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Review

The anti-hyperglycemic property of different ginseng partitions

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SUMMARY

Ginseng is a popular medicinal plant highly valued throughout the world. Asian ginseng is one of the most common species of ginseng. It has long occupied a significant position in oriental medicine and has been justified its name as the "king herb". As a nutritional supplement, ginseng is an extremely common and popular herbal medicine in the United States and Canada in recent decades. The multiple constituents of ginseng possess equally multifaceted pharmacological actions as demonstrated by numerous studies. Ginseng root and its constituents influenced the central nervous system, endocrine, cardiovascular, gastrointestinal system, sexual, renal organ and immune system, *etc.* One important action is its anti-hyperglycemic effect. Previous studies on ginseng demonstrate that only the root of ginseng has been used in the treatment of diabetes, while the other parts of ginseng plant were always neglected. Recently, we analyzed the constituents of ginseng berry, leaf and discovered that ginseng berry, leaf extracts and its total ginsenosides have the ability to reduce hyperglycemia and body weight and increase the peripheral glucose utilization in obese or diabetic *ob/ob* or *db/db* mice. Our data suggest that all parts of ginseng plant, including root, berry, leaf and stem exhibit potent anti-hyperglycemic and anti-obese effects and may provide an opportunity to develop a novel class of anti-diabetic agents.

Key words: Ginseng; Anti-hyperglycemic effect; Anti-obese effect; Ginseng root; Berry; Leaf; *ob/ob* and *db/db* mice

INTRODUCTION

Diabetes mellitus is increasing rapidly and vast amounts of resources are spent across the globe. In the U.S., diabetes is both serious and costly. The overall prevalence of diabetes is approximately 7.9% of the total population (16.7 million people), of which 90% have type II diabetes (Skyler, 2004). Although oral hypoglycemic agents or insulin are the mainstay for the treatment of diabetes and effective in controlling hyperglycemia, they have prominent side effects and fail to significantly alter the course of diabetic complications. Also, currently available therapeutic options for non-insulin-dependent diabetes mellitus such as dietary modification, hypoglycemics and insulin have limitations of their own (Rang and Dale, 1991). Therefore, there is a need to look for new drug or complementary and alternative medicine to modify the course of diabetes. According to previous reports,

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ginseng is a best one for controlling hyperglycemia and obesity. This article discusses the antihyperglycemic effects of different ginseng partitions, including root, berry, and leave, as well as possible mechanisms of the anti-diabetic action.

BASIC COMPOSITION AND MAJOR PHARMACOLOGICAL PRROPERTIES OF GINSENG

At about 2000 years ago, ginseng was described by the oldest medicinal encyclopedia of China (*The Herbal Classic of the Divine Plowman*). "Ginseng has a sweetish taste and a slightly cooling nature, as well as a slightly warming nature, non-toxic (*i.e.* no drastic drug action), it is a tonic for the five viscera, it calms the mind and pacifies the spirit (soul), it allays fear and stops palpitation, it wards off evil 'chi' brightens the eye, improves the intelligence. Prolonged use leads to longevity and a light body. It cures gastro-instestinal inactivity, tympanites and pain in the abdomen, congestion in the chest and ribs, diarrhoea and vomitting. It regulates the central functions, quenches thirst, improves circulation, breaks up hardened nodules and improves the memory" (Cheung *et al.*, 1983). It must be pointed out that the function of "quench thirst" may be an anti-diabetic activity in traditional Chinese Medicine.

To date, over 2,000 ginseng research papers have been compiled, strongly supporting that ginseng root possesses multiple constituents and multifaceted pharmacological actions (Lee, 1992). Recent studies have demonstrated that *Panax ginseng* and its major bio-active components (ginsenosides) consist of complex constitution and multifaceted pharmacological functions (Gillis, 1997; Attele *et al.*, 1999; Attele *et al.*, 2002). Table 1 summarizes the basic component of ginseng root (Hasegawa and Saiki, 2003). Generally, ginseng root includes organic (80-90%) and inorganic substances (10-20%). Organic substances contain a number of bio-active constituents, such as saponins (3-6%), carbohydrates (60-70%), nitrogenous substances (9-15%), fat soluble components (2%) and vitamins (0.05%) *etc.* Inorganic

Table 1. Basic ingredients of ginseng root

Composition			Content (%)
Organic	Carbohydrates	60-70	-Saccharides(mono-, Di-, Tri-, and poly-) -Crude fibers -Pectins
	N-Containing substances	9-15	-Proteins -Peptides -Amino acids -Nucleic acids -Alkaloeds
	Saponin	3-6	-Protopanaxadiol glucosides -Protopanaxatriol glycosides -Oleanolic acid glycoside
	Fat soluble components	2	-Lipids -Fatty acids -Essential oils -Phytosterols -Organic acids -Phenolics -Polyacetylenes -Terpenes
	Vitamins	0.05	-Water soluble vitamins
Inorganic	Ash	4	-Minerals
	Moistures	5-10	

substances contain ash (4%) and moistures (5-10%) *etc.*

Volumes have been written on pharmacological effects of ginseng root, ginseng root extracts and its constituent ginsenosides (Gillis, 1997; Attele *et al.*, 1999; Attele and Xie, 2002; Hasegawa and Saiki, 2003). Among the effects demonstrated by animal experimentation are: the central nervous system; including learning, memory, and behavior (Saito *et al.*, 1977; Benishin *et al.*, 1991; Bhattacharya and Mitra, 1991; Yuan *et al.*, 1998; Zhao and McDaniel, 1998); endocrine system (Yoshizato *et al.*, 1999; Broadhurst *et al.*, 2000); cardiovascular system (Kaku *et al.*, 1975; Lee *et al.*, 1981; Kim *et al.*, 1992; Zhang and Liu, 1994; Han *et al.*, 1998; Inoue *et al.*, 1999); sexual organ (Chen and Lee, 1995; Murphy *et al.*, 1998; Murphy and Lee, 2002); gastrointestinal system (Sun *et al.*, 1991; Yuan *et al.*, 1998; Kase *et al.*, 1999;); Renal organ (Yokozawa *et al.*, 1994) and immune system (Gaffney *et al.*, 2001; Wang *et al.*, 2003a, Wang *et al.*, 2003b) *etc.* It is also known that ginseng and its components possess anti-stress (Banerjee and Izquierdo, 1982; Awang, 1998), anti-fatigue (Banerjee and Izquierdo, 1982), anti-tumor (Yun *et al.*, 1993; Mochizuki *et al.*, 1995; Yun and Choi, 1995; Wakabayashi *et al.*, 1998; Hasegawa and Saiki, 2003), anti-diabetic (Kimura, 1980; Kimura and Suzuki, 1981; Kimura *et al.*, 1981a; Kimura *et al.*, 1981b; Kimura *et al.*, 1999; Attele *et al.*, 2002; Xie *et al.*, 2002a; Xie *et al.*, 2002b; Wang *et al.*, 2003a), antiviral (Cho *et al.*, 2001), antidotal , anti-ischemia-reperfusion (Zhang and Liu, 1994; Maffei Facino *et al.*, 1999) and antioxidant effects (Kim *et al.*, 1992; Chen, 1996; Shao *et al.*, 1999; Shao *et al.*, 2001; Shao *et al.*, 2004). Therefore, ginseng is reputed to be a king herb of oriental medicine and occupies a dominant persona among herbal remedies in the world. Table 2 summarizes the major pharmacological actions of ginseng root and berry (Hasegawa and Saiki, 2003). It should be pointed out, however, that even though ginseng possesses multifaceted and salutary effects, and has a well-established safety record, inappropriate use of ginseng leads to adverse effects (Siegel, 1979; Gillis, 1997; Harkey *et al.*, 2001).

