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Antihyperglycemic Effect of Ginsenoside Re and its Possible Mechanisms

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ABSTRACT

Ginsenoside Re (G-Re), a single compound extracted from ginseng, shows multifaceted pharmacological activities. Reports have demonstrated that one of the most important pharmacological functions of G-Re is antihyperglycemia, including decreased blood glucose, improved glucose tolerance, and improved insulin resistance. The mechanism of the anti-diabetic effect of G-Re, however, is not entirely understood. The possible mechanism may be through several complex bioactive procedures, such as molecular biological and antioxidant mechanisms *etc*. In this mini-review, we will discuss the antihyperglycemic property of G-Re and its possible mechanisms.

Keywords: antihyperglycemic effect, diabetes mellitus, ginseng, ginsenoside Re, molecular biological mechanisms
Abbreviations: AGBE, American ginseng berry extract; **AGLE**, American ginseng leaf extract; **AUC**, area under the curve; **CGBE**, Chinese ginseng berry extract; **GABA**, gamma-aminobutyric acid; **G-Re**, ginsenoside Re; **HFD**, high-fat diet; **IR**, insulin receptor; **IPGTT**, intraperitional glucose tolerance test; **ROS**, reactive oxidative species

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INTRODUCTION

Botanically, ginseng is a slow-growing, deciduous, perennial plant of the Araliaceae family which includes *Panax ginseng* (Renshen, Chinese or Korean ginseng), *Panax japonicus* (Japanese ginseng), and *Panax quinquefolius* (American ginseng, Xiyangshen) (Xie *et al.* 2005a; Seely *et al.* 2008). As a king herbal medicine in China, *P. ginseng* has been used in medical purposes in more than 5000 years (Chevallier 2000). *P. quinquefolius* is increasingly and widely used as a dietary supplement in the United States and Canada (Cheng 2000).

Diabetes mellitus is a devastating endocrine disease characterized by hyperglycemia and long-term complications affecting the eye, kidney, nerve, and blood vessel (Cho *et al.* 2006a). Diabetes mellitus is classified into two major categories: Type I diabetes (formerly known as insulin-dependent diabetes mellitus, or IDDM), and Type II diabetes (formerly known as noon-insulin dependent diabetes mellitus, or NIDDM) (Skyler 2004). Between 85 and 90% of diabetes patients suffer from Type II diabetes (Attele *et al.* 2002). Currently, available pharmacological agents for Type II diabetes, however, have a number of limitations and adverse effects. Therefore, diabetic patients and healthcare professionals are considering complementary and alternative approaches, including the use of medicinal herbs with antihyperglycemic activities (Attele *et al.* 2002; Xie *et al.* 2004). In fact, ginseng is the best choice of herbal medicines that show promising result in the treatment of diabetes (Xie *et al.* 2005a, 2005b).

Historical records on traditional medicine systems reveal that *P. ginseng* has the multifaceted pharmacological functions. A number of reports have demonstrated that ginseng extract, including its parts, root, beery, and leaf-stem possesses markedly antihyperglycemic effect in different animal models (Wang *et al.* 1957; Kimura *et al.* 1981b; Attele *et al.* 2002; Xie *et al.* 2002, 2004, 2005a, 2005b; Peng *et al.* 2008; Wang *et al.* 2009) and in clinical trials (Vuksan *et al.* 2000a, 2000b, 2006). Several studies indicated that the pharmacological effect of ginseng extract

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could be attributed to G-Re which is a major bioactive ginsenoside in ginseng (Attele *et al.* 2002; Xie *et al.* 2005b). To the best of our knowledge, however, the antihyperglycemic effect of G-Re has not yet been shown in the review literature. The present mini-review discusses the anti-diabetic activity of G-Re and its possible mechanisms.

CHEMISTRY AND PURIFICATION

Chemical studies of ginseng root, berry, and leaf-stem demonstrated that ginsenosides are principal bioactive single constituents and the pharmacological properties of ginseng extracts are mainly attributed to ginsenosides (Attele *et al.* 1999; Xie *et al.* 2006a). Ginsenosides belong to a chemical group called saponins, which are similar in composition and structure to steroids (Xie *et al.* 2006a). Ginsenoside compounds derived from two general groups: 20(S)-protopanaxatriol (Rg1, Rg2, Rg3, Re, and Rf, *etc*) and 20(S)-protopanaxadiol (Rb1, Rb2, Rc, and Rd, *etc*). G-Re is a ginsenoside in the 20(S)-protopanaxatriol group (**Fig. 1**).

