were greater than those in pair-fed rats, suggesting that the anti-hyperglycemic effect of Rb1 is only partially attributable to reduced food intake and body weight. Importantly, at an effective dose, acute intraperitoneal administration of Rb1 dose-dependently suppressed food intake that was not caused by taste aversion (Table 2) Rb1-treated obese rats also had no obvious health problems, e.g. diarrhea. Additionally, no chronic non-specific toxic effects were observed (assessed by end-study plasma ALT, AST, and creatinine concentrations) [52].

Human Subjects Trials

Studies investigating the anti-diabetic properties of ginseng in humans have only recently appeared. In this review, we only discuss 18 human trials that are double (or single)-blinded placebo-controlled studies. The majority of these reports indicate that ginseng does indeed have anti-diabetic potential.

In 1995, as a result of their research involving 36 diabetic patients, Sotaniemi et al. [7] suggested that ginseng would be a useful therapeutic adjunct in the management of T2D. Oral ginseng (100 or 200 mg/day) for 8 weeks normalized HbA1c levels, reduced fasting blood glucose concentrations, and reduced body weight, while simultaneously elevating mood and improving psychophysical performance and physical activity [7].

Later, several reports from a group in the United Kingdom confirmed ginseng's effects in regulation of blood glucose in human subjects. In their 3 single-dose trials, involving more than 87 healthy individuals, 200 mg and 400 mg of orally-provided ginseng significantly reduced blood glucose at all three of the post-treatment follow-ups [8-10]. However, the authors were unable to find a long-term effect on glucose regulation when non-diabetic participants (n=31) were provided *Panax ginseng* for 8 weeks, suggesting against the chronic use of ginseng in individuals with normal glucose control [11].

Multiple reports from a research group in Canada observed that American ginseng (AG) and Korean red ginseng (KRG; *Panax ginseng* that has been heated) affect postprandial glycemia in humans; the exception being null effects from one batch of AG that had marked decrements in total ginsenosides. In their first report, including 10 non-diabetic subjects, significant reductions in area under the glycemic curve (18 ± 31%) were observed when ginseng (3 g) was taken orally 40 min before the glucose challenge; there were no differences in effect if the ginseng and glucose were administered together. In 9 diabetic patients,

Groups	Nation	Model	Ginseng type	Research outcome (year)
Kimura	Japan	Mice(Alloxan diabetic)	Ginseng extract	+(1980)[23] +(1981)[43] +(1981)[24] +(1999)[25]
Chung	Korea	Diabetic mice (KKAy, ICR, db/db, C57BL/KsJ) Rat(STZ treated)	Ginseng, Rg3, compound K,	+(2001)[26] +(2004)[27] +(2007)[28] +(2007)[29] +(2007)[30] +(2008)[31] +(2011)[78] +(2010)[47]
Yuan	USA	Diabetic mice (db/db, ob/ob)	American Ginseng extract, berry/leaf/ root	+(2002)[32] +(2002)[33] +(2002)[34] +(2003)[35] +(2004)[37] +(2007)[36] +(2009)[38]
Cheng	Taiwan	Mice(STZ treated) Rat(insulin resistant, or STZ treated)	Ginseng Ginseng, Rh2	+(2010)[39] +(2005)[48] +(2006)[49] +(2006)[50] +(2007)[51]
Kim	Korea	Rat(fatty,Dawley)	Korea red Ginseng	+(2005)[44] +(2009)[45]
Lee	Korea	Rat(fatty,Long-Evans)	Korea red Ginseng	+(2009)[46]
Liu	USA	Rat(obese)	Rb1	+(2010)[52]

+: indicating antidiabetic effects.

Table 2: Summary of Animal Studies.

