

## Review

# Ginseng on Hyperglycemia: Effects and Mechanisms

John Zeqi Luo<sup>1</sup> and Luguang Luo<sup>2</sup>

<sup>1</sup>PLME Department of Medicine, Brown University, Providence, RI 02912 and <sup>2</sup>The Center for Stem Cell Biology, Department of Research, Roger Williams Hospital, Providence RI 02908, USA

It has been reported that American ginseng attenuates hyperglycemia and may present itself as a supplement to diabetes therapy. However, the lack of standardization in the usage of ginseng root leads to inconclusive results when applied to diabetes treatment. The mechanisms of American ginseng root in the treatment of diabetes remains a mystery. This greatly limits the effective utilization of American ginseng in facilitating diabetic therapy. Initiating studies have shown that American ginseng increases insulin production and reduces cell death in pancreatic  $\beta$ -cells. Also, studies have revealed American ginseng's ability to decrease blood glucose in type II diabetes patients as well as in streptozotocin-induced diabetic animals (STZ-diabetic mice). These data suggest that effects of ginseng in improving hyperglycemia may alter mitochondrial function as well as apoptosis cascades to ensure cell viability in pancreatic islet cells. This review briefly summarizes current knowledge of ginseng components and clinical studies related to diabetes. Further research will be needed to explore and identify the component(s) of ginseng, which may be responsible for the beneficial effects observed in animal studies which could then be extrapolated to human islets.

**Keywords:** ginseng–blood glucose–STZ diabetic animals–apoptosis–UCP-2

## Introduction

Due to a 3-fold increase in the consumption of herbal remedies in the United States along with a staggering popularity of the ginseng herb as a method of sustaining good health, significant focus have been placed on two widely used types of ginseng, American (*Panax quinquefolius* L.) (1) and Asian ginseng (*Panax ginseng* CA Meyer) (2–4). The usage of ginseng root for medicinal purposes have been recorded for millennia, known as a tonic capable of sustaining longevity as well as maintaining viability (5,6). The two species display different effects, possibly due to the different active chemical makeup of each other. Asian ginseng is said to facilitate blood flow, alleviate fatigue as well as relieve oxidative stress in diabetic conditions through various mechanisms such as the inhibition of

lipid peroxidation (7) (Table 1). American ginseng has been reported to have stress-relieving qualities, anti-aging effects and aids in digestion (3). Clinical studies have reported that ginseng improves psychological function, immune function and conditions associated with diabetes (8). Ginseng root has been reported to treat diabetic symptoms in the Compendium of Materia Medica (Ben Cao Gang Mu) by Dr Li (Li, ShiZhen, Ming Dynasty from 1368 to 1644, in China). This is the most complete and comprehensive pre-modern herbal textbook. The symptom was called Xiao Ke described as over eating, drinking and losing energy, body weight which are typical diabetic symptoms in modern medicine. Common methods of treatment for hyperglycemia (high glucose) include both mono-therapy and combination therapy with insulin, metformin, rosiglitazone and acarbose. These treatments have been shown to help control blood glucose levels but do not solve the problem—no pancreatic  $\beta$ -cell function, which results in numerous diabetic complications (9). Developmental information shows American ginseng may correct hyperglycemia.

For reprints and all correspondence: Dr Luguang Luo, The Center for Stem Cell Biology, Department of Research, Roger Williams Hospital, Boston University, Medical School, 825 Chalkstone Avenue, Providence, RI 02908, USA. Tel: +1-401-456-5344; Fax: +1-401-456-5759; E-mail: Lluo@rwhmc.org

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**Table 1.** Differing effects of American and Asian ginseng

American ginseng ( <i>Panax quinquefolius</i> L.)	Asian ginseng ( <i>Panax ginseng</i> CA Meyer)
<b>Differing Effects</b>	
Anti-aging effects (human, rat) (37,38)	Increases blood flow (human) (13,39)
Anti-hyperglycemia (human, mice) (3,4,40,41)	Decreases fatigue (human) (13,42)
Aids in digestion (rat) (43)	Stimulates nervous system (rat, cell) (2,44)
Reduces Stress (rat) (45)	Anti-inflammatory agent (cell) (46-48)
Enhances memory (rat) (49)	Liver-protection (rat)(50)
Reduces cholesterol (cell) (5)	Endurance (rat) (51)
Improves sexual function (rat) (52)	Anti-Depression (mice) (53)

