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Review Article

Antihyperglycemic effects of ginseng and possible mechanisms

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Abstract

Ginseng is a medicinal plant valued throughout the world and is considered the king of herbs in traditional Chinese/Oriental medicine. Ginseng has gained popularity as a dietary supplement in the United States and Canada in recent decades. The multiple constituents of ginseng possess equally multifaceted pharmacological functions, as demonstrated by numerous studies. According to previous reports, ginseng root and its constituents influence the central nervous system (CNS), endocrine, cardiovascular, gastrointestinal, sexual, renal and immune systems, etc. One important function of the ginseng plant is its antihyperglycemic effect. Ginseng extracts have been commonly used in Chinese/Oriental medicine to treat diabetes-like conditions. Our recent data suggest that all the main parts of the ginseng plant (including berry, root, leaf and stem) exhibit potent antihyperglycemic effects and may provide an opportunity to develop a novel class of antidiabetic agents. In the current article, we focus on the antihyperglycemic effects of ginseng root, berry and leaf extracts, as well as on the possible mechanisms of the antihyperglycemic action.

Introduction

Diabetes is a devastating disease affecting approximately 8% of the total population in the United States and 3% of the population worldwide, of which 90% suffer from type 2 diabetes (1). It is a chronic metabolic condition that has a significant impact on the health, quality of life and life expectancy of patients, as well as the healthcare system. Since the pathogenesis of diabetes has not yet been fully deciphered, we are still far from successfully curing this disease, even though modern medicine has greatly contributed to the control and treatment of diabetes (2). As the limitations of current drugs for diabetes have become apparent, the need to discover more effective agents with fewer side effects has become evident. This has led to the search for alternative therapies that may have a similar degree of efficacy without the troublesome side effects usually associated with conventional drug treatment. The identification of compounds with antihyperglycemic activity from medicinal plants may provide an opportunity to develop a new class of antidiabetic agents (3), and a few reports indicated that ginseng is one of the most important and valuable plants with antidiabetic properties (4, 5).

Ginseng is a shade-loving, slow-growing, deciduous perennial plant that belongs to the Araliaceae family (5). Seven major species of ginseng are distributed in East Asia, Central Asia and North America. Most studies on ginseng, including those cited in this review, have utilized the constituents from three common species, Asian/Chinese ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*) and Japanese ginseng (*Panax japonicus*) (6, 7).

Ginseng, known as the king of herbs, holds an important position in traditional Chinese/Oriental medicine. Ginseng has been used for over 2,000 years and is believed to be a panacea and to promote longevity in Oriental countries. Historical records on traditional medicinal systems also reveal that ginseng has been used to treat a condition corresponding to diabetes (8). In the ancient Chinese materia medica, a description of ginseng's medicinal effects indicates its ability to "quench thirst", among other wide-ranging beneficial effects (9). The earliest accounts of ginseng's therapeutic uses were recorded in the oldest comprehensive materia medica, "The Herbal Classic of the Divine Plowman" ("Shen Nong Ben Cao Jing" in Chinese), in approximately 101 B.C. (6).

Ginseng was introduced outside Oriental countries by Arabs, probably in the 9th century (10). Reports by Marco Polo, the most famous traveler from medieval Europe in the 13th century, described the silk trade as the possible avenue for bringing Chinese ginseng to Europe. Later on, the herb gradually attracted scientific attention in Europe and North America (11). Originally, ginseng grew in northeastern China, Korea and eastern Siberia, but the wild plant is very rare at present. Currently, this highly valued plant is cultivated in China, Korea, Japan and Russia, as well as in the United States and Canada (12-14).