Groups	Nation	Human subjects	Ginseng type and dose	Outcome(year)
Sotaniemi	Finland	T2D(30)	Ginseng(100-200mg,8 week oral)	+(1995)[7]
Reay	UK	Norm(30) Norm(57) Norm(41)	Ginseng(1 dose, 200-400mg oral) Ginseng(1 dose) Ginseng(200mg, 8 week oral)	+(2005)[8] +(2006)[9] [10] - (2009)[11]
Vuksan	Canada	T2D(9) T2D(19) Norm(10) Norm(10) Norm(10) Norm(12) Norm(12) Norm(19) Norm(12) Norm(13) Norm(12) Norm(12) Norm(22)	American Ginseng(1 dose) Korean red Ginseng(6g/d,12 week oral) American Ginseng(1 dose) American Ginseng(1 dose) American Ginseng(1 dose) Asian Ginseng(1 dose) Asian ginseng(1 dose) Korean red Ginseng (1 dose) Asian Ginseng(1 dose) Korean red Ginseng(1 dose) Asian Ginseng(1 dose) Asian ginseng(1 dose) Asian ginseng(1 dose)	+(2000)[12] +(2008)[19] +(2000)[12] +(2000)[13] +(2000)[14] +(2001)[15] +(2004)[16] +(2006)[18] +(2007)[17] +(2011)[20] - (2004)[16] - (2003)[53] - (2003)[54]
Reed	USA	T2D(14)	Korea red ginseng/Re (3-8g/d, 4 week oral)	- (2011)[22]
Others	Japan Korea		Ginseng extract	+*[55] [56] [57]

*: lipid metabolism; T2D = type 2 diabetes, Norm = healthy people, number of individuals in bracket; 1 dose = 1 single dose experiment. +: positive in antidiabetic effect; -: null in antidiabetic effect.

Table 3: Summary of Human Trials.

AG attenuated postprandial glycemia by similar amount (19 ± 22% and 22 ± 17%, respectively), regardless if the ginseng administration was before or at same time as the glucose challenge [12]. They further demonstrated that 3 g AG was sufficient to achieve maximal glucose reduction. AG reduced postprandial glycemia at 30 min irrespective of dose and time of administration [13]. In non-diabetic individuals, 3, 6, or 9 g of AG (taken 40, 80, or 120 minutes before a glucose challenge) similarly improved glucose tolerance; all treatments reduced area under the incremental glucose curve (26.6%-38.5%) [14]. While 1, 2, or 3 g of AG are equally effective in reductions in glycemia (around 10%), the blood glucose concentration during the last hour of the test was significantly lower when ginseng was administered 40 min before the challenge, rather than 0, 10, or 20 min pre-glucose challenge [15]. Among the 8 commonly-used ginseng sources (American, American-wild, Asian, Asian-red, Vietnamese-wild, Siberian, Japanese-rhizome, and Sanchi ginseng), only American ginseng and Vietnamese ginseng lowered plasma glucose at 90 min in 12 healthy participants given 3 g of ginseng, while the other species of ginseng had opposite effects, actually elevating glucose levels [16]. American ginseng (9 g) administered 40 min before a 2-h OGTT, also significantly reduced glycemia by 27.7% and insulin increase by 23.8%, relative to the non-treated control [17]. However, in 2 additional trials, normal subjects were provided Asian ginseng or a different batch of AG (6 g, 40 min prior to a 75 g OGTT). In these studies, there was no significant effect on the incremental plasma glucose, incremental plasma insulin, or the insulin sensitivity index. However, they found marked decrements in total ginsenosides and Rb1/Rg1 ratio in those batches of AG, which might be an explanation for the contradictory results [53,54].

When evaluating the different forms of ginseng, Sievenpiper et al. demonstrated that 2 g of KRG-rootlets (40 min prior to oral glucose test) is sufficient to achieve reproducible reductions (29%) in postprandial glycemia [18]. Long-term outcomes (efficacy and safety) of KRG are also encouraging. Nineteen well-controlled type 2 diabetics (sex: 11 M, 8 F; age: 64 ± 2 years) took 2 g KRG (total 6 g/day) 40 min prior to each meal for 12 weeks as an adjunct to their usual anti-diabetic therapy (diet and/or medications). Improvements in glycemic control were observed; although HbA1c did not improve, plasma glucose was reduced by 8-11%, fasting and OGTT plasma insulin was increased y 33-38%, and insulin sensitivity increased by 33%, compared with placebo-treated controls [19]. Interestingly, the KRG rootlets had >6-fold more total ginsenosides than the KRG-body, but did not significantly affect postprandial glucose. However, despite this reduced ginsenoside profile, KRG-body lowered postprandial glucose levels at 45, 60, 90, and 120 min during the glucose tolerance test, rendering an overall reduction of 27% (AUC) compared to the control ($p < 0.05$). This suggests a potential therapeutic dose range for ginsenosides [20].