### A Breakdown of Ginseng Components

A range of chemical components of ginseng such as ginsenosides, alkaloids, polypeptides and polysaccharides has been identified with their biological activity. The elements Phosphorus (P), Potassium (K), Calcium (Ca), Thallium (Tl), Manganese (Mn), Iron (Fe), Copper (Cu), Zinc (Zn) and Strontium (Sr) were detected by screening the components of ginseng (10). Other minor components include volatile oils (member of vitamin B complex), manganese, vanadium, copper, cobalt, fatty acids, amino acids, simple sugars and other carbohydrates (11). Aside from the basic elemental components of ginseng, glycosides have been reported to be the active component in ginseng responsible for ginseng's medicinal value. Glycoside is a naturally occurring substance consisting of a sugar and non-sugar moiety. A group of saponins (glycoside which produces froth by reducing water surface tension) in ginseng were named ginsenosides, and were classified into subclasses Ro, Ra, Rb, Rc, Rd, Re, Rf, Rg and Rh. These ginsenosides were differentiated based on their retention factor values in thin layer chromatography (TLC), which is the distance that the ginsenosides travel up the TLC column (12). More than 60 ginsenosides have been found in different parts of the ginseng plant (13). Asian ginseng can be distinguished from American using ginsenoside profiles since Asian and American ginseng contains various ginsenosides (14). A recent study analyzed the ginsenoside composition of Asian and American ginseng through observing 12 commercially available ginsenosides. Asian ginseng contains ginsenoside Rf (15) and Rg2, but American ginseng does not. Also, Rg1 content is over 10-folds as compared with American ginseng. However, American ginseng contains twice the level of ginsenoside Re. (16).

Since the usage of ginseng root extracts lacks standardization due to the different levels of ginsenosides in different batches, purified ginsenosides have been used to test whether the effects of ginseng root lies on one

ginsenoside or a combination of various ginsenosides. The anti-hyperglycemic effects of the total ginsenosides extracted from Asian ginseng were evaluated in diabetic C57BL/6J ob/ob mice. Total ginsenosides had significant anti-hyperglycemic and anti-obesity properties in a diabetic ob/ob mouse model (17). In the same model, Ginsenoside Re showed to improve muscle metabolism and reduce inflammation through increase C-reactive protein levels, leading to an anti-hyperglycemic effect (18). Ginsenoside Rh2 was able to lower plasma glucose in STZ-diabetic rats in a dosage dependent manner (19). Rh2 has also been noted to have the ability to regulate glucose by increasing insulin secretion through the control of nerve terminals, signifying that the effects of ginsenosides encompass the entire body (20). There were no reports of ginsenosides affecting pancreatic function in the mentioned studies. It is possible that ginsenoside components create an anti-hyperglycemic effect, which aids pancreatic function as well.

### Ginseng Aids the Normalization of Hyperglycemia

There have been numerous reports of ginseng root (American and Asia ginseng) improving diabetic conditions in both humans as well as animal studies. In animal studies, orally administered ginseng root was able to counteract the effects of high-fructose induced insulin resistance in rats after 4 weeks, decreasing glucose concentrations, as well as inhibit insulin resistance (21). Ethanol extract of ginseng root prevented weight gain, fasting blood glucose, triglyceride and high free fatty acid levels in a high-fat induced hyperglycemia mouse model (22). Ginsenoside Re reduced blood glucose levels, cholesterol and triglyceride levels as well as reduced oxidative stress in the eye and kidney of diabetic rats (2). Clinical studies have reported that American ginseng has the ability to lower blood glucose in diabetic patients. (3) In some cases, both type II diabetic patients and non-diabetic subjects showed to benefit from an intake of American ginseng in terms of stabilizing post-prandial glycemia after meals, suggesting that the intake of ginseng may also benefit healthy individuals. American ginseng did not have adverse effects on healthy individuals but rather beneficial effects in post-prandial glycemia compared with placebo when administered together with the glucose challenge. In subjects with type II diabetes mellitus, significant reductions were observed when ginseng was taken 40 min before the glucose challenge (3). In both clinical and animal studies, ginseng root has shown to have the ability to improve hyperglycemia in diabetic conditions.