Historical records reveal that in traditional medical systems, a disease corresponding to type II diabetes was treated with plant extracts (Ackerknecht, 1982). Evaluation of pharmacological activity of ginseng root on blood sugar levels started early last century. Between 1921 and 1932, Japanese scientists reported that ginseng root decreased baseline blood glucose and reduced hyperglycemia caused by adrenaline or high concentration glucose administration (Wang, 1965; Wang, 1980). Ginseng root has since been used to treat diabetic patients (Bensky and Gamble, 1993; Huang, 1999). Since the 1980's, the number of published studies on ginseng root in treating diabetes increased remarkably. Results of *in vitro* and *in vivo* experiments (Kimura, 1980; Kimura and Suzuki, 1981; Kimura *et al.*, 1981a; Kimura *et al.*, 1981b; Yokozawa *et al.*, 1985; Kimura *et al.*, 1999) and clinical trial (Sotaniemi *et al.*, 1995; Vuksan *et al.*, 2000-a; Vuksan *et al.*, 2000-b) investigations strongly support the claim that ginseng root possesses anti-diabetic property.

Recently, we have observed that *Panax ginseng* berry and leaf extracts, which have distinct ginsenoside profiles compared to the profile of the root, have the ability to reduce hyperglycemia and body weight in diabetic and obese C57BL/6J (*ob/ob*) mice and C57BL/KsJ (*db/db*) mice (Attele *et al.*, 2002; Xie *et al.*, 2002a; Xie *et al.*, 2002b; Yuan, 2002; Dey *et al.*, 2003;). In this article, we focus on the anti-diabetic effects of ginseng root, berry and leaf extracts, as well as on the possible mechanisms of hypoglycemic action.

GINSENG ROOT

Animal experimental data showed that ginseng root and its extracts lower blood sugar levels significantly in diabetic mice. Kimura *et al* indicated that some fractions extracted from ginseng caused hypoglycemic effect on alloxan mice (Kimura and Suzuki, 1981; Kimura *et al.*, 1981a; Kimura *et al.*,

Table 2. Major pharmacological effects of ginseng

Pharmacological Effects		Dose (mg/kg)	Subjects	References
Central nervous system	Stimulated & inhibited effects	Extract,saponin, Rg,	Rat	(Saito *et al.*, 1977)
	Antistress & antifatigue	Extract, 200	Mice	(Banerjee *et al.*, 1982)
	Enhancement of nerve growth	Saponin	Chicken	(Takemoto *et al.*, 1984)
	Effect on nerve endings	Rb_1, 2, 5	Rat	(Benishin *et al.*, 1991)
	Anxiolytic effect	Power, 20, 40	Rat	(Bhattacharya *et al.*, 1991)
	Improvement of learning and memory	Extract, 3-300	Rat	(Petkov *et al.*, 1987)
	Cognitive enhancer	Extract, 40, 80	Rat	(Zhao *et al.*, 1998)
	Inhibition of brain Na^+ channels	Extract(1 mg/ml)Rb,c,d,e,g	Cells	(Liu *et al.*, 2001)
	Improving brain ischemia	Rh, 2,100	Rat	(Park *et al.*, 2004b)
Cardiovascular system	Effect on blood pressure	Saponin	Rat	(Jeon *et al.*, 2000)
		Red ginseng, 4.5g/day	Human	(Han *et al.*, 1998)
	Anti-ischemia/reperfusion effects	Ginsenoside,Rb,	Human	(Zhan *et al.*, 1994)
	Vasodilation effect	Extract, 40	Dog	(Lee *et al.*, 1981)
	Cardiovascular protection	Ginsenoside,	Rabbit, Dog	(Chen, 1996)
	Cardiac contractility effect	Extract, 150	Rat	(Toh, 1994)
	Endothelium-dependent-relaxation	Saponin, 50	Rabbit	(Kang *et al.*, 1995)
	Hyperlipidemia	Saponin, 10	Rabbit	(Inoue *et al.*, 1999)
Endocrine system	Neuroendocrinologic effects	Extract, 500	Rat	(Yoshizato *et al.*, 1999)
	Increase corticosterone	Ginsenoside, 70	Rat	(Wang *et al.*, 1984)
		Total saponin, 5, 20	Mice	(Kim *et al.*, 2003)
	Hypoglycemic effect	Extract, 200	Mice	(Ohnishi *et al.*, 1996)
	Antidiabetic effect	Extract, 10-15	Mice	(Kimura *et al*, 1981a)
	Anti-hyperglycemic effect	Berry, Re, 50, 150	*ob* Mice	(Attele *et al*, 2002)
		Berry, 50, 150	*ob*, *db* Mice	(Xie *et al*, 2002a, b)
Digestive system	Antidiarrhoeal effect	Saponin, 10, 30	Rat	(Kase *et al.*, 1999)
	Gastric modulating effect	Extract, 300 μg/ml	Rat	(Yuan *et al.*, 1998)
	Stimulation of liver regeneration	Extract, 125, 250	Rat	(Cui, 1997)
	CCl_4 induced hepatotoxicity	Polysaccharide, 100, 200	Rat	(Kim, 1995)
Immune system	Increasing NK cells activity	Extract, 50.100	Mice	(Kim *et al.*, 1990)
	Morphine-induced immune suppression	Saponin, 100	Mice	(Kim *et al.*, 1999)
	Irradiation-induced immune suppression	Extract, 1600	Mice	(You *et al.*, 1995)
Renal system	Renal failure	Saponin, 25	Rat	(Yokozawa *et al.*, 1994)
	Antidiuretic effects	Ginsenoside, 126	Rats	(Huang, 1999)
Respiratory system	Protective effects	Ginsenoseds, 50, 200 μg/ml	Cells	(Kim *et al.*, 1992)
		Extract, G115, 40-50	Rabbit	(Rimar *et al.*, 1996)
Reproductive system	Corpus cavernosum	Ginsenoside, 250, 500, 750	Cells	(Chen *et al.*, 1995)
	Copulatory behavior	Extract, 100	Rat	(Murphy *et al.*, 1998)
Antitumor effects	Antimetastasis	Rb_2, 5-50	Mice	(Mochizuki *et al.*, 1995)
		Saponin, 20-40 μM	Cells	(Wakabayashi *et al.*,1998)
	Anticarcinogenesis	Extract, 420	Mice	(Hasegawa *et al.*, 2003)
		Polysaccharide, 150, 300	Mice	(Yun *et al.*, 1993)
Antioxidant effects	Antioxidant activity	Extract, 0.01-10 mg/ml	Mice	(Kitts *et al.*, 2000)
	Scavenging free radicals	Extract, 0.1-1.0 mg /ml	Cells	(Shao *et al.*, 2004)
Antiallergic effects	Inhibitory activity	Extract, Rb_1,Rb_2,Rc,Rd,	Cells	(Choo *et al.*, 2003)
	Antiallergic activity	Rh_1 25	Cells	(Park *et al.*, 2004a)

1981b). They also demonstrated that ginsenosides, Rb_1 and Rg_1 decreased the insulin content of islet cells in pancreas to undetectable levels, suggesting release of insulin. The insulin-releasing action being the anti-diabetic effect of ginseng root and leaf tincture was confirmed in other studies demonstrating increased blood level of insulin in alloxan diabetic rats (Kimura and Suzuki, 1981; Kimura *et al.*, 1981a; Kimura *et al.*, 1981b; Waki *et al.*, 1982; Molokovskii *et al.*, 1989).

