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Ginseng and Diabetes

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Abstract: Ginseng is a well-known medicinal plant used in traditional Oriental medicine. In recent decades, ginseng root has gained popularity as a dietary supplement in the United States. Ginseng has also been commonly used in Oriental medicine to treat diabetes-like conditions. The present review discusses the research on the anti-diabetic effects of ginseng and the possible mechanisms of its anti-diabetic actions.

Keywords: Ginseng; Root; Berry; Leaf; Anti-diabetic Effect; Anti-Obese Effect; *Panax ginseng*; *Panax quinquefolius*.

History of Ginseng and Its Use in Diabetes

Ginseng, often described as the "king herb," holds an important position in traditional Oriental medicine in many countries. The highly valued plant is currently cultivated in China, Korea, Japan, Russia, and in the United States and Canada as well (Lee, 1992). Of the several species of ginseng, the root of the Asian and American varieties (*Panax ginseng* C.A. Meyer and *Panax quinquefolius* L., respectively) is a popular dietary supplement in the United States (Harkey *et al.*, 2001; Barnes *et al.*, 2004).

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 2000 years ago (Huang, 1999). Ginseng was introduced outside the Oriental countries by Arabs, probably in the 9th century (Phillipson and Anderson, 1984). The accounts by Marco Polo, the most famous of medieval European travelers in the 13th century, describe Chinese ginseng being brought to Europe possibly along with the silk trade. Gradually, the herb was brought to the attention of scientists in Europe and North America (Blumenthal *et al.*, 2000). The increasing interest of the scientific community in ginseng's medicinal use is demonstrated by the fact that, to date, over 2000 papers have been published on the multiple chemical components and the

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multifaceted pharmacological actions of ginseng root and its principal active components, ginsenosides (Lee, 1992; Gillis, 1997; Attele *et al.*, 1999; Attele *et al.*, 2002; Hasegawa and Saiki, 2003).

Historical records on traditional medicinal systems reveal that ginseng root was used to treat a disease corresponding to diabetes (Ackerknecht, 1982). Description of ginseng's medicinal effects found in the ancient Chinese materia medica (Huang, 1999) contained a reference to ginseng's ability to "quench thirst," amongst the other wide-ranging beneficial effects (Cheung *et al.*, 1983). This effect, as per traditional Chinese medicine, could be related to the anti-diabetic activity of ginseng. Research on the effects of treatment with 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). Results of *in vitro* studies, animal experiments (Kimura *et al.*, 1981a and b; Yokozawa *et al.*, 1985), and clinical trials (Sotaniemi *et al.*, 1995; Vuksan *et al.*, 2000) strongly support the claim that ginseng root possesses anti-diabetic properties.

The need to further explore potent herbs like ginseng in the treatment of type 2 diabetes arises from the fact that the initial line of therapy of oral anti-diabetic drugs is unable to maintain long-term glycemic control (Charpentier, 2002). The failure of these drugs is caused by the continually deteriorating function of insulin-producing pancreatic β cells (Skyler, 2004). The poor glycemic control causes high morbidity, which could be improved only by initiation of insulin therapy. Therefore novel therapies, herbal and others, are being researched for agents that improve glycemic control by preserving β cell function, and result in delaying or preventing insulin use. Since an herb/herbal medication, with its variety of constituents, is postulated to act via complementary mechanisms, it is possible that ginseng targets various pathogenic mechanisms in diabetes. It is definitely worthwhile, therefore, to research ginseng as a therapeutic option for long-term glycemic control (Kimura *et al.*, 1981a; Waki *et al.*, 1982; Attele *et al.*, 2002; Rotshteyn and Zito, 2004; Xie *et al.*, 2005).

Constituents of Ginseng

The root of the ginseng plant is constituted of organic (80%–90%) and inorganic substances (approximately 10%) and consists of a number of active constituents, such as saponins or ginsenosides, carbohydrates (including polysaccharides), nitrogenous substances, amino acids, peptides, phytosterol, essential oils, organic acids, vitamins, and minerals (Hasegawa and Saiki, 2003). Of these, the extract fractions containing ginsenosides and polysaccharides have demonstrated hypoglycemic activity.