### Multiple Mechanisms Behind the Effects of Ginseng

A limited amount of mechanism studies have been done on the effects of American ginseng on either the pancreas or

any other organ. According to the mechanistic studies, which have been performed, ginseng root and components seem to exert its effect through several different mechanisms, suggesting that we have merely scraped the surface in discovering the effects of ginseng and its components. Studies have shown that ginseng and its components attenuate hyperglycemia in two ways, the first through enhancing pancreatic  $\beta$ -cell function and the other through reducing insulin resistance. This leads us to believe that ginseng may have benefits for both type I and type II diabetes.

American ginseng root extracts have been shown to affect pancreatic  $\beta$ -cells through altering cell metabolism, increasing insulin production and reducing apoptosis in a dosage dependent manner (23). Ginseng extracts were able to enhance ATP production and in turn increase insulin production, as insulin deficiency is often linked to a lack of ATP produced (24,25). Along with an increase in ATP production, ginseng reduced mitochondrial protein UCP-2, which negatively regulates insulin secretion (13,25–28). Aside from affecting insulin production, ginseng may have the ability to target various glucose receptors, creating an antilipolytic effect, thus attenuating hyperglycemia (12,29). This suggests that there exist other pathways through which ginseng acts through. Overall, ginseng is able to enhance insulin production through regulating cell metabolism.

Though UCP-2 regulates insulin secretion, it has also been reported to decrease cell longevity (12,30). Apoptosis is one of the common causes of cell death in pancreatic  $\beta$ -cells. Resulting in the destruction of genetic material, apoptosis is regulated by factors such as Bcl-2, which protects against apoptosis and Caspase-3/9, which promotes death through the caspase cascade (8,31,32). American ginseng reduces apoptosis by promoting caspase-3/9 and enhanced cell protective Bcl-2 protein levels, resulting in protecting cells against apoptosis (23). Preventing apoptosis allows for further cell function and insulin production in pancreatic  $\beta$ -cells.

Aside from affecting cell metabolism and longevity, ginseng has the ability to change neuropeptide through Rh2, a ginsenoside derived from *Panax ginseng*, in STZ-diabetic rats. Rh2 lowered plasma glucose due to an increase in beta-endorphin secretion that activates opioid mu-receptors thereby resulting in an increased expression of GLUT 4, a glucose transporter in fat and muscle tissue (19). Protopanaxatriol, a ginsenoside metabolite, also increased GLUT4 and improved insulin resistance (33). The up-regulation of GLUT-4 signalizes that ginseng has an effect on fat/muscle tissue, possibly decreasing insulin resistance.

Along with mechanisms pertaining to specific organs and tissues, ginseng components have shown to have general effects as well. Ginsenoside Re prevented oxidative stress in (2) and reduce inflammation in STZ-diabetic rats (34). In cellular models, ginseng reduces H<sub>2</sub>O<sub>2</sub> induced

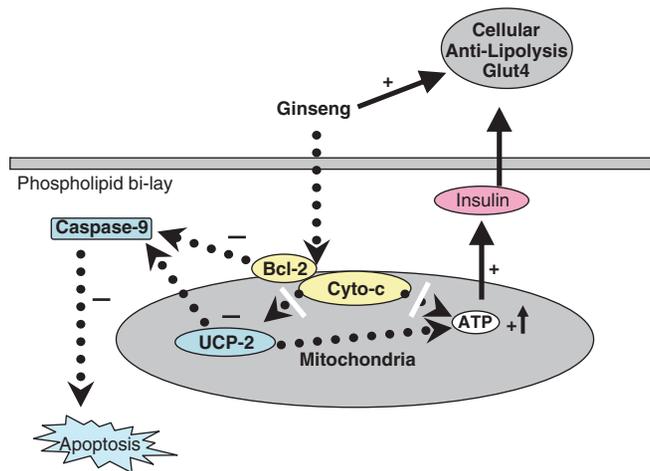
oxidative damage and enhances superoxide dismutase and catalase to create a protective effect in a dosage dependent manner (1). Ginseng leaf and berry extracts also show high antioxidant activities which detoxify free radicals excessively produced in diabetic environments (35). Currently, studies show ginseng as having general anti-oxidative properties in specific cells and tissue such as pancreatic  $\beta$ -cells and fat/muscle tissue. We feel that there are many more undiscovered mechanisms which ginseng acts through.