There may be complex hypoglycemic components in ginseng root. Five types of substances have been discovered (Konno *et al.*, 1984; Ng and Yeung, 1985). The constituents include five glycans designated panaxans A, B, C, D, and E, adenosine, a carboxylic acid, a peptide lacking basic amino acid residues, and a fraction designated DPG-3-2 prepared from the water extract of ginseng (Konno *et al.*, 1984; Konno *et al.*, 1985). The structure of panaxan A has been partially elucidated and the glycans have been demonstrated to elicit hypoglycemia in both normal and diabetic mice (Tomoda *et al.*, 1984). Four other glycans, panaxans I, J, K and L, isolated from ginseng root remarkably reduced blood sugar levels both in normal and alloxan-induced hyperglycemic mice (Oshima *et al.*, 1985). Another five hypoglycemic constituents named panaxans Q, R, S, T and U have been obtained (Konno *et al.*, 1985). On the other hand, there were three hypoglycemic constituents obtained from American ginseng (*Panax quinquefolium* L.) root, quinquefolans A, B, and C. These water extracts also displayed anti-diabetic effect in normal and hyperglycemic mice (Oshima *et al.*, 1987). A later study showed that both the white ginseng radix (Ginseng Radix Alba, GRA) and the rootlet (Ginseng Radix Palva, GRP) have anti-diabetic activity (Chung *et al.*, 2001). After a four-week oral administration, the fasting blood glucose levels in the GRA- and GRP-treated groups were lowered than the control group. The results strongly suggest that GRA can reduce hyperglycemia in KKAy mice, possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase, and GRP through the up-regulation of adipocytic PPAR-y protein expression as well as inhibiting intestinal glucose absorption (Chung *et al.*, 2001).

In clinical studies, ginseng root has been shown to have beneficial effects in both IDDM and NIDDM patients. Oral administration of ginseng root tablets (100 or 200 mg daily for 8 weeks) to patients elevated mood, improved physical performance, and reduced fasting blood glucose and body weight (Miller, 1998; World Health Organization, 1999). The authors observed that ginseng root has had favorable results in a double-blind, placebo-controlled study of 36 newly diagnosed patients with type II 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 anti-diabetic effects have been attributed to ginsenoside Rb_2 and more specifically to panaxans I, J, K, and L. (Oshima *et al.*, 1985). Certainly more studies are warranted regarding ginseng's use in the population with diabetes. Fasting blood glucose decreasing without change in immunoreactive insulin suggests improved insulin sensitivity. The authors concluded that ginseng might be a useful therapeutic adjunct in the management of NIDDM patients.

Other clinical trials also support the notion that ginseng root possesses anti-hyperglycemic activity (Vuksan *et al.*, 2000-a; Vuksan *et al.*, 2000-b). It was reported that American ginseng root attenuated postprandial glycemia in both the non-diabetic group and the type II diabetes groups. In non-diabetic subjects, postprandial glycemia was attenuated only if the ginseng was administered prior to the glucose challenge. However, in subjects with type II diabetes mellitus, the postprandial glycemia was significantly attenuated irrespective of the timing of ginseng administration in relation to the glucose challenge. The authors also suggested that no more than 3 g American ginseng root was required at

any time in relation to the challenge to achieve reductions in blood glucose.

GINSENG BERRY

Throughout history, mentioning ginseng is synonymous with the main dried root of ginseng. People used to believe that nutrients 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 activity. Botanically, ginseng plant consists of six parts: root, rhizome, stem, leaf, flower, and fruit. To develop ginseng plant, it is important to analyze, determine, and compare with ginseng root. Recently, we were stunned by how different the berry and leaf are from the root in terms of their chemical profile and by how effective it is in correcting the multiple metabolic abnormalities associated with diabetes.

The chemical constituent of American ginseng berry

The American ginseng berry extract (AGBE) was analyzed by using high performance liquid chromatography (HPLC) in our laboratory. Six main ginsenosides, including Rb_1, Rb_2, Rc, Rd, Re, and Rg_1, of American ginseng berry was determined and compared with American ginseng root and leaf. It has been discovered that American ginseng berry has a distinct ginsenoside profile compared to the profile of the root (Xie *et al.*, 2002a). Our results indicated that there are different compositions in distinct parts of ginseng. Total ginsenosides (%) are different in ginseng berry, root, and leaf. The rank order of the total ginsenoside concentration is leaf > berry > root. The content of ginsenoside, Re in berry is much higher than in root. The rank order of the quantity of Re was leaf > berry > root (Xie *et al.*, 2002a; Xie *et al.*, 2004b).

Anti-diabetic effect

In our previous study, we used the *ob/ob* mouse model, which exhibits profound obesity and hyperglycemia that phenotypically resemble human type II diabetes. Another animal model, diabetic C57BL/KsJ (*db/db*) mice, was also utilized to test pharmacological effects of Chinese ginseng (*Panax ginseng* C. A. Meyer) berry extract (CGBE). C57BL/KsJ 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 occurred spontaneously (Shafrir, 1992). Through the use these obese and diabetic *ob/ob* and/or *db/db* mice, we have demonstrated that both AGBE and CGBE have the ability to reduce hyperglycemia and body weight (Attele *et al.*, 2002; Xie *et al.*, 2002a; Xie *et al.*, 2002b; Yuan, 2002; Dey *et al.*, 2003).

Table 3 shows the effects of American and Chinese ginseng berry and leaf extracts on fasting blood glucose levels in diabetic *ob/ob* mice. Blood glucose levels after 4 hr fasting in *ob/ob* mice were measured on Day 0, Day 5 and Day 12 after daily intraperitoneal administration of CGBE or AGBE or vehicle. In this experiment, *ob/ob* mice had significantly higher fasting blood glucose levels compared to lean controls on Day 0. On Day 12, *ob/ob* mice treated with AGBE or CGBE have normoglycemic effect. The similar effects of ginseng berry on the blood glucose on Day 5 were also observed in our experiments. The blood glucose concentrations of lean mice, however, did not change sizably in

Table 3. Effect of American ginseng berry extract (AGBE), Chinese ginseng berry extract (CGBE) and American ginseng leaf extract (AGLE, all doses: 150 mg/kg) 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

*P<0.05, **P<0.01 compared to Day 0.

response to treatment with the extracts on either of those days (data did not show in Table 3). The results demonstrated that both AGBE and CGBE possess anti-diabetic property in obese *ob/ob* mice and/or in diabetic *db/db* mice. As previous report (Xie *et al.*, 2002b), *db/db* mice had higher fasting blood glucose levels compared to the lean mice in the control condition. The extract markedly lowered incremental blood glucose level in *db/db* mice.