The increasing interest of the scientific community in ginseng's medicinal use is demonstrated by the fact that, to date, more than 2,000 papers have been published on the multiple chemical components, the multifaceted pharmacological actions and the clinical use of ginseng root and its principal active components, ginsenosides (15-17). Its medicinal effects have been documented in animals in the CNS (18-21), endocrine (22, 23), cardiovascular (24-26), renal (27, 28), gastrointestinal (29, 30), sexual organ (31, 32) and immune systems (33-36), among others. It is also known that ginseng and its components possess antistress (37, 38), antifatigue (37, 39), antitumor (40-43) and antiviral effects (44), efficacy against ischemia/reperfusion injury (45, 46) and antioxidant effects (47-50). Therefore, ginseng occupies a dominant position among herbal remedies in the world. One important pharmacological action is its antihyperglycemic activity. Our data suggest that parts of the ginseng plant, including root, berry and leaf, and its major constituents, ginsenosides and polysaccharides, possess antihyperglycemic properties. The present review discusses the research on the antihyperglycemic effects of ginseng parts and the possible mechanisms of action.

Major constituents and basic pharmacology of ginseng

The root of the ginseng plant is comprised of organic (80-90%) and inorganic substances (approximately 10%) and consists of a number of active constituents, such as saponins and ginsenosides, carbohydrates (including polysaccharides), nitrogenous substances, amino acids, peptides, phytosterol, essential oils, organic acids, vitamins and minerals (42). Based on the chemical structure, there are two major groups, panaxadiols and panaxatriols, in ginseng extracts. Ginsenosides (except Ro) belong to a family of steroids named steroidal saponins. Of these, the extract fractions containing ginsenosides and polysaccharides have demonstrated antihyperglycemic activity.

There is a wide variation (2-20%) in ginsenoside content in different species of ginseng (51-54). The ginsenosides are the principal bioactive constituents of ginseng and have also been used as marker compounds for the *Panax* species (12, 55). We analyzed the ginsenoside content of extracts of American ginseng root, berry and leaf using high-performance liquid chromatography (HPLC) and found that the rank order of the total ginsenoside concentration is: leaf > berry > root (56, 57). The data indicate different compositions in distinct parts of ginseng. Additionally, we also demonstrated that the profile of the six main ginsenosides (Re, Rb1, Rb2, Rc, Rd and Rg1) in the root, berry and leaf extracts was different. The concentration of ginsenosides Re and Rd in American ginseng berry extract is significantly higher than in the root. The rank order for the quantity of Re is: leaf > berry > root. Since some ginsenosides have demonstrated hypoglycemic properties, it is possible that the relative concentrations of specific ginsenosides determine the antidiabetic activity of the different parts of ginseng (57-59).

Antihyperglycemic effects of ginseng

Botanically, the ginseng plant consists of six parts: root, rhizome, stem, leaf, flower and fruit (berry). To develop ginseng-related antihyperglycemic agents, it is important to individually analyze and determine the effects of different parts of ginseng and compare them with ginseng root. Previous studies in animals showed that the main parts of the ginseng plant, including root, berry and leaf, have antihyperglycemic effects. We have recently demonstrated a similar activity for the berry and leaf extracts of Chinese and American ginseng in diabetic (*db/db*) and obese (*ob/ob*) transgenic mouse models.

Ginseng berry

Until recently, ginseng was considered to be synonymous with the main dried root of the plant. People used to believe that nutrients were accumulated in the root, and thus shied away from testing the berry, leaf and other parts for medicinal effects. Therefore, no precise information is available on the effect of ginseng berry on blood glucose and other biological activities. Recently, we were surprised by how different the berry and leaf were from the root in terms of their chemical profile and how effective they were in correcting the multiple metabolic abnormalities associated with diabetes. In our laboratory, we used the *ob/ob* mouse as a model of hyperglycemia and obesity that phenotypically resembles human type 2 diabetes. Another animal model, diabetic C57BL/KsJ (*db/db*) mice, was also utilized to test the pharmacological effects of American and Chinese ginseng berry extract. The C57BL/KsJ mouse is an inbred strain distinct from the C57BL/6J strain, which serves as the recipient of the *ob* gene. In the C57BL/KsJ strain of mice, the diabetes *db* gene mutation occurs spontaneously (60).