According to the information provided by Jilin Hongjiu BioTech Co., Ltd of China, the simple procedure of extraction and purification of G-Re is as follows. The G-Re was isolated from protopanxatriol ginsenoside of leaf-stem by using silica gel column and solvent chloroform and methanol. The 21 g ginsenoside Re was obtained from 100 g protopanxatriol ginsenoside. The G-Re was purified further by crystallization. The purity and yield are 98 and 18%, respectively by using this method. G-Re also can be extracted and purified from radix of ginseng (Xie *et al.* 2009).

MULTIFACETED PHARMACOLOGY

G-Re is the most representative ginsenoside in this herbal medicine and has been investigated in depth. Studies indicated that G-Re is a major ginsenoside and an important compound in ginseng (Xie *et al.* 2004, 2005b). Many results demonstrated that G-Re not only has anti-diabetic activity described below, but also possesses several other multifaceted pharmacological functions both *in vivo* (Jin *et al.* 1994; Kim *et al.* 1998; Bai *et al.* 2003, 2004) and *in vitro* studies (Jin 1996; Kim *et al.* 2003; Wang *et al.* 2004; Mehendale *et al.* 2005; Xie *et al.* 2006b).

These multiple beneficial effects of G-Re may involve protective functions on the cardiovascular system (Jin *et al.* 1994; Wang *et al.* 2008), anti-arrhythmic effect (Wang *et al.* 2004), inotropic and chronotropic effects on cardiac cells (Kang *et al.* 1995; Jin 1996), anti-ischemic effect (Liu *et al.* 2002a), anticancer effects (Lee *et al.* 2003), and inhibitory effect on chemogenic pain (Shin *et al.* 1997), and so on. Here, only the antihyperglycemic activity of G-Re and its possible mechanisms will be discussed in this mini-review.

ANTIHYPERGLYCEMIC EFFECT

Decrease blood glucose

Xie *et al.* evaluated the hypoglycemic effects of G-Re in diabetic adult male C57BL/5J *ob/ob* mice (Attele *et al.* 2002; Xie *et al.* 2002, 2005b). Diabetic *ob/ob* mice with fasting blood glucose levels of approximately 230 mg/dl received daily intraperitoneal injections of G-Re for 12 consecutive days. As shown in **Table 1**, fasting blood glucose levels were significantly decreased after treatment with G-Re (approximate 180 mg/dl, $P < 0.01$ compared to vehicle group).

In addition, dose-dependent effects of G-Re on fasting blood glucose levels were observed in this experiment. Xie *et al.* also noticed that the antihyperglycemic effect of this G-Re persisted even at 3 days of treatment cessation. Unlike ginseng berry, root, and leaf-stem extracts, however, G-Re did not affect the body weight and body temperature of mice in the experiments (Xie *et al.* 2005a, 2005b).

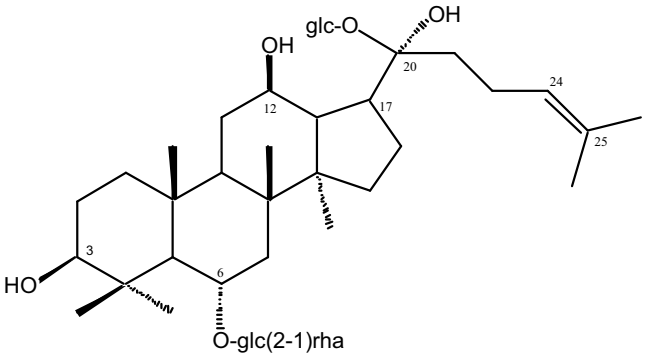

Fig. 1 Chemical structure of ginsenosides Re. (From Xie *et al*. 2005b)

Table 1 Effect of G-Re (20 mg/kg) and AGBE, CGBE, AGLE (150 mg/kg) on fasting blood glucose in *ob/ob* mice.

Groups	Fasting Blood Glucose (mg/dl)		
	N	Day 0	Day 12
G-Re	11	226 ± 18.9	180 ± 10.8**
Vehicle	6	235 ± 12.6	239 ± 13.3
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

G-Re: ginsenoside Re, AGBE: American ginseng berry extract, CGBE: Chinese ginseng berry extract, AGLE: American ginseng leaf extract
*$P < 0.05$, ** $P < 0.01$ compared to vehicle group.