To explore what chemical constituents of ginseng berry extracts play an important role in the anti-diabetic property, we designed new experiments to test the effect of different chemical constituents of ginseng berry on anti-hyperglycemic activity. We have discovered that both ginsenoside, Re and polysaccharides fraction from American ginseng berry possess the anti-diabetic property (Attele *et al.*, 2002; Xie *et al.*, 2004a). The data indicated that ginsenoside Re, one of the major active molecules from ginseng berry, plays a significant role in anti-hyperglycemic action. This anti-diabetic effect of Re was not associated with body weight changes, suggesting that other constituents in the berry extract have distinct pharmacological actions on energy metabolism. In the other experiments, we observed that another constituent, polysaccharides fraction also possesses anti-diabetic effect both in *ob/ob* and *db/db* mice. The polysaccharides fraction, however, can not affect body weight changes in diabetic mice (Xie *et al.*, 2004a).

Intraperitoneal glucose tolerance test (IPGTT)

To evaluate the peripheral glucose utilization and to determine whether ginseng berry treatment could lead to improvement of glucose tolerance, IPGTT was performed with *ob/ob* and *db/db* mice (Verspohl EJ. 2002). In this test, glucose disposal was evaluated, prior to and 12 days post treatment with the extract or vehicle. The results showed that *db/db* mice had basal hyperglycemia on Day 0, and this hyperglycemia 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 CGBE 150 mg/kg, there was a significantly higher rate of glucose disposal at 30, 60 and 120 min. However, no significant changes were seen in *db/db* mice after treatment with vehicle. The same results were obtained from *ob/ob* mice by using the same IPGTT method (Attele *et al.*, 2002; Xie *et al.*, 2002a). The results indicated that both CGBE and AGBE improved glucose intolerance and increased the peripheral glucose utilization in diabetic animals.

Anti-obese effect

In our experiment (Attele *et al.*, 2002; Xie *et al.*, 2002a), the average body weight of adult *ob/ob* mice is almost twice as great of their lean littermates. Using these animals, we have demonstrated that both AGBE and CGBE decreased body weight significantly. Table 4 shows the effects of AGBE and CGBE on body weight in *ob/ob* mice. The body weight of animals in the vehicle-treated group showed a tendency to increase from Day 0 to Day 12. After treatment with AGBE and CGBE at 150 mg/kg for 12 days, however, body weight reduced markedly. The data strongly suggested that both AGBE and CGBE lowered body weight significantly in obese *ob/ob* mice. More interestingly, following the cessation of treatment of CGBE, *ob/ob* mice gradually regained weight, and their body weight approached that of vehicle treated *ob/ob* mice after 22 days. This result indicates that ginseng berry extract has a prolonged effect of lowering the body weight.

Table 4. Effect of American ginseng berry extract (AGBE), Chinese ginseng berry extract (CGBE) and American ginseng leaf extract (AGLE, all doses: 150 mg/kg) on body weight in *ob/ob* mice

Groups	Body Weight (g)		
	N	Day 0	Day 12
AGBE	8	59.2±0.6	55.0±0.7*
Vehicle	6	58.9±0.7	61.0±0.8
CGBE	8	51.7±1.9	45.7±1.2*
Vehicle	7	53.6±0.7	55.7±0.8
AGLE	5	48.5±0.7	48.9±1.3**
Vehicle	5	49.3±0.9	51.6±0.8

*$P<0.01$, **$P<0.05$ compared to Vehicle group.

Antioxidant effect

It is clear that antioxidant activity is important in diabetes, with low levels of plasma antioxidant implicated as a risk factor for the development of the disease and circulating levels of radical scavengers impaired throughout the progression of diabetes (McCune and Johns, 2002). Therefore, antioxidant property is very significant for anti-diabetic agents. Recently, we used a cardiomyocyte culture model to measure the antioxidant effect of AGBE and ginsenoside, Re (Shao *et al.*, 2004). A significant degree of acute oxidant generation can be induced consistently in this model, which is measured using intracellular fluorescent probes. Effective antioxidant protection by exogenous administration of putative antioxidant compounds can be demonstrated by reduced oxidant-dependant fluorescence and attenuated oxidant-induced cell death. We investigated the antioxidant properties of AGBE in chick cardiomyocytes exposed to exogenous H_2O_2 or to mitochondrial electron transport chain site III inhibitor, Antimycin A. Similar data were obtained in culture cardiac single cells after administration of Re. Our results demonstrated that AGBE and Re attenuated oxidant stress and protected cells from lethal oxidant damage. We concluded that AGBE and Re possess antioxidant property.

GINSENG LEAF

Anti-diabetic effect

There are only scarcity of published reports on ginseng leaf extract and its anti-diabetic effect (Molokovskii *et al.*, 1989; Davydov *et al.*, 1990). One research exhibited that ginseng leaf and root tinctures have anti-hyperglycemic effect in mice and rats with alloxan diabetes (Molokovskii *et al.*, 1989). The authors discussed mechanisms of anti-diabetic, insulinotropic and hypoglucagonemic action of the effective plant pharmaceuticals and the prospects of their use in multimodality therapy of type 1 diabetes. The other report showed that ginseng root and leaf extracts increased the basal content of insulin in blood and the glucose-dependent secretion of this hormone (Davydov *et al.*, 1990).

To further medicinal plant--ginseng, the anti-hyperglycemic property of American ginseng leaf extract (AGLE) was investigated in *ob/ob* mice in our lab by using the similar experimental protocol (Xie *et al.*, 2004b). On Day 12, the glucose levels in ginseng leaf extract-treated groups (150 mg/kg) reduced significantly compared to vehicle group. Therefore, like ginseng berry and root, AGLE also possesses lowering blood glucose effect significantly in *ob/ob* mice. The anti-diabetic activity of AGLE was also demonstrated by IPGTT experiment in our lab.

Effect of AGLE on body weight

Table 3 also displayed the effect of AGLE on body weight in *ob/ob* mice. The data indicated that the body weight of in the vehicle-treated group showed a tendency to increase from Day 0 to Day 12. In the low dose of AGLE (50 mg/kg) group, body weight did not change significantly on Day 5 and Day 12. In the high dose of leaf extract (150 mg/kg) group, body weight did not decrease on Day 12, however, compared to the vehicle group, body weight lowered significantly. The results may demonstrate that, like ginseng berry, AGLE also decreased body weight at a high dose.

POSSIBLE MECHANISMS OF ACTION

The mechanisms for improved blood glucose level associated with ginseng partition extracts and its major active components may be multifaceted, but is still unclear so far. However, there are several plausible hypotheses that may work independently or be generally accepted.

Inhibiting digestion and increasing energy expenditure

A modulating effect of ginseng on digestion may be involved. Our results have demonstrated that

ginseng berry extract significantly decreased food intake activity in *ob/ob* mice that decreased the source of sugar (Attele *et al.*, 2002). Energy expenditure values were obtained in *ob/ob* mice treated with vehicle or CGBE. After the 12-day treatment, there was a significant increase in energy expenditure of the berry extract-treated group compared to the vehicle-treated group. On the other hand, we also have demonstrated that ginseng berry extract increased body temperature significantly in *ob/ob* mice. Increase in body temperature suggested that the carbohydrate metabolism in the mice should be enhanced, consistent with the increased basal metabolic rate.