Using obese *ob/ob* and diabetic *db/db* mice, we have demonstrated that American ginseng berry extract (AGBE) and leaf extract (AGLE), Chinese ginseng berry extract (CGBE), total ginsenosides in Chinese ginseng (CGTG), the polysaccharide extract of American ginseng berry (PEAGB), ginsenoside Re (G-Re) and American ginseng berry juice (AGBJ) have the ability to ameliorate hyperglycemia (56, 57, 59, 61-66). Table I shows the effects of AGBE, AGLE, CGBE, CGTG, PEAGB and G-Re on fasting blood glucose levels in *ob/ob* and *db/db* mice. Blood glucose levels after 4-h fasting were mea-

Table I: Effect of AGBE, CGBE, AGLE, CGTG, PEAG and G-Re on fasting blood glucose in ob/ob mice.

Groups	Fasting blood glucose (mg/dl)		
	n	Day 0	Day 12
AGBE	6	183 ± 8.6	147 ± 5.8*
Vehicle	6	212 ± 14.9	212 ± 20.8
CGBE	6	236 ± 5.8	137 ± 6.7**
Vehicle	4	222 ± 16.2	211 ± 19.6
AGLE	5	245 ± 5.5	180 ± 10.0**
Vehicle	6	260 ± 16.0	268 ± 10.0
CGTG	5	210 ± 16.7	180 ± 10.0**
Vehicle	5	210 ± 14.6	211 ± 13.8
PEAGB	5	236 ± 18.1	149 ± 17.6*
Vehicle	5	231 ± 13.5	240 ± 12.3
G-Re	11	226 ± 18.9	180 ± 10.8**
Vehicle	6	235 ± 12.6	239 ± 13.3

*$p < 0.05$, **$p < 0.01$ compared to Day 0. AGBE, American ginseng berry extract (150 mg/kg); CGBE, Chinese ginseng berry extract (150 mg/kg); AGLE, American ginseng leaf extract (150 mg/kg); CGTG, total ginsenosides in Chinese ginseng (300 mg/kg); PEAGB, polysaccharide extract of American ginseng berry (150 mg/kg); G-Re, ginsenoside Re (20 mg/kg).

sured on days 0, 5 and 12 (or day 10 in the AGBJ experiment) after daily i.p. or p.o. administration of ginseng extracts or vehicle. In this experiment, both *ob/ob* and *db/db* mice had significantly higher fasting blood glucose levels compared to lean controls on day 0. On day 12, *ob/ob* and *db/db* mice treated with American or Chinese ginseng extracts were normoglycemic. The blood glucose concentrations of lean mice, however, did not substantially change in response to treatment with the extracts on either of those days (data not shown in Table I). The results demonstrated that all ginseng extracts used in these experiments possess antidiabetic effects in obese *ob/ob* mice and diabetic *db/db* mice. It must be pointed out that *db/db* mice had higher fasting blood glucose levels compared to lean mice under control conditions. The extract markedly lowered increased blood glucose levels in *db/db* mice (56).

To evaluate peripheral glucose utilization and determine whether ginseng berry treatment could lead to improvement in glucose tolerance, an i.p. glucose tolerance test (IPGTT) was performed in *ob/ob* and *db/db* mice (67). In this test, glucose disposal was evaluated prior to and 12 days after treatment with the extract or vehicle. The results showed that *ob/ob* and *db/db* mice had hyperglycemia on day 0, which was exacerbated by the i.p. glucose load and did not return to baseline after 120 min, indicating glucose intolerance and impaired disposal. After 12 days of treatment with ginseng berry extract (150 mg/kg), there was a significantly higher rate of glucose disposal at 30, 60 and 120 min. No significant change, however, was seen in the animals treated with vehicle (61, 62). Similar results were obtained using AGLE, CGTG, PEAGB and G-Re in experiments in *ob/ob* and *db/db* mice. The data indicated that extracts from both American and Chinese ginseng berry improved glucose tolerance and increased peripheral glucose utilization in diabetic animals.