Improve glucose tolerance

To further study the anti-diabetic effect of G-Re, glucose tolerance was also measured by intraperitional glucose tolerance test (IPGTT) on Day 0 and Day 12. On Day 0, *ob/ob* mice showed basal hyperglycemia. This hyperglycemia was exacerbated by the intraperitional glucose load, and did not improve significantly after 120 min indicating glucose intolerance and impaired glucose disposal (**Fig. 2A**). After 12 days of 10 mg/kg G-Re treatment (**Fig. 2B**), however, glucose disposal improved markedly. The blood glucose level is significantly lower in the G-Re-treated mice compared with that in the vehicle-treated mice at 60 min and 120 min (both $P < 0.01$). To evaluate the overall glucose exposure, the glucose area under the curve (AUC) was calculated, which was decreased by 17.8% in G-Re-treated animals compared to vehicle-treated group. There was a significant improvement in glucose exposure from 779 mg/mL•min of Day 0 to 640 mg/mL•min of Day 12 ($P < 0.05$). Glucose tolerance test data indicated that, after G-Re treatment, there was a significant higher rate of glucose disposal. In addition, in these experiments both fed and fasting serum insulin levels reduced after G-Re treatment. These effects are beneficial for the improvement of blood glucose disposal.

Pursuant to the results described above, the authors suggested that G-Re possesses significant antihyperglycemic activity in diabetic *ob/ob* mice and may be a useful anti-diabetic drug after successful clinical trial.

To confirm the anti-diabetic activity of G-Re in different animal model, Cho *et al* studied the hypoglycemic effect of G-Re (20 mg/kg/day for 2 weeks) with orally administration in streptozotocin-induced diabetic rats (Cho *et al.* 2006a, 2006b). Consistent with the results of Xie *et al*, they demonstrated that the orally administered G-Re had significant antihyperglycemic effect and effectively normalized the impaired oxidative stress in the kidney and eye of diabetic rats. Furthermore, the study also indicated that G-Re exhibited definitive actions towards hypercholesterolemia and hypertriglycerilemia associated with diabetes.

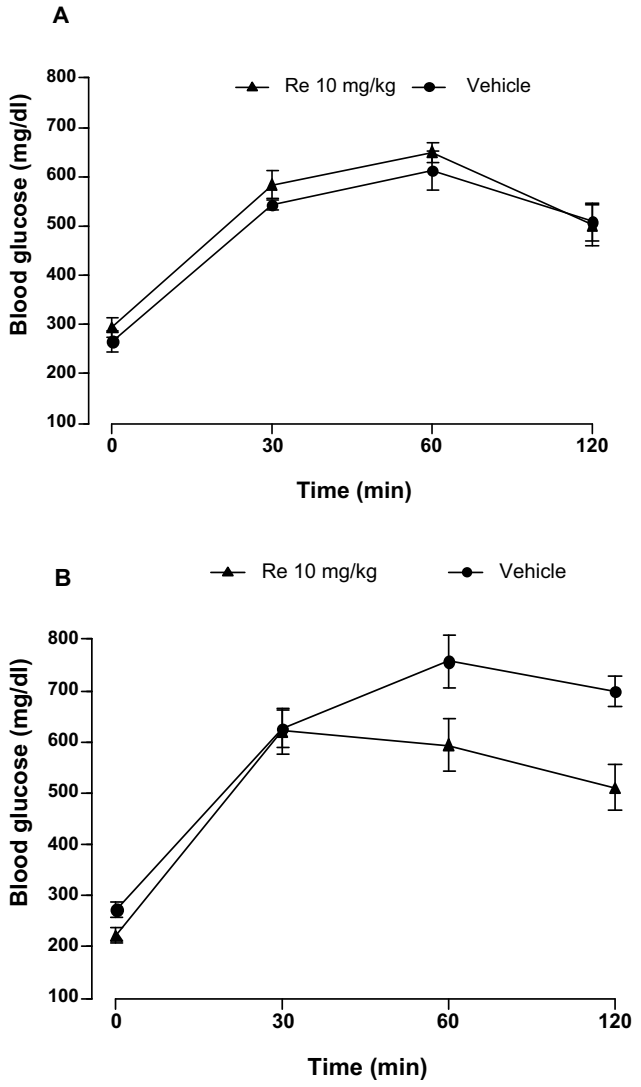

Fig. 2 Intraperitoneal glucose tolerance test in diabetic *ob/ob* mice before, during and after 10 mg/kg G-Re treatment. (**A**) Day 0 (before treatment). (**B**) Day 12 (last day of treatment), with a significantly higher rate of glucose disposal at 60 and 120 min ($P < 0.01$ compared to vehicle-treated mice). (From Xie *et al*. 2005b)

The promising antioxidant and antihyperlipidemic efficacies of G-Re demonstrated in this study may open new avenues in the treatment of diabetes and its complications.