Another possible site of action for ginseng berry extract that contributes to its hypoglycemic effect is in the gastrointestinal action. Gastric vagal afferents are the primary neuroanatomical link between the stomach and the CNS. In a previous study, we reported that ginseng extract, via gastric vagal afferents, inhibited brainstem neuronal activity (Yuan *et al.*, 1998). The other report indicated that ginseng extract inhibited intestinal glucose absorption (Chung *et al.*, 2001) and gastric secretion was inhibited by ginseng (Suzuki *et al.*, 1991). These results suggest that ginseng extracts may slow the digestion of food and decrease the rate of carbohydrate absorption. Inhibiting digestion should diminish the sources of blood glucose and increasing energy expenditure should enhance expending of glucose. The total result is that the blood sugar should be lowered in the animals.

Improving sensitivity to insulin and change blood insulin level

Prospective studies of populations at high risk for type II diabetes suggest that in most patients, the initial inherited lesion is insulin resistance (Lillioja *et al.*, 1993; Taylor *et al.*, 1994). The *ob/ob* mice mimic these characteristics of type II diabetes mellitus and demonstrate insulin resistance and hyperinsulinemia, by six weeks of age (Genuth *et al.*, 1971). Our study confirmed these characteristics and showed reduced glucose disposal rates during the glucose clamp study in vehicle-treated *ob/ob* mice, which suggested insulin resistance partly due to reduced insulin receptor sensitivity. Treatment with ginseng berry extract improved peripheral insulin action as suggested by the significantly improved insulin-stimulated glucose disposal. Improvement in peripheral insulin sensitivity should increase tissue glucose uptake and utilizing, lowering blood glucose levels towards normal (Attele *et al.*, 2002), and should also result in reduced insulin requirement. This is consistent with our data, which demonstrates significant reduction in serum insulin levels following treatment with ginseng berry extract, accompanied by improved peripheral insulin action.

While we have indicated a decreased serum insulin level with ginseng treatment, there are reports in the literature that ginseng treatment increased serum insulin. Kimura *et al* demonstrated that administration of ginseng fractions to alloxan-treated rats resulted in increased serum insulin levels (Kimura *et al.*, 1981a). Obviously the effect of ginseng on the serum insulin level is dependent on the animal model used. The *ob/ob* mice show typical characteristics similar to type II diabetes mellitus, where impaired glucose tolerance is caused by decreased peripheral insulin sensitivity and a compensatory excess insulin release, which is corrected by ginseng treatment. On the other hand, alloxan-treated diabetic animal model is characterized by chemical destruction of pancreatic islets and a decreased insulin level. Ginseng treatment in this model caused stimulation of the residual islets and increased serum insulin and glucose-stimulated insulin secretion (Kimura *et al.*, 1981a). Since nitric oxide (NO) is known to stimulate glucose-dependent secretion of insulin in rat islet cells (Spinas *et al.*, 1998), ginseng extract could have mediated the insulin release through NO release (Gillis, 1997; Roy *et al.*, 1998). Thus, ginseng may act through both mechanisms in exerting its anti-diabetic effect; however, the more relevant mechanism in the type II diabetes model

would be improved insulin sensitivity and thereby reducing insulin requirements and resultant decreased serum insulin.

Insulin resistance is very often accompanied by obesity. Obesity not only increases the chance of developing type II diabetes, it is independently associated with insulin resistance and other morbidity (Kruszynska and Olefsky, 1996). Thus, the insulin resistance in obese patients with type II diabetes is significantly worse than the insulin resistance of non-obese diabetic individuals (Seely and Olefsky, 1993). Therapeutic agents with both anti-diabetic and anti-obese effects are, therefore, particularly beneficial. Our results show that *ob/ob* mice treated with ginseng berry extract underwent a dose- and time-dependent reduction in body weight. In this study, we observed, for the first time, that both American and Chinese ginseng berry has an anti-obese effect in addition to an anti-diabetic effect. It is yet to be determined whether this anti-diabetic effect is primarily due to the anti-obese action of the ginseng berry. Other studies have shown that insulin sensitivity in type II diabetes patients improves with body weight loss, possibly due to an improvement in insulin-stimulated glucose transport into muscle (DeFronzo and Ferrannini, 1991; Friedman *et al.*, 1992). A similar mechanism may operate in ginseng berry extract-treated *ob/ob* mice to improve insulin resistance. The extract could exert its anti-diabetic effect through action, which involves improvement of insulin receptor sensitivity.

Other possible mechanisms

Increasing glucose transporter protein (Attele and Xie, 2002): Ginseng part extracts may exert the anti-diabetic effect through modulation of glucose transport measured the glucose transporter (GLUT2) protein content in hyperglycemic mice was measured in a study (Ohnishi *et al.*, 1996). The data indicated that the hypoglycemic activity of ginseng radix is presumably due, at least in part, to the increment of glucose transporter protein content. This action may be mediated by NO (Roy *et al.*, 1998). This study showed 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 (Gillis, 1997).

Wang *et al* have demonstrated that ginseng glycopeptides lowered blood glucose significantly and liver glycogen levels both in normal and hyperglycemic animals, including rats, mice and rabbits (Wang *et al.*, 2003a, Wang *et al.*, 2003b). Advanced study indicated that the anti-hyperglycemic effect of glycopeptides might be attributed to the enhancement of aerobic glycolysis through stimulation of β-adrenoceptor and increase of various rate-limiting enzyme activities related to tricarboxylic acid cycle. To date, the anti-diabetic mechanism of ginseng is not very clear and more extensive studies are needed to elucidate the mechanisms of action.

In summary, the partitions of ginseng possess multiple constituents and multifaceted pharmacological actions. Both American and Chinese ginseng, including root, berry, leaf, and stem, and their constituents have an ability to reduce blood glucose level. The anti-diabetic effect of ginseng may provide an opportunity to develop one or more new anti-diabetic agents if these data can be validated in future clinical trails.

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REFERENCES

Ackerknecht EH. A short history of medicine. Baltimore/London: Johns Hopkins University Press, 1982.

Attele AS, Wu JA, Yuan CS. (1999) Ginseng pharmacology: multiple constituents and multiple actions. *Biochem. Pharmacol.* **58**, 1685-1693.

Attele AS, Xie JT. (2002) Evidence based herbal pharmacology: An example using ginseng. In: *A*

textbook of complementary and alternative therapies, edited by Beiber E. pp. 202-218 CRC Press Company, Boca Raton, London, New York, Washington, D.C.

Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, Yuan CS. (2002) Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component. *Diabetes* **51,** 1851-1858.

Awang DVC. (1998) The anti-stress potential of North American ginseng (Panax Quinquefolius L.). *J. Herbs Spices Med. Plants* **6,** 87-91.

Banerjee U, Izquierdo JA. (1982) Antistress and antifatigue properties of Panax ginseng: comparison with piracetam. *Acta Physiol. Lat. Am.* **32,** 277-285.