Ginsenosides are the principal bioactive constituents of ginseng that have also been used as marker compounds for the *Panax* species (Attele *et al.*, 1999; Harkey *et al.*, 2001). We analyzed the ginsenoside content of the 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 (Xie *et al.*, 2002a and 2004a). Additionally, we also demonstrated that the profile of six main ginsenosides, (Rb_1, Rb_2, Rc, Rd, Re, and Rg_1) in the root, berry, and leaf extracts were different. Since some ginsenosides have demonstrated hypoglycemic properties, it is possible that relative concentrations of specific ginsenosides determine the anti-diabetic activity of the different plant parts of ginseng (Xie *et al.*, 2005; Waki *et al.*, 1982).

Anti-diabetic Effects of Ginseng

The hypoglycemic ability of ginseng root extracts has been known since a few decades. Our laboratory has recently demonstrated a similar activity in the berry and leaf extracts of Asian ginseng (*Panax ginseng* C.A. Meyer) and American ginseng (*Panax quinquefolius* L.) in diabetic and obese transgenic mouse models (Attele *et al.*, 2002; Yuan, 2002; Xie *et al.*, 2002a and b; Dey *et al.*, 2002 and 2003; Xie *et al.*, 2004a). The total ginsenoside concentration and the proportion of specific ginsenosides in the root, berry, and leaf of ginseng plants are different and could account for the differences in their anti-diabetic effects, which are described in the following sections.

Ginseng Root

Asian ginseng root extracts administered to alloxan-treated and genetic (KK-CAy mice) diabetic mouse models decreased blood glucose levels significantly (Kimura *et al.*, 1981a and b; Waki *et al.*, 1982; Molokovskii *et al.*, 1989). Some observed acute effects such as increased blood insulin level, reduced blood glucagon level, and increased hepatic glycogen deposition support ginseng's anti-diabetic effects. Complex components in the carbohydrate fraction of ginseng root extract, including different panaxans A, B, C, D, E, panaxans I, J, K, L, and panaxans Q, R, S, T, U also demonstrated hypoglycemic properties in normal and alloxan-induced hyperglycemic mice (Konno *et al.*, 1984 and 1985; Oshima *et al.*, 1985). Similar to Asian ginseng, three constituents obtained from the water extracts of American ginseng root, viz. quinquefolans A, B, and C displayed hypoglycemic actions in normal and hyperglycemic mice (Oshima *et al.*, 1987). A subsequent study showed that both ginseng radix and its rootlet have distinct anti-diabetic properties (Chung *et al.*, 2001).

Few clinical studies have also supported the efficacy of ginseng root in type 2 diabetic patients. A double blind, placebo-controlled study in which ginseng root tablets (100 or 200 mg daily for 8 weeks) were orally administered to 36 newly diagnosed type 2 diabetes patients showed a reduction in fasting blood glucose and glycosylated hemoglobin (Sotaniemi *et al.*, 1995). Other clinical trials have also reported anti-hyperglycemic activity when a single dose of 3 g American ginseng root was administered in both non-diabetic and type 2 diabetic individuals (Vuksan *et al.*, 2000).

Ginseng Berry

Until recently, any reference to ginseng has been synonymous with the dried main root of ginseng. Researchers believed that nutrients did not accumulate beyond the root, and thus shied away from testing the berry and leaf for medicinal effects. Not surprisingly, there was no information on the biological activity of ginseng berry prior to our report. We recently demonstrated significant anti-hyperglycemic activity in the ginseng berry extract (Xie *et al.*, 2002a and b; Yuan, 2002; Attele *et al.*, 2002; Dey *et al.*, 2003).