It is generally accepted that oxidative stress has been implicated in the pathogenesis of diabetes and its complications. The study revealed that the glutathione (the primary endogenous antioxidant) and malondialdehyde (an index of endogenous lipid peroxidation) levels in the eye and kidney of the diabetic rats were restored to normal levels after treatment with G-Re. Thus, G-Re ameliorated the antioxidant status in the kidney and eye (Cho *et al.* 2006a). According to the results above, it is suggested that G-Re possesses a potential antihyperglycemic effect in this animal model.

Recently, Yang *et al.* explored the antihyperglycemic activity of G-Re which was extracted from *Panax notoginseng* in KK-Ay diabetic animal model (Yang e*t al.* 2010). The results showed that G-Re possess a decreasing trend after the 12-day treatment. They have discussed that compared to our results (Xie *et al.* 2005a, 2005b) the mild hypoglycemic effect of G-Re may be not due to the dosage, but due to different models. Therefore, further research of antihyperglycemic activity of G-Re in the different animal models will be necessary.

POSSIBLE MECHANISMS

The antihyperglycemic mechanism of G-Re is not yet understood completely. However, previous studies provided several evidences that G-Re may exert their anti-diabetic actions through three biological levels: molecular biological level, cellular biological level, and integral biological level, etc.

The molecular biological level

To investigate the molecular biological mechanisms of G-Re, Xie *et al.* compared the gene expression profile of G-Re treated *ob/ob* mice with that of vehicle group using high-density oligonucleotide arrays (Xie *et al.* 2005b). The microarray data suggested that G-Re treatment induced differential expression of genes mainly involved in muscle and lipid-related metabolic pathways. Some of genes expression changes induced by G-Re might be beneficial for the treatment of obesity and diabetes.

In another study, Cho *et al.* (2006b) adopted the high throughput proteomic approach to investigate the anti-diabetic effect of 2 weeks' G-Re administration in streptozotocin-induced diabetic rats. Employing surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS) and bioinformatics, 432 cluster peaks were detected in the samples, among them 293 potential biomarkers were found to have significant differentiations between the diabetic and control normal rats. They found that the potential biomarker, C-reactive protein, significantly reduced in G-Re-treated diabetic rats than in control (Cho *et al.* 2006b). This result demonstrated that the intake of G-Re could reduce the elevation of C-reactive protein in diabetes, implying G-Re may improve diabetes and its complications by reducing inflammation.

More interestingly, the basic molecular biological molecular mechanism of antihyperglycemic action of G-Re was studied both *in vivo* and *in vitro* (Zhang *et al.* 2008). In order to dissect the antihyperglycemic molecular mechanism of G-Re, the insulin signaling and the anti-inflammatory effect by G-Re were assessed in 3T3-L1 adipocytes and in high-fat diet (HFD) rats. The insulin signaling cascade, including insulin receptor (IR) substrate-1, phosphatidylinositol 3-kinase, Akt and Akt substrate of 160 kDa, and glucose transporter-4 translocation are examined. Also, c-Jun NH2-terminal kinase (JNK), AMP-activated protein kinase (MARK), and nuclear factor (NF)-kB signaling cascades were assessed in this research. The main results indicated that G-Re (10 μM) promoted basal and insulin-stimulated glucose uptake in 3T3-L1 adipocytes and improved insulin resistance by increasing the glucose infusion rate in HFD rats. The activation of insulin signaling by G-Re is initiated at IR substrate-1 and further passes on through phosphatidylinositol 3-kinase and downstream signaling cascades. They concluded that 1) G-Re has an anti-inflammatory effect, which is associated with an antihyperglycemic action in the state of insulin resistance. 2) G-Re reduces insulin resistance in 3T3-L_1 adipocytes and HFD rats through inhibition of c-Jun NH2-terminal kinase and nuclear factor (NF)-kB activation (Zhang *et al.* 2008). Therefore, the authors suggest that G-Re may be promising to be developed as an anti-diabetic medicine.