Benishin CG, Lee R, Wang LC, Liu HJ. (1991) Effects of ginsenoside Rb_1 on central cholinergic metabolism. *Pharmacology* **42,** 223-229.

Bensky D, Gamble A. (1993) Chinese Herbal Medicine, Materia Medica. In: *Ginseng*. pp. 314-317 Eastland Press, Seattle, WA.

Bhattacharya SK, Mitra SK. (1991) Anxiolytic activity of Panax ginseng roots: an experimental study. *J. Ethnopharmacol.* **34,** 87-92.

Broadhurst CL, Polansky MM, Anderson RA. (2000) Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro. *J. Agric. Food. Chem.* **48,** 849-852.

Chen X, Lee TJ. (1995) Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. *Br. J. Pharmacol.* **115,** 15-18.

Chen X. (1996) Cardiovascular protection by ginsenosides and their nitric oxide releasing action. *Clin. Exp. Pharmacol. Physiol.* **23,** 728-732.

Cheung SC, Kwan PS, Kong YC. (1983) An Introduction to Pen-ts'ao Study. In: *Ben cao yan jiu ru men*, edited by Zhuang ZX, pp. 162, Chinese University Press, Hong Kong.

Cho YK, Sung H, Lee HJ, Joo CH, Cho GJ. (2001) Long-term intake of Korean red ginseng in HIV-1-infected patients: development of resistance mutation to zidovudine is delayed. *Int. Immunopharmacol.* **1,** 1295-1305.

Choo MK, Park EK, Han MJ, Kim DH. (2003) Antiallergic activity of ginseng and its ginsenosides. *Planta Med.* **69,** 518-522.

Chung SH, Choi CG, Park SH. (2001) Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKAy mice. *Arch. Pharm. Res.* **24,** 214-218.

Cui X. (1997) Orally administered ginseng extract stimulates liver regeneration in partially hepatectomized rats. *Acta. Med. Biol.* **45,** 161-166.

Davydov VV, Molokovskii DS, Limarenko A. (1990) Efficacy of ginseng drugs in experimental insulin-dependent diabetes and toxic hepatitis. *Patol. Fiziol. Eksp. Ter.* **5,** 49-52.

DeFronzo RA, Ferrannini E. (1991) Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* **14,** 173-194.

Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan CS. (2003) Anti-hyperglycemic effects of ginseng: comparison between root and berry. *Phytomedicine* **10,** 600-605.

Friedman JE, Dohm GL, Leggett-Frazier N, Elton CW, Tapscott EB, Pories WP, Caro JF. (1992) Restoration of insulin responsiveness in skeletal muscle of morbidly obese patients after weight loss. Effect on muscle glucose transport and glucose transporter GLUT4. *J. Clin. Invest.* **89,** 701-705.

Gaffney BT, Hugel HM, Rich PA. (2001) Panax ginseng and Eleutherococcus senticosus may exaggerate an already existing biphasic response to stress via inhibition of enzymes which limit the binding of stress hormones to their receptors. *Med. Hypotheses* **56,** 567-572.

Genuth SM, Przybylski RJ, Rosenberg DM. (1971) Insulin resistance in genetically obese, hyperglycemic mice. *Endocrinology* **88,** 1230-1238.

Gillis CN. (1997) Panax ginseng pharmacology: a nitric oxide link? *Biochem. Pharmacol.* **54,** 1-8.

Han KH, Choe SC, Kim HS, Sohn DW, Nam KY, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. (1998) Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension. *Am. J. Chin. Med.* **26,** 199-209.

Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. (2001) Variability in commercial ginseng products: an analysis of 25 preparations. *Am. J. Clin. Nutr.* **73,** 1101-1106.

Hasegawa H, Saiki I. (2003) Cancer prevention by ginseng via it intestinal bacterial metabolites. pp. 16-26. Yushima, Bunkyu-ku, Tokyo, Japan: Art Village Inc.

Hu SY. (1977) A contribution to our knowledge of ginseng. *Am. J. Chin. Med.* **5,** 1-23.

Huang K. (1999) *The Pharmacology of Chinese Herbs.* Edited by Huang KC, pp. 17-44, Boca Raton, FL.: CRC Press.

Inoue M, Wu CZ, Dou DQ, Chen YJ, Ogihara Y. (1999) Lipoprotein lipase activation by red ginseng saponins in hyperlipidemia model animals. *Phytomedicine* **6,** 257-265.

Jeon BH, Kim CS, Park KS, Lee JW, Park JB, Kim K-J, Kim SH, Chang SJ, Nam KY. (2000) Effects of Korea red ginseng on the blood pressure in conscious hypertensive rats. *Gen. Pharmacol.* **35,** 135-141.

Kaku T, Miyata T, Sako I, Kinoshita A. (1975) Chemico-pharmacological studies on saponins of Panax ginseng. *Arzneim. Forsch.* **25,** 539-547.

Kang SY, Kim SH, Schini VB, Kim ND. (1995) Dietary ginsenosides improve endothelium-dependent relaxation in the thoracic aorta of hypercholesterolemic rabbit. *Gen. Pharmacol.* **26,** 483-487.

Kang SY, Kim SH, Schini VB, Kim ND. (1995) Dietary ginsenosides improve endothelium-dependent relaxation in the thoracic aorta of hypercholesterolemic rabbit. *Gen. Pharmacol.* **26,** 483-487.

Kase Y, Saitoh K, Makino B, Hashimoto K, Ishige A, Komatsu Y. (1999) Relationship between the antidiarrhoeal effects of Hange-Shashin-To and its active components. *Phytother. Res.* **13,** 468-473.

Kim DH, Moon YS, Jung JS, Min SK, Son BK, Suh HW, Song DK. (2003) Effects of ginseng saponin administered intraperitoneally on the hypothalamo-pituitary-adrenal axis in mice. *Neurosci. Lett. Suppl.* **343,** 62-66.

Kim H, Chen X, Gillis CN. (1992) Ginsenosides protect pulmonary vascular endothelium against free radical-induced injury. *Biochem. Biophys. Res. Commun.* **189,** 670-676.

Kim JY, Germolec DR, Luster MI. (1990) Panax ginseng as a poential immunomodulator: studies in mice. *Immunopharmacol. Immunotoxicol.* **12,** 2578.

Kim YR, Lee SY, Shin BA, Kim KM. (1999) Panax ginseng blocks morphine-induced thymic apoptosis by induction plasma corticosterone level. *Gen. Pharmacol.* **32,** 647-652.

Kim YS. (1990) Protective effect of ginseng polysaccharude fraction on CCl_4-induced hepatotoxicity in vitro and in vivo. *Korean J. Ginseng Sci.* **19,** 108-113.

Kimura I, Nakashima N, Sugihara Y, Fu-jun C, Kimura M. (1999) The antihyperglycaemic blend effect of traditional Chinese medicine byakko-ka-ninjin-to on alloxan and diabetic KK-CA(y) mice. *Phytother. Res.* **13,** 484-488.

Kimura M, Suzuki J, Koizumi T. (1981a) Glucose tolerance curves in genetically diabetic KK-CAy mice: the pharmacokinetic analysis for humping effect. *J. Pharmacobio-Dyn.* **4,** 149-161.

