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Ginseng and Diabetes: The Evidences from *In Vitro*, Animal and Human Studies

Hai-Dan Yuan[1], Jung Tae Kim[1], Sung Hoon Kim[2], and Sung Hyun Chung[1*]

[1]Department of Pharmacology and Clinical Pharmacy, College of Pharmacy, Kyung Hee University, Seoul 130-701, Korea
[2]Cancer Preventive Material Development Research Center, College of Oriental Medicine, Kyung Hee University, Seoul 130-701, Korea

Panax ginseng exhibits pleiotropic beneficial effects on cardiovascular system, central nervous system, and immune system. In the last decade, numerous preclinical findings suggest ginseng as a promising therapeutic agent for diabetes prevention and treatment. The mechanism of ginseng and its active components is complex and is demonstrated to either modulate insulin production/secretion, glucose metabolism and uptake, or inflammatory pathway in both insulin-dependent and insulin-independent manners. However, human studies are remained obscure because of contradictory results. While more studies are warranted to further understand these contradictions, ginseng holds promise as a therapeutic agent for diabetes prevention and treatment. This review summarizes the evidences for the therapeutic potential of ginseng and ginsenosides from *in vitro* studies, animal studies and human clinical trials with a focus on diverse molecular targets including an AMP-activated protein kinase signaling pathway.

Keywords: *Panax ginseng*, Ginsenosides, Diabetes mellitus, AMP-activated protein kinase (AMPK)

INTRODUCTION

Despite enormous efforts to search for cure, diabetes mellitus (often simply referred to as diabetes) still remains as a formidable challenge for public health. As of 2000 at least 171 million people worldwide suffer from diabetes or 2.8% of the population [1], and the prevalence of diabetes will rise to 11.4% in 2030 [2,3]. The increased prevalence is likely attributable to rapid economic development, improved living standards, an aging population, and a westernized lifestyle. Epidemiological studies and clinical trials strongly support the notion that hyperglycemia is the principal cause of microvascular and macrovascular complications such as renal failure, neuropathy, retinopathy, coronary and cerebral artery diseases, and amputation. Therefore, effective blood glucose control is the key to preventing or reversing diabetic complications and improving quality of life in diabetic patients [4,5]. Although no cure is yet available for type 2 diabetes, oral hypoglycemic agents have been developed and are widely used. Current medications, however, are not adequately effective in maintaining long-term glycemic control in most patients, even when used in combination, leaving diabetics susceptible to developing life threatening and debilitating complications. Therefore, there is an urgent need for more potent and safe therapeutic agents with noble mechanisms of action [6]. In this context, the practice of diabetes prevention by use of herbal remedy is considered to be an alternative, but more realistic and fundamental strategy for the management of this dread disease.

One of the promising medicinal plants with anti-dia-

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***Corresponding author**
E-mail: suchung@khu.ac.kr
Tel: +82-2-961-0373, Fax: +82-2-957-0384

betic potential is ginseng [7]. The English word ginseng derives from the Chinese term rénshēn (人蔘), literally 'man root' (referring to the root's characteristic forked shape, resembling the legs of a man). The botanical/genus name *Panax* means 'all-heal' in Greek, sharing the same origin as 'panacea'. Both American ginseng (AG, *P. quinquefolius*) and Asian ginseng (*P. ginseng* Meyer) roots are taken orally as adaptogens, aphrodisiacs, nourishing stimulants, and in the treatment of type 2 diabetes, as well as for sexual dysfunction in men. Therapeutic uses of ginseng were recorded in the oldest comprehensive Materia Medica (Shen Nong Ben Cao Jing [神農本草經]) about 2000 years ago [8], and anti-diabetic potential of ginseng was found in another compendium of Materia Medica (Ben Cao Gang Mu [本草綱目] written by ShiZhen Li). The symptoms was called Xiao Ke (消渴) described as hyperphagia, excessive drinking and losing body weight which are cardinal diabetic symptoms in modern medicine. This medicinal plant has attracted considerable attention from diabetes researchers as well as general public since 1995, when Sotaniemi *et al*. [9] published an article demonstrating anti-diabetic activity of ginseng. Shortly thereafter, there has been a steady progress in uncovering the therapeutic efficacy and molecular mechanisms of anti-diabetic properties of ginseng. This review is intended to shed light on pharmacological and therapeutic activities, and action mechanisms of ginseng (and its active components) as an anti-diabetes agent.