Cellular biological level – Antioxidant activity

Previous studies revealed that diabetes is associated with increased oxidative stress and raised glucose levels have been linked to reactive oxidative species (ROS) generation. On the other hand, hyperglycemia may be the cause of oxidative stress in organisms, including in pancreatic β–cells (Ihara *et al.* 1999; Mohanty *et al.* 2000; Cho *et al.* 2006a). Thus, antihyperglycemic effect of G-Re may be caused by its antioxidant activity at least partly.

Liu *et al.* raised the question "can ginsenosides protect human erythrocytes against free-radical-induced hemoly-

sis?" (Liu *et al.* 2002b). The half maximal inhibitory concentration (IC_{50}) of AAPH-induced (2,2V-azobis2-amidinopropane hydrochloride, AAPH) hemolysis of the erythrocyte has been studied. They found that the order of IC_{50} is G-Rb3 ~ G-Rb1 << Rg2 < Re < Rg1 ~ Rc < Rh1 < R1, but not all these ginsenosides have the ability to protect human erythrocytes against AAPH-induced hemolysis. Meanwhile, the synergistic antioxidative properties of various individual ginsenosides with α-tocopherol (TOH) are also evaluated in their experiment. It was found that the order of synergistic antioxidative properties with TOH is Rb1 > Rc > Re > Rh1 > R1 > Rg2 > Rb3, Rd and Rh2. The antioxidative mechanism of various ginsenosides is not clear and will be further studied in detail, but the obtained information may be useful in the clinic usage of ginsenosides.

Antioxidants are compounds that protect cells against the damaging effects of ROS. Some ROS, such as superoxide and hydrogen peroxide, are normally produced in cells as by-products of biochemical reactions or as signaling molecules. When ROS-generating reactions are activated excessively, pathological quantities of ROS are released to create an imbalance between antioxidants and ROS, resulting in cellular damage. Oxidative stress has been linked with the pathogenesis of many human diseases including cancer, aging, and atherosclerosis (Sauer *et al.* 2001). Antioxidant therapy, therefore, has become an attractive strategy. It has been revealed that the majority of ginseng's and ginsenoside's pharmacological activities have been closely linked to its antioxidant property (Zhang *et al.* 1996; Keum *et al.* 2000; Kitts *et al.* 2000; Mantle *et al.* 2000; Bae *et al.* 2004).

Xie *et al.* further explored this activity of G-Re (Xie *et al.* 2006b) and American ginseng berry extract using the chick cardiomyocyte model of oxidant injury (Shao *et al.* 2004). In cells exposed to 2 hours of H_2O_2 (0.5 mM), pretreatment with G-Re significantly attenuated 2',7'-dichlorofluorescein (DCF) fluorescence by 51% ($P < 0.001$), and remarkably reduced cell death ($P < 0.001$, compared to the control). Similar results were also observed in cells exposed to antimycin A (100 μM), a mitochondrial electron transport chain site III inhibitor which increases endogenous oxidative stress. In an ESR cell-free study, however, G-Re failed to reduce the formation of the superoxide/DMPO adduct and DPPH radicals. These results suggest that G-Re functions as an antioxidant, protecting cardiomyocytes from oxidant injury induced by both exogenous and endogenous oxidants, and that its protective effects may be mostly attributed to scavenging H_2O_2 and hydroxyl radicals (Xie *et al.* 2006b). Therefore, the antihyperglycemic effect of G-Re may be caused partly by the antioxidant property.

Integral biological level – Reduction of insulin resistance

To understand the possible mechanisms of antihyperglycemic action of G-Re, the serum insulin levels were measured in diabetic *ob/ob* mouse model in the integral biological level (Xie *et al.* 2005b). As shown in **Fig. 3**, in parallel with the reduction of blood glucose levels, there was significant decrease in both fed (**Fig. 3A**) and fasting (**Fig. 3B**) serum insulin levels in animal treated with G-Re (10 mg/kg). This result suggested that G-Re improved insulin resistance in the *ob/ob* mice markedly. It is widely accepted that diabetes is characterized by a progressive decrease in insulin action, followed by an inability of the β-cell to compensate for insulin resistance (Saltiel 2001). Improvement of insulin resistance by G-Re may play a key role in treatment of diabetes and reduction of the related complication (Zhang *et al.* 2008).