Kimura M, Suzuki J. (1981) The pattern of action of blended Chinese medicine to glucose tolerance curves in genetically diabetic KK-CAy mice. *J. Pharm. Dyn.* **4,** 907-915. saponin

Kimura M, Waki I, Chujo T, Kikuchi T, Hiyama C, Yamazaki K, Tanaka O. (1981b) Effects of hypoglycemic components in ginseng radix on blood insulin level in alloxan diabetic mice and on insulin release from perfused rat pancreas. *J. Pharmacobio-Dyn.* **4,** 410-417.

Kimura M. Hypoglycemic component in ginseng radix and its insulin release. In: *Proceedings of the 3rd International Ginseng Symposium.* Korean Ginseng Research Institute, Seoul, Korea, 1980.

Kitts DD, Wijewickreme AN, Hu C. (2000) Antioxidant properties of a North American ginseng extract. *Mol. Cell. Biochem.* **203,** 1-10.

Konno C, Murakami M, Oshima Y, Hikino H. (1985) Isolation and hypoglycemic activity of panaxans Q, R, S, T and U, glycans of Panax ginseng roots. *J. Ethnopharmacol.* **14,** 69-74.

Konno C, Sugiyama K, Kano M, Takahashi M, Hikino H. (1984) Isolation and hypoglycaemic activity of panaxans A, B, C, D and E, glycans of Panax ginseng roots. *Planta Med.* **50,** 434-436.

Kruszynska YT, Olefsky JM. (1996) Cellular and molecular mechanisms of non-insulin dependent diabetes mellitus. *J. Invest. Med.* **44,** 413-428.

Lee DC, Lee MO, Kim CY, Clifford DH. (1981) Effect of ether, ethanol and aqueous extracts of ginseng on cardiovascular function in dogs. *Canadian Journal of Comparative Medicine* **45,** 182-187.

Lee FC. (1992) *Facts about Ginseng, the Elixir of Life.* Edited by Lee FC, pp. 13-23, Elizabeth, NJ: Hollyn International Corp.

Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. (1993) Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent

diabetes mellitus. Prospective studies of Pima Indians. *N. Engl. J. Med.* **329,** 1988-1992.

Liu D, Li B, Liu Y, Attele AS, Kyle JW, Yuan CS. (2001) Voltage-dependent inhibition of brain Na^+ Channels by American ginseng. *Eur. J. Pharmcol.* **413,** 47-54.

Maffei Facino R, Carini M, Aldini G, Berti F, Rossoni G. (1999) Panax ginseng administration in the rat prevents myocardial ischemia-reperfusion damage induced by hyperbaric oxygen: evidence for an antioxidant intervention. *Planta Med.* **65,** 614-619.

McCune LM, Johns T. (2002) Antioxidant activity in medicinal plants associated with the symptoms of diabetes mellitus used by the indigenous peoples of the North American boreal forest. *J. Ethnopharmacol.* **82,** 197-205.

Miller LG. (1998) Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch. Intern. Med.* **158,** 2200-2211.

Mochizuki M, Yoo YC, Matsuzawa K, Sato K, Saiki I, Tono-oka S, Samukawa K, Azuma I. (1995) Inhibitory effect of tumor metastasis in mice by saponins, ginsenoside-Rb2, 20(R)- and 20(S)-ginsenoside-Rg3, of red ginseng. *Biol. Pharm. Bull.* **18,** 1197-1202.

Molokovskii DS, Davydov VV, Tiulenev VV. (1989) Deistvie adaptogennykh fitopreparatov pri eksperimental' nom alloksanovom diabete. *Problemy. Endokrinologii.* **35,** 82-87.

Murphy L, Lee T. (2002) Ginseng, sex behavior, and nitric oxide. *Ann. NY. Acad. Sci.* **962,** 372-377.

Murphy LL, Cadena RS, Chavez D, Ferraro JS. (1998) Effect of American ginseng (*Panax quinquefolium*) on male copulatory behavior in the rat. *Physiol. Behav.* **64,** 445-450.

Ng TB, Yeung HW. (1985) Hypoglycemic constituents of Panax ginseng. *Gen. Pharmacol.* **16,** 549-552.

Ohnishi Y, Takagi S, Miura T, Usami M, Kako M, Ishihara E, Yano H, Tanigawa K, Seino Y. (1996) Effect of ginseng radix on $GLUT_2$ protein content in mouse liver in normal and epinephrine-induced hyperglycemic mice. *Biol. Pharmaceutic. Bull.* **19,** 1238-1240.

Oshima Y, Konno C, Hikino H. (1985) Isolation and hypoglycemic activity of panaxans I, J, K and L, glycans of Panax ginseng roots. *J. Ethnopharmacol.* **14,** 255-259.

Oshima Y, Sato K, Hikino H. (1987) Isolation and hypoglycemic activity of quinquefolans A, B, and C, glycans of Panax quinquefolium roots. *J. Nat. Prod.* **50,** 188-190.

Park EK, Choo MK, Han MJ, Kim DH. (2004a) Ginsenoside Rh1 possesses antiallergic and anti-Inflammatory activities. *Int. Arch. Allergy. Immunol.* **133,** 113-120.

Park EK, Choo MK, Oh JK, Ryu JH, Kim DH. (2004b) Ginsenoside Rh_2 reduces ischemic brain injury in rats. *Biol. Pharm. Bull.* **27,** 433-436.

Petkov VD, Mosharrof AH. (1987) Effects of standardized ginseng extract on learning, memory and physical capabilities. *Am. J. Chin. Med.* **15,** 19-29.

Rang HP, Dale MM. (1991) *The endocrine system pharmacology,* Second ed. pp.504-508, UK. Longman Group Ltd.

Rimar S, Lee-Mengel M, Gillis CN. (1996) Pulmonary protective and vasodilator effects of a standardized Panax ginseng preparation following artificial gastric digestion. *Pulm. Pharmacol.* **9,** 205-209.

Roy D, Perreault M, Marette A. (1998) Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO dependent. *Am. J. Physiol.* **274,** E692-699.

Saito H, Tsuchiya M, Naka S, Takagi K. (1977) Effects of *Panax Ginseng* root on conditioned avoidance response in rats. *Jpn. J. Pharmacol.* **27,** 509-516.

Seely B, Olefsky J. (1993) Potential cellular and genetic mechanisms for insulin resistance in common disorders of obesity and diabetes. In: *Insulin resistance and its clinical disorders,* edited by Moller D. pp. 187 252 Chichester, John Wiley & Sons.

Shafrir E. (1992) Animal models of non-insulin-dependent diabetes. *Diabetes Metab. Rev.* **8,** 179-208.

Shao ZH, Xie JT, Vanden Hoek TL, Mehendale S, Aung H, Li CQ, Qin Y, Schumacker PT, Becker LB, Yuan CS. (2004) Antioxidant effects of American ginseng berry extract in cardiomyocytes exposed to acute oxidant stress. *Biochim. Biophys. Acta* **1670,** 165-171.

Siegel RK. (1979) Ginseng abuse syndrome. Problems with the panacea. *JAMA.* **241,** 1614-1615.

Skyler JS. (2004) Diabetes mellitus: Pathogenesis and treatment strategies. *J. Med. Chem.* **47,** 4113-4117.