### Controversies Around the Benefits of Ginseng on Diabetes

The usage of herbs and spices has long been documented than modern pharmaceuticals. Unlike modern pharmaceuticals, which utilize small molecular weight compounds consumed in a purified form, herbs are eaten in combinations of unmeasured quantities. It is almost certain the herbs contain beneficial qualities and that the goal should not be to ask if they have effects but rather what effects do they have (36). Since herbs have been consumed in its natural form for the major duration of history, very little attention has been paid to the standardization in this industry. It could be possible that the positive effects of ginseng on hyperglycemia may not hold true for all ginseng products due to differences in batches. Sievenpiper, Arnason *et al* discovered that Asian ginseng showed both null and opposing effects on indices of acute post-prandial plasma glucose and insulin, which contrasted the findings with ginseng, thus showing that different species attribute to different functions (3). As with all chemical components, the metabolized form could generate three possibilities: enhance activity, become toxins, or have no effect. Currently, no studies have taken this factor into consideration. Three main concerns limiting the usage of ginseng include the ubiquitous lack of standardization, in depth mechanism studies, as well as widespread clinical studies (3). Standardization of ginseng components would be the first step to ensuring that there are no unnecessary variations in the data.

### Conclusion

It seems that ginseng and ginsenosides are beneficial for diabetes therapy. Although single ginsenosides have shown to have positive effects, whether a single component or a mixture of components maximizes the therapeutic effect of ginseng on diabetes is still unclear. Many steps have been taken to standardize the usage of ginseng root through isolating specific ginsenosides, which is an effective way to maintain dosages and specificity. It is more than likely that ginseng affects not only the pancreas to increase insulin production but also other tissue to utilize insulin as well as



**Figure 1.** The mechanisms of ginseng activation proposed here in scheme summarizes that the active components of ginseng regulate Uncoupling Protein-2 (UCP-2), which results in a decrease in apoptosis and an increase of ATP production and thus insulin production, which will stimulates cellular glut4 activation to promote metabolism. Ginseng also activates cytochrome-c related Bcl-2 expressing, leading to an inhibition of caspase-9 triggered apoptosis cascade (23). '+': positive effects '-': negative effects 'solid-line arrow': known actions 'dotted-line arrow': recently discovered actions.

decrease insulin resistance through its various components (15). Ginseng root has been shown to be effective in cell cultures, animal studies, as well as clinical practice. Root extracts and components exhibited anti-hyperglycemic activities and reduced insulin resistance and increased insulin production. Since the mechanisms behind ginseng's effects have not yet been fully discovered, we cannot understand the full extent of its potential. Ginseng root is able to increase insulin production and decrease cell apoptosis in pancreatic  $\beta$ -cells, which signifies that ginseng affects the pancreas directly. Also, ginseng has been shown to mediate various mechanisms related to muscle and fat tissue such as the GLUT4 pathway (see proposed mechanism of ginseng's activation in Fig. 1). Despite the lack of sufficient widespread clinical, mechanistic studies and standardization for immediate therapeutic uses greatly hinders the possibility of practical applications, current reports of ginseng and ginsenosides point to the possibility of ginseng as a candidate for complementary diabetes therapy.

### Future Direction

In order to effectively apply ginseng on diabetes therapy, three fronts must be expanded. First, standardization of ginseng root has to be taken into consideration as different batches contain different concentrations of ginsenosides. Second, more clinical studies have to be performed to confirm effects of ginseng on both type I and type II diabetic patients. Third, the mechanisms behind ginseng's therapeutic effects have to be examined closely to see the

mechanisms which specific components of ginseng act through. Taking these three routes into consideration, the evident yet mysterious effects of ginseng could be elucidated and applied to future therapies.

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Received July 5, 2007; accepted August 6, 2007



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