ANTI-DIABETIC ACTIVITY AND ACTION MECHSNISMS OF GINSENG

The hypoglycemic activity of ginseng extract and its active ingredients has been known since 1980s. In 1980s, several glycans including panaxans and quinquefolans were isolated from Asian ginseng and AG, respectively, and they were known to be hypoglycemic constituents [10-13]. Now, it is generally accepted that the triterpene β-glycoside, known as ginsenosides, are the major active constituents in ginseng [14]. Along with this notion, different batches contain different profiles of ginsenosides, which may result in inconsistent outcomes.

Until 2000, we are only aware of 3 published long-term studies investigating the anti-diabetic efficacy of ginseng from any source in people with type 2 diabetes. In the first study, 8 wk of treatment with 100 and 200 mg/d of an unspecified ginseng improved fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1c}), respectively [9]. But this was confounded by a significant weight loss on ginseng. The second study showed that 24 mo of treatment with 3 to 4.5 g of a Korean red ginseng (KRG) extract decreased HbA_{1c} by an unspecified magnitude [15]. Finally, the third study represents the original 'proof-of-concept' for an acute clinical screening-model used to select a ginseng with sustainable efficacy and safety. Vuksan *et al*. [16] showed that 8 wk of supplementation with an AG extract at the dose of 1 g (prandial agent 40 min before each meal) similarly improved FPG and HbA_{1c}. These effects appeared to be mediated by a possible insulinotropic mechanism, as opposed to the insulin sensitizing mechanism proposed for the selected KRG treatment [16]. Taken together, the suggestion is that different ginseng sources, especially American ginseng and KRG, can be selected to have clinical efficacy in type 2 diabetes. This efficacy, nevertheless, may be mediated by different mechanisms.

Despite the recent conclusion that the best evidence for anti-hyperglycemic efficacy among complementary alternative medicine therapies is for AG [17], there remains limited clinical data to support the efficacy and safety of a KRG source. Vuksan and Sievenpiper [18] conducted clinical trial to explore the acute and chronic effects of American and Asian ginseng in subjects with and without diabetes by using a randomized, double-blind and placebo-controlled protocol: highly variable acute glycemic effects are observed secondary to the ginsenoside profile as it varies across ginseng batch, preparation, variety, and species. This situation necessitates that compositional markers of its anti-hyperglycemic effects be identified. This includes other unmeasured saponin and non-saponin constituents must also be considered. They concluded that without these data the consumer cannot be assured of the safety and efficacy of ginseng products and the calls from the medical community for randomized controlled trials and standardization of ginseng are needed. As show Table 1, Vuksan *et al*. [24] performed the first randomized, double-blind and placebo-controlled crossover clinical studies to examine the long-term anti-diabetic efficacy and safety of a KRG, selected based upon an acute-screening model [19,20,22]. Nineteen participants with well-controlled type 2 diabetes completed the study. Using a double-blind, randomized, crossover protocol, each participant received 2 g of KRG (rootlets) at 40 min before each meal (total 6 g/d) for 12 wk as an adjunct to their usual anti-diabetic therapy (diet and/or medications). They concluded that although clinical efficacy, as assessed by HbA_{1c}, was not demonstrated, supplementation with the selected KRG treatment for 12 wk maintained good glycemic control and improved plasma glucose and plasma insulin regulation safely be-