Sohn HO, Lim HB, Lee YG, Lee DW, Kim YT. (1993) Effect of subchronic administration of antioxidants

against cigarette smoke exposure in rats. *Arch. Toxicol.* **67,** 667-673.

Sotaniemi EA, Haapakoski E, Rautio A. (1995) Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetes Care* **18,** 1373-1375.

Spinas GA, Laffranchi R, Francoys I, David I, Richter C, Reinecke M. (1998) The early phase of glucose-stimulated insulin secretion requires nitric oxide. *Diabetologia* **41,** 292-299.

Sun XB, Matsumoto T, Kiyohara H, Hirano M, Yamada H. (1991) Cytoprotective activity of pectic polysaccharides from the root of panax ginseng. *J. Ethnopharmacol.* **31,** 101-107.

Suzuki Y, Ito Y, Konno C, Furuya T. (1991) Effects of tissue cultured of ginseng on gastric secretion and pepsin activity. *Yakugaku Zasshi.* **111,** 770-774.

Takemoto Y, Ueyama T, Saito H, Horio S, Sanada S, Shoji J, Yahara S, Tanaka O, Shibata S. (1984) Potentiation of nerve growth factor-mediated nerve fiber production in organ cultures of chicken embryonic ganglia by ginseng saponins: structure--activity relationship. *Chem. Pharm. Bull.* **32,** 3128-3133.

Taylor SI, Accili D, Imai Y. (1994) Insulin resistance or insulin deficiency. Which is the primary cause of NIDDM? *Diabetes* **43,** 735-740.

Toh H. (1994) Improved isolated heart contractility and mitochondrial oxidantion after chronic treatment with Panax ginseng in rats. *Am. J. Chin. Med.* **22,** 275-284.

Tomoda M, Shimada K, Konno C, Sugiyama K, Hikino H. (1984) Partial structure of panaxan A, a hypoglycaemic glycan of Panax ginseng roots. *Planta Med.* **50,** 436-438.

Verspohl EJ. (2002) Recommended testing in diabetes research. *Planta Med.* **68,** 581-590.

Vuksan V, Sievenpiper JL, Koo VY, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E. (2000-a) American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch. Intern. Med.* **160,** 1009-1013.

Vuksan V, Stavro MP, Sievenpiper JL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Xu Z. (2000-b) Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. *Diabetes Care* **23,** 1221-1226.

Wakabayashi C, Murakami K, Hasegawa H, Murata J, Saiki I. (1998) An intestinal bacterial metabolite of ginseng protopanaxadiol saponins has the ability to induce apoptosis in tumor cells. *Biochem. Biophys. Res. Commun.* **246,** 725-730.

Waki I, Kyo H, Yasuda M, Kimura M. (1982) Effects of a hypoglycemic component of ginseng radix on insulin biosynthesis in normal and diabetic animals. *J. Pharmacobiodyn.* **5,** 547-554.

Wang B. (1965) Advances in study of pharmacology of ginseng. *Acta Pharmaceut. Sin.* **12,** 477-586.

Wang B. (1980) Recent advances in study of pharmacology of ginseng. *Acta Pharmaceut. Sin.* **15,** 312-320.

Wang B. (1984) The ginseng research, Tianjin, China: Tianjin Scientific Publisher, p 135.

Wang BX, Zhou QL, Yang M, Wang Y, Cui ZY, Liu YQ, Ikejima T. (2003a) Hypoglycemic activity of ginseng glycopeptide. *Acta Pharmacol. Sin.* **24,** 50-54.

Wang BX, Zhou QL, Yang M, Wang Y, Cui ZY, Liu YQ, Ikejima T. (2003b) Hypoglycemic mechanism of ginseng glycopeptide. *Acta Pharmacol. Sin.* **24,** 61-66.

World Health Organization. (1999) Radix Ginseng. In: *WHO monographs on selected medicinal plants (Volume 1).* pp. 168-182, Malta, Geneva.

Xie JT, Aung HH, Wu JA, Attele AS, Yuan CS. (2002a) Effects of American ginseng berry extract on blood glucose levels in *ob/ob* mice. *Am. J. Chin. Med.* **30,** 187-194.

Xie JT, Dey L, Wu J, Yuan C. (2004a) Anti-hyperglycemic effect of polysaccharides fraction from American ginseng beery extract in *ob/ob* mice. *Phytomedicine* **11,** 182-187.

Xie JT, Mehendale A, Wang A, Aung H, Wu J, Osinski J, Yuan CS. (2004b) American ginseng leaf: Ginsenoside analysis and hypoglycemic activity. *Pharmacol. Res.* **49,** 113-117.

Xie JT, Zhou YP, Dey L, Attele A, Wu J, Gu M, Polonnsky K, Yuan C. (2002b) Ginseng berry reduces blood glucose and body weight in *db/db* mice. *Phytomedicine* **9,** 254-258.

Yokozawa T, Kobayashi T, Oura H, Kawashima Y. (1985) Studies on the mechanism of the hypoglycemic activity of ginsenoside-Rb2 in streptozotocin-diabetic rats. *Chem. Pharm. Bull. (Tokyo)* **33,** 869-872.

Yokozawa T, Zhou J, Hattori M, Inaba S, Okada T,

Oura H. (1994) Effects of ginseng in nephrectomized rats. *Biol. Pharm. Bull.* **17,** 1485-1489.

Yoshizato H, Fujikawa T, Shibata M, Tanaka M, Nakashima K. (1999) Stimulation of growth hormone gene expression in the pituitary and brain by *Panax ginseng* C. A. MEYER. *Endocr. J.* **46 (Suppl),** S85-S88.

You J, Hau D, Chen K, Huang H. (1995) Combined effects of ginseng and radiotherapy on experiemntal liver cance. *Phytother. Res.* **9,** 331-335.

Yuan CS, Wu JA, Lowell T, Gu M. (1998) Gut and brain effects of American ginseng root on brainstem neuronal activities in rats. *Am. J. Chin. Med.* **26,** 47-55.

Yuan CS. (2002) Anti-diabetic and anti-obese effects of ginseng: From root to berry. In: *Advances in ginseng research,* edited by Baek IN. pp. 129-144 The Korean Society of Ginseng, Seoul, Korea.

Yun T, Choi S. (1995) Preventive effect of ginseng intake against various human cancers: a case study on 1987 pairs. *Cancer Epidem Biomarker Prev.* **4,** 401-408.

Yun Y, Lee Y, Jo S, IS. J. (1993) Inhibition of autochthonous tumor by ethanol insoluble fraction from Panax ginseng as an immunomodulator. *Planta Med.* **59,** 521-524.

Zhan Y, Xu XH, Jiang YP. (1994) Effects of ginsenosides on myocardial ischemia/reperfusion damage in open-heart surgery patients. *Med. J. China.* **74,** 626-628.

Zhang Y, Liu T. (1994) Protective effects of total saponins of P ginseng on ischemia-reperfusion injury in rat brains. *Chin. J. Pharmacol. Toxicol.* **8,** 7-12.

Zhao R, McDaniel W. (1998) Ginseng improves strategic learning by normal and brain-damaged rat. *Neuro. Rep.* **9,** 1619-1624.

Zhonghua Bencao Editor. Zhonghua Bencao (Chinese Herbal Medicine). P. 1269-1298. Shanghai Science and Technology House. 1996.