To explore which chemical ingredients of ginseng berry extracts play an important role in the antihyperglycemic effect, we designed experiments to test the antihyperglycemic effect of different chemical constituents of ginseng berry *in vivo*. We discovered in these experiments that both Re, a major component of ginsenoside in ginseng berry, and the polysaccharide fraction from American ginseng berry possess antidiabetic activity (61, 65). The data indicate that G-Re and the polysaccharide fraction may play a significant role in the antihyperglycemic action. In addition to the decrease in blood glucose levels, we also found a significant body weight-reducing effect for American and Chinese ginseng berry extracts in *ob/ob* and *db/db* mice (56, 61) (data not shown). The weight-reducing property was further indicated by the fact that *ob/ob* mice gradually regained weight comparable to the vehicle-treated *ob/ob* mice within 12 days of cessation of treatment with the berry extract. Since body weight reduction is associated with improvement in insulin resistance (68), this may be one of the mechanisms by which ginseng exerts its antihyperglycemic effect.

More interestingly, we observed an antihyperglycemic effect for AGBJ in *ob/ob* mice. If American ginseng berry can be useful as a dietary supplement, simple preparation and oral intake would be convenient, safe and practical for consumers. Therefore, the ease of preparation of berry juice was analyzed using HPLC and it was then administered orally to *ob/ob* mice. The animals received 0.6 ml/kg berry juice daily or vehicle for 10 consecutive days (Fig. 1). The data showed that baseline or day 0 fasting blood glucose levels were very high in both the vehicle group (n=5) and the AGBJ group (n=5), *i.e.,* 230.0 ± 9.7 and 228.0 ± 14.5 mg/dl, respectively. After daily administration of AGBJ for 10 days, blood glucose concentrations in *ob/ob* mice were significantly decreased to 157.8 ± 13.9 mg/dl ($p < 0.01$ compared to the vehicle

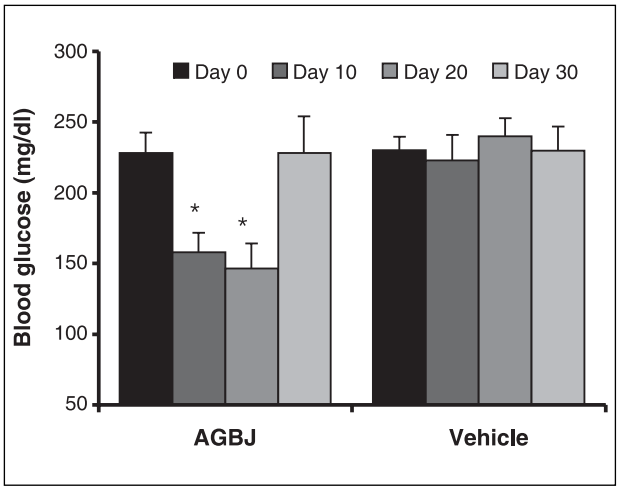

Fig. 1. Effect of American ginseng berry juice (AGBJ) on fasting blood glucose levels in adult *ob/ob* mice. The glucose levels decreased significantly in animals treated with 0.6 ml/kg p.o. AGBJ on day 10 (treatment cessation) and day 20. *$p < 0.01$ compared to vehicle-treated mice.

group value of 223.0 ± 18.0 mg/dl). Glucose levels did not change significantly over 10 days in the vehicle group. The results demonstrated that oral juice administration significantly lowered fasting blood glucose levels, and this effect continued for at least 10 days after cessation of treatment. In addition, AGBJ also significantly reduced body weight in this experiment. Our data suggest that the berry juice as a dietary supplement may be associated with functional improvement in patients with diabetes.

Ginseng root

Numerous animal experiments have shown that ginseng root extracts significantly lower blood sugar levels in diabetic mice. Kimura *et al.* demonstrated that the administration of Asian ginseng root extracts to alloxan-treated and genetically diabetic (KK-CAy) mice significantly decreased blood glucose levels (58, 69-71). The authors also indicated that ginsenosides Rb1 and Rg1 decreased the insulin content in pancreatic islet cells to undetectable levels, which suggests insulin release. This insulin-releasing action-induced antihyperglycemic effect of ginseng root and leaf tincture was confirmed in other studies by increased blood levels of insulin in alloxan-treated diabetic rats (58, 69-72).

In several clinical studies, ginseng root has been shown to have beneficial effects in both insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetes patients. Oral administration of ginseng root as tablets (100 or 200 mg/day for 8 weeks) in type 1 and type 2 diabetes patients elevated mood, improved physical performance and reduced fasting blood glucose and body weight (73, 74). The authors found that ginseng root had favorable results in a double-blind, placebo-controlled study in 36 newly diagnosed patients with type 2 diabetes. A 200-mg dose improved the subjective ratings of mood, vigor and well-being, which was associated with increased physical activity and reduced weight. A lower fasting blood glucose level was also associated with ginseng treatment, but not with placebo. The antidiabetic effects were attributable to ginsenoside Rb2 and more specifically to panaxans I, J, K and L (75). Certainly, more studies are warranted regarding ginseng's use in patients with diabetes. A decrease in fasting blood glucose without a change in immunoreactive insulin suggests improved insulin sensitivity. The authors concluded that ginseng might be a useful therapeutic adjunct in the management of type 2 diabetes patients.

Other clinical trials also support the notion that ginseng root and Korean red ginseng possess antihyperglycemic activity (76-78). It was reported that American ginseng root attenuated postprandial glycemia in both nondiabetic subjects and patients with type 2 diabetes. In nondiabetic subjects, postprandial glycemia was attenuated only if ginseng was administered prior to glucose challenge. In subjects with type 2 diabetes, however, postprandial glycemia was significantly attenuated irrespective of the timing of ginseng administration in relation to the glucose challenge. Vuksan *et al.* also suggested that no more than 3 g of American ginseng root was required at any time in relation to the challenge to achieve reductions in blood glucose.

Research on the components of ginseng root has resulted in the discovery of five types of substances (79, 80). Complex components in the carbohydrate fraction of ginseng root extract, including panaxans A, B, C, D and E, panaxans I, J, K and L, and panaxans Q, R, S, T and U, also exhibited antihyperglycemic properties in normal and alloxan-induced hyperglycemic mice (75, 79, 81). Similar to Asian ginseng, three constituents obtained from the water extracts of American ginseng root, *i.e.,* quinquefolans A, B and C, displayed antihyperglycemic actions in normal and hyperglycemic mice (82). A subsequent study showed that both the ginseng radix and its rootlet have distinct antidiabetic properties (83).

Ginseng leaf

Only a few reports are available on ginseng leaf extract and its antihyperglycemic effects. Molokovskii *et al.* demonstrated that ginseng leaf and root tinctures have antihyperglycemic effects in mice and rats with alloxan-induced diabetes (71). They discussed mechanisms of antidiabetic, insulinotropic and hypoglucagonemic actions of the effective plant pharmaceuticals and the prospects for their use in multimodal therapy of type 1 diabetes. Davydov *et al.* reported that ginseng root and leaf extracts increased the basal content of insulin in blood and the glucose-dependent secretion of this hormone (84).

The antihyperglycemic effect of AGLE was investigated in *ob/ob* mice in our laboratory using a similar experimental protocol as described previously (57). On day 12, glucose levels in ginseng leaf extract-treated groups (150 mg/kg) were significantly decreased compared to the

vehicle-treated group. Therefore, like ginseng berry and root, AGLE also possesses a significant blood glucose-lowering effect in *ob/ob* mice. The antihyperglycemic activity of AGLE was also demonstrated in an IPGTT experiment in our laboratory.

Possible mechanisms of ginseng's antihyperglycemic effects

The mechanisms of the antihyperglycemic effect of ginseng extracts and its major bioactive components may be multifaceted, but this is still unclear. However, several plausible hypotheses are generally accepted.

Inhibition of digestion and increase in energy expenditure

Several studies indicated that a modulating effect of ginseng on digestion may be involved. Ginseng berry extract significantly lowered food intake in *ob/ob* mice and in turn reduced the source of sugar (61). Energy expenditure values were obtained in *ob/ob* mice treated with ginseng berry extract or vehicle. After 12-day treatment, there was a significant increase in energy expenditure of the berry extract-treated group compared to the vehicle-treated group. More interestingly, we also observed that ginseng berry extract significantly increased body temperature in *ob/ob* mice. The increase in body temperature suggested that carbohydrate metabolism is enhanced, which is consistent with the increased basal metabolic rate.

Gastric vagal afferents are the primary neuroanatomical link between the stomach and the CNS. In a previous study, we reported that ginseng extract inhibited brainstem neuronal activity via gastric vagal afferents (85). Another report indicated that ginseng extract inhibited intestinal glucose absorption (83) and gastric secretion (86). These results suggest that ginseng extracts may slow the digestion of food and decrease the rate of carbohydrate absorption. Inhibiting digestion will reduce the source of blood glucose. Increasing energy expenditure should enhance glucose disposal and blood sugar will eventually be lowered in the animals.

Improvement in insulin sensitivity and change in blood insulin level

Reports have indicated that the antihyperglycemic effect of ginseng may be mediated by a variety of factors, including actions on insulin-secreting pancreatic β-cells and the target tissues that take up glucose. Ginseng extract increased insulin release from pancreatic β-cells, which is probably due to increased β-cell stimulation and increased insulin synthesis (58, 69, 87). Recent studies indicated that ginsenoside Rh2 has the ability to improve insulin sensitivity (88) and American ginseng extract is able to stimulate insulin production by inhibiting mitochondrial uncoupling protein 2 (UCP 2) (89). Also, long-term treatment with ginseng resulted in an increased metabolic rate and improved insulin-stimulated glucose disposal (61). The increased metabolic rate may be due to ginseng's ability to increase aerobic glycolysis (35). Ginseng is believed to increase the activity of a glucose transporter protein, reduce the rate of glucose absorption and glycogenolysis, and in turn lower blood glucose (83, 90, 91). Additionally, we have demonstrated the ability of ginsenoside Re to reduce the expression of enzymes involved in lipid metabolism, which could be beneficial in diabetes (92). Other properties, such as the antioxidant activity of ginseng extracts, may also help in protecting the pancreas and other tissues from oxidant stress during hyperglycemia (93-95).

Other possible mechanisms

Increasing glucose transporter proteins may be another mechanism involved in ginseng's antihyperglycemic activity (17). Ginseng extracts may exert antidiabetic effects by modulating glucose transport. In a study to quantify the glucose transporter (GLUT2) protein content in hyperglycemic mice (90), the antihyperglycemic effects of ginseng radix were presumably due, at least in part, to the increase in glucose transporter protein content. This may be mediated by nitric oxide (NO) (96) and indicates that insulin-stimulated glucose uptake in rat skeletal muscles and adipose tissue is NO-dependent. Enhanced NO synthesis by ginseng has also been observed in other experiments (16).

On the other hand, Wang *et al*. have demonstrated that ginseng glycopeptides significantly lowered blood glucose and liver glycogen levels in both normal and hyperglycemic animals, including rats, mice and rabbits (34, 35). An advanced study demonstrated that the antihyperglycemic effect of glycopeptides might be attributable to the enhancement of aerobic glycolysis through stimulation of β-adrenoceptors and an increase in the activity of various rate-limiting enzymes related to the tricarboxylic acid cycle. Thus, the antihyperglycemic mechanism of ginseng is not yet clear and more extensive studies are needed to elucidate the mechanism of its effects.

Conclusions

The different ginseng parts possess multiple constituents and multifaceted pharmacological actions. Both American and Chinese ginseng, including root, berry, leaf and stem extracts, and their major bioactive constituents, ginsenoside Re and a polysaccharide extract, have the ability to reduce blood glucose levels *in vivo*. The mechanism of the antihyperglycemic effect of ginseng is still unclear. This antihyperglycemic effect, however, may provide an opportunity to develop new antidiabetic agents if these data can be validated in future clinical trials.

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