Table 1. Effects of ginseng on diabetes-related parameters in human studies

Material	Design	Drug dose (duration)	Result	Reference
American ginseng				
Root	Single-blind (10 type 2 diabetic patients)	3, 6,or 9 g at 120, 80 or 40 min before 25 g glucose challenge	Improve postprandial glycemia, but no differences between the 3, 6, or 9 g doses and any of the times of administration.	[19]
	Single-blind (9 type 2 diabetic patients, 10 non-diabetic subjects)	3 g at 40 or 0 min before 25 g oral glucose challenge	Reductions in AUC were 18±31% for non-diabetics (-40 min) and 19±22% and 22±17% for type 2 diabetics administered before or together with the glucose challenge, respectively.	[20]
	Single-blind	Acute study: AG 3, 6, 9 g	Insulin secretion ↑	[21]
		Long term study: 4 wk	AG extract added to the conventional treatment of diabetes significantly improved glycemic and blood pressure control beyond conventional treatment alone.	
	Random crossover (12 healthy individuals)	1,2 or 3 g at 40, 20, 10 or 0 min before 25 g glucose challenge	Postprandial glycemia↓ These reductions were time dependent but not dose dependent: an effect was seen only when the ginseng was administered 40 min before the challenge. Dose within the range of 1-3 g were equally effective.	[22]
Asian ginseng				
Root	Randomized single-blind placebo-controlled crossover trial (11 healthy volunteers)	Study 1: 1,2, or 3 g Study 2: 3,6 or 9 g at 40 min before 75 g oral glucose challenge	Glucose & insulin ↑ Two-hour plasma glucose significantly higher for pooled Asian ginseng treatment than placebo.	[23]
	Randomized double-blind placebo-controlled crossover trial (19 type 2 diabetic patients)	KRG 6 g/d for 12 wk as an adjunct to their usual anti-diabetic therapy	HbA1c × Glucose & insulin ↓	[24]
	Randomized double-blind placebo-controlled crossover trial (20 diabetic patients)	2×369 mg 3 times daily for 4 wk	Glucose & insulin↓, HOMA-IR ↓, antioxidant biomarkers ×. Ginseng supplementation can salvage at-risk subjects or delay the onset of diabetes by decreasing insulin resistance.	[25]
	Double-blind placebo-controlled crossover trial (study 1: 25 healthy volunteer, study 2: 18 healthy volunteers)	Study 1: 2×100 mg/d of G115 Study 2: 2×100 mg/d of KRG for 57 d	Glucose ×, HbA1c ×, insulin ×. The benefits to glucose regulation associated with long-term ginseng use may only be present in populations with compromised glucose control.	[26]
	Randomized double-blind placebo-controlled trial (15 overweight /obese with impaired glucose tolerance or type 2 diabetics)	KRG extract 3 g/d for 2 wk, then 8 g/d for 2 wk	No evidence to improve β-cell function or insulin sensitivity possibly due to poor bioavailability after oral ingestion	[27]
American, American-wild, Asian, Asian-red, Vietnamese-wild, Siberian, Japanese-rhizome, and Sanchi ginsengs				
Root	Double-blind randomized crossover trial (12 healthy volunteers)	10 Times of 3 g for each ginseng extract at 40 min before 75 g oral glucose challenge	Increase in AUC for Siberian and Asian, decrease in AUC for American ginseng. Ginseng has variable glycemic effects, in which the PPD:PPT-ginsenoside ratio might be involved.	[28]
PPT type saponin				
Rb_1, Rg_1		41 mg/d Rb_1 and Rg_1 for 2 wk	PPAR-γ in macrophage ↑, TC, TG & glucose↓	[29]
Re	Randomized double-blind placebo-controlled crossover trial (15 overweight /obese with impaired glucose tolerance or type 2 diabetics)	250 mg/d for 2 wk, then 500 mg/d for 2 wk	β-cell function or insulin sensitivity × Ginsenoside Re was not detectable in plasma after treatment ginsenoside Re.	[27]

AUC, area under the curve; HbA1c, glycosylated hemoglobin; HOMA, homeostasis model assessment; KRG, Korean red ginseng; PPAR-γ, peroxisome proliferator-activated receptor γ; PPD, protopanaxadiol; PPT, protopanaxatriol; TC, total cholesterol; TG, triglyceride.

yond usual therapy in people with well-controlled type 2 diabetes. Safety was not compromised by the observed metabolic benefits. The number or severity of adverse events did not differ between the selected KRG treatment and placebo. Hepatic, renal, hemostatic, and blood pressure variables were also not altered on the selected KRG treatment as compared with placebo. The demonstrated safety is noteworthy, as reviews have consistently warned of adverse effects of ginseng that include impaired hemostatic function and elevated blood pressure [30,31]. But owing to the large number of dropouts and problems regarding participants who may not represent typical candidates for adjunctive therapy, these benefits can only be considered as preliminary support for the possibility that further investigation with the selected KRG treatment may show clinical efficacy.

However, recent clinical trials independently performed by Reay *et al*. [26] and Reeds *et al*. [27] may fall into decline the ginseng's reputation as a potential therapeutic agent for type 2 diabetics. Healthy volunteers ingested either the G115 (ginseng product; Pharmaton Inc., Lugano, Switzerland) or KRG in placebo-controlled, double-blind, crossover studies. It was found that *P. ginseng* had no effect on any gluco-regulatory parameter investigated, suggesting that chronic use of *P. ginseng* by non-diabetic individuals will have little long-term effect on glucose regulation. In other clinical trial, conducted by Reeds *et al*. [27], to determine whether ginseng or ginsenoside Re improves β-cell function and insulin sensitivity in insulin-resistant subjects, fifteen overweight or obese adults were randomly assigned to 4 wk treatment with either: placebo capsule, KRG extract (3 g/d for 2 wk and 8 g/d for 2 wk), ginsenoside Re (250 mg/d for 2 wk, followed by 500 mg/d for 2 wk). They found no evidence that oral ginseng or ginsenoside Re therapy improves β-cell function or insulin sensitivity in overweight or obese subjects with impaired glucose tolerance or newly diagnosed type 2 diabetes. Although they cannot exclude the possibility that other ginsenosides and their metabolites or non-ginsenoside components of ginseng extract are bioavailable when given orally, they suggest that poor systemic bioavailability might be responsible for the absence of a therapeutic effect of KRG extract and ginsenoside Re.

A growing evidences of rigorously conducted cell and animal studies are pointing to different ginsenosides for anti-diabetic indications. Both protopanaxadiol (PPD)-type saponins (Rb_1, Rb_2, Rc, Rg_3, Rh_2, compound K, and PPD) and protopanaxatriol (PPT)-type saponins (Re, Rg_1, Rg_2, and PPT) were reported to possess anti-diabetic activity in cell and animal studies (Tables 2 and 3). The mechanisms underlying ginseng's hypoglycemic effect are not fully elucidated at present. However, animal and cell data would suggest four possible mechanisms that could potentially account for the modulation in blood glucose levels: 1) modulation of insulin production and secretion, 2) modulation of glucose metabolism, 3) modulation of glucose uptake, and 4) modulation of inflammatory pathway.

First, AG and KRG stimulate insulin secretion in HIT-T15 cells and isolated rat pancreatic islets, respectively [33,36], and other studies also demonstrate AG and KRG increase insulin production and secretion through inhibition of cytokine-induced β-cell apoptosis [34,35]. Lee *et el*. [78] demonstrated that intravenous injection of ginsenoside Rh_2 into Wistar rats decreased the plasma glucose levels parallel with increase in plasma insulin levels, and this effect is mediated by stimulating muscarinic M_3 receptors in pancreatic cells. In our previous study, PPD ginsenosides potentiated an insulin secretion stimulated by a low concentration of glucose. Compound K (also known as IH-901), an active metabolite of PPD ginsenosides, showed the most potent insulin secretion stimulating activity. *In vitro* studies using HIT-T15 cells and primary cultured islets, compound K enhanced the insulin secretion and this effect was completely abolished in the presence of diazoxide (K