The similar results were obtained in pancreatic β-cells and MIN-6 cells (a pancreatic insulinoma β-cells) in cellular level experiments (Lin *et al.* 2008). In the study, these cells showed a dose-dependent response to hydrogen peroxide at 100-500 μM. Under the acute conditions when cells were treated for 10 min, the oxidant injury was reduced with G-Re treatment. Chronic treatment with high concentration of G-Re (0.5 mg/ml) for 48 h also demonstrated attenuation of oxidative stress in the cells. In these experiments, G-Re appeared to produce antioxidant effect significantly. The data shows G-Re may improve insulin secretion by enhancing pancreatic β-cell function under oxidative stress. The authors suggested that the antihyperglycemic property of G-Re may be linked to its antioxidant effects on pancreatic β-cells.

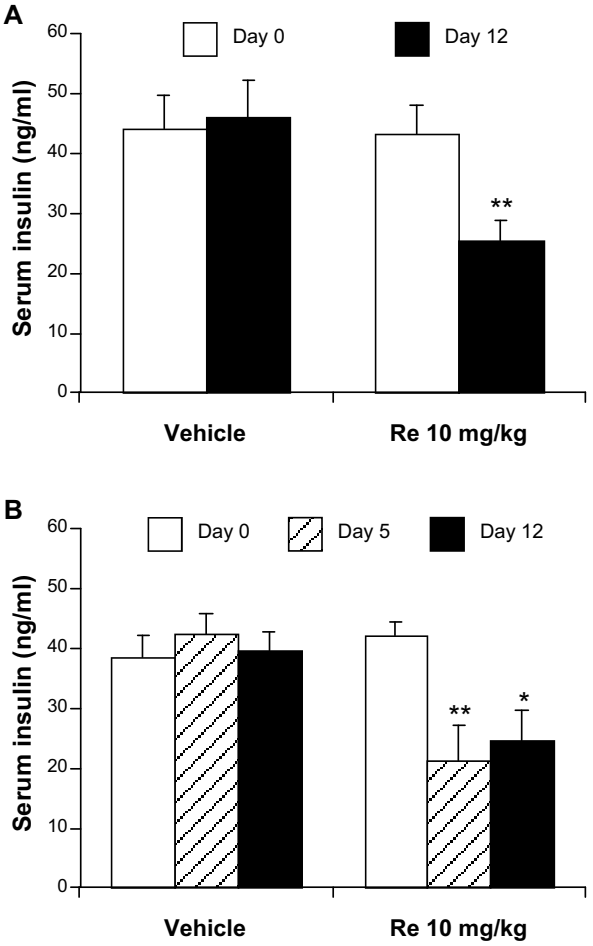

Fig. 3 Effect of G-Re on serum insulin concentrations in fed (**A**) and fasting (**B**) *ob/ob* mice (From Xie *et al.* 2005b). (**A**) Serum insulin levels reduced significantly under fed state after 12-day treatment with G-Re 10 mg/kg (** $P < 0.01$). (**B**) Fasting serum insulin levels also reduced significantly after 5-day and 12-day G-Re treatment. * $P < 0.05$ and ** $P < 0.01$ compared to vehicle-treated mice.

In addition to the possible mechanisms described above, G-Re may exert the multiple pharmacological functions through several other mechanisms, such as cell receptors (GABA, dopamine, and pain receptor etc), membrane channels (the inward Ca^{2+} currents, the L-type Ca^{2+} current etc), hypothalamo-pituitary-adrenal axis, and cell-to-cell communication. In a word, the mechanism of anti-diabetic effect of G-Re is unclear and further extensive studies including both *in vitro* and *in vivo* are needed to elucidate the mechanism of its effect.

CONCLUSIONS

Previous reports demonstrated that G-Re, as a major compound of ginseng, possesses antihyperglycemic effect. Studies showed that 1) G-Re lowers blood glucose level in *ob/ob* mice and diabetic rats, and 2) improves glucose tolerance. However, the mechanism of the anti-diabetic property of G-Re is not clear completely. A few studies suggested that it might be through three biological levels to reduce blood sugar: molecular biological level, cellular biological

level, and integral biological level, *etc*". The antihyperglycemic effect of G-Re may provide an opportunity to develop a new anti-diabetic agent if these animal data can be validated in further clinical trials.

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