We used the C57BL/6J (*ob*/*ob*) mouse model, which exhibits profound obesity and hyperglycemia to test the pharmacological effects of ginseng berry. The model phenotypically resembles human type 2 diabetes (Shafrir, 1992). Another mouse model, the diabetic C57BL/KsJ (*db*/*db*) mice, which demonstrates a more severe form of hyperglycemia (Shafrir, 1992), was also used. We demonstrated that both American and Asian ginseng berry extracts reduce fasting hyperglycemia and body weight following a 12-day treatment (Xie *et al.*, 2002a and b; Yuan, 2002; Attele *et al.*, 2002; Dey *et al.*, 2003). Our results indicated that berry extracts improve glucose tolerance significantly, which suggests that insulin sensitivity improved with the treatment. When comparing the effects of the Asian ginseng root and berry, we found that the berry extract exhibited significantly more potent anti-diabetic effects than the root extract (Dey *et al.*, 2003). We propose that the difference in ginsenoside Re content between root and berry extracts, as suggested by our HPLC analysis, may account for the difference in the pharmacology (Attele *et al.*, 2002; Xie *et al.*, 2004a). We also observed that the polysaccharide fraction from American ginseng berry possesses anti-diabetic property (Xie *et al.*, 2004b), similar to the polysaccharide fractions of the root extracts.

In addition to decrease in blood glucose levels, we observed a significant weight-reducing effect of American and Asian ginseng berry extracts in *ob*/*ob* and *db*/*db* mice, which was not observed in animals treated with the root extracts (Xie *et al.*, 2002b; Attele *et al.*, 2002). The weight reducing property was further stressed by the fact that *ob*/*ob* mice gradually regained weight comparable to the vehicle-treated *ob*/*ob* mice within 10 days of cessation of treatment with the berry extract (Xie *et al.*, 2002b; Attele *et al.*, 2002). These results indicate that long-term administration of ginseng berry extract may result in reduced body weight. Since weight reduction is associated with improvement in insulin resistance (Wing *et al.*, 1994), this might be one of the mechanisms by which ginseng exerts anti-diabetic effects.

Ginseng Leaf

There is a scarcity of reports investigating the anti-diabetic effect of ginseng leaf extract. One study demonstrated an anti-hyperglycemic effect of ginseng leaf in mice and rats with alloxan-induced diabetes (Molokovskii *et al.*, 1989). The other report showed that treatment with ginseng leaf extract increased glucose-dependent secretion of insulin in alloxan-treated diabetic mice (Davydov *et al.*, 1990). We recently studied the hypoglycemic effect of American ginseng leaf extract in *ob*/*ob* mice following a 12-day

treatment (Xie *et al.*, 2004a). Like ginseng berry and root, American ginseng leaf extract also significantly decreased fasting blood glucose and improved glucose disposal in *ob*/*ob* mice suggesting an improvement in insulin sensitivity.

Possible Modes of Anti-diabetic Actions

Ginseng might mediate its anti-diabetic actions through a variety of mechanisms including actions on the insulin-secreting pancreatic β-cells and the target tissues that take up glucose. Ginseng treatment increased insulin release from pancreatic β-cells, which is probably caused by increased β-cell stimulation and increased insulin synthesis (Kimura *et al.*, 1981a; Waki *et al.*, 1982; Rotshteyn and Zito, 2004). Our data indicated that long-term treatment with ginseng resulted in an increased metabolic rate and improved insulin-stimulated glucose disposal (Attele *et al.*, 2002). The increased metabolic rate may be due to ginseng's ability to increase aerobic glycolysis (Wang *et al.*, 2003). Ginseng is also believed to increase the activity of a glucose transporter protein, reduce the rate of glucose absorption and reduce glycogenolysis, thus reducing hyperglycemia (Ohnishi *et al.*, 1996; Yuan *et al.*, 1998; Chung *et al.*, 2001). Furthermore, we have demonstrated the effect of ginsenoside Re in reducing expression of enzymes involved in lipid metabolism, which could be beneficial in diabetes (Xie *et al.*, 2005). Other properties such as the antioxidant activity of the ginseng extracts may help protect pancreas and other tissues from the oxidant stress during hyperglycemia (Kitts *et al.*, 2000; Evans *et al.*, 2002; Shao *et al.*, 2004).

In summary, both American and Asian ginseng, including root, berry, and leaf demonstrate a significant potential in treating diabetes mellitus. We propose, therefore, that ginseng should be further evaluated to decipher the mechanisms of its anti-diabetic actions. In particular, the mechanisms that may result in preservation of β-cell function and improvement in insulin sensitivity are interesting, since they could be responsible for delaying the onset of the disease.

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