However, more recent research from a group in the United States observed no anti-diabetic effect from AG. Fifteen overweight or obese subjects (sex: 14 F, 1 M; BMI = 34 ± 1; age = 46 ± 3 yr) with impaired glucose tolerance or newly diagnosed T2D were randomized to 30 days of treatment with ginseng root extract (8 g/day), ginsenoside Re (250-500 mg/day), or placebo. Beta cell function was assessed as the disposition index (DI); oral glucose tolerance test and insulin sensitivity (IS) were also monitored. Values for DI and IS were not different among the placebo, ginseng, and ginsenoside Re-treated groups. Ginsenosides Re, Rb_1, and Rb_2 were not detectable in plasma after treatment with ginseng root extract or ginsenoside Re (Table 3). They argued that poor systemic bioavailability might be responsible for the absence of a therapeutic effect [22].

In addition to blood glucose regulatory effect, oral administration of ginseng has also been observed to have effects on lipid metabolism in human [55-57].

Discussion

In the development of T2D, both islet beta-cell dysfunction and muscle insulin resistance play important roles [58,59]. Evidence from cell studies indicates that ginseng (both Asian ginseng [*Panax ginseng*] and American ginseng [*Panax quinquefolius*]) could protect islet beta-cell function and enhance glucose uptake, both supportive of ginseng being a potent anti-diabetic supplement. Twenty-eight animal studies from seven different international research groups confirm these effects and suggest ginseng may delay diabetes progression. *In vivo* anti-hyperglycemia mechanisms of ginseng involve increased insulin secretion, insulin sensitization and islet protection with additional anti-obesity, anti-oxidation, energy expenditure and glucose absorption effects. Interestingly, ginseng is found to synergize with metformin but may have adverse interactions with other herbs. Positive outcomes from long-term studies (>40 weeks) indicate ginseng may be beneficial for chronic use in diabetic individuals. Overall, evidence-based data

acquired from animal studies support the anti-diabetic effects of ginseng.

In human studies, among 18 trials (299 human subjects) from four research groups, only 4 trials (74 cases) are T2D patients, with most being non-diabetic volunteers; In addition, only 4 studies are long-term (>4 weeks) trials. The majority, if not all, of one dose trials observed anti-hyperglycemic effects for both American ginseng and *Panax ginseng*. In three long-term independent trials with T2D patients, two trials demonstrated positive effects (invovling 30 patients) [7], while one showed no effects (involving 14 patients) [19]. The failure to observe anti-diabetic effects in some of the human trials may be due to the difference in batches of Ginseng used, of which ginsenoside levels may differ. Yet, the genetic and metobolic differences of human subjets among the trial groups should also be considerd. Since drug pharmacokinetic and pharmacodynamic differences exist among different populations [60,61] and between genders [61,62]. Different response rates to specific drugs also exist [63], even the gut microbiome (important for human health) could be different due to genetic background, gender [64] and diet habits [65]. Thus, different populations may absorb/metaoblize ginseng differently, which would affect the bioavailability of the effective compounds in Ginseng. Therefore in the future, while more T2D patients and research centers are inclined to participte in ginseng trials, it is also necessary to investigate the pharmacodynamic differences of ginseng among different populations. In Chinese medicine, ginseng is primarily administered in low doses in combination with other herbs for synergistic effects, therefore it will also be necessary to define how ginseng synergizes with other natural dietary supplements or with routinely used anti-diabetic drugs in diabetes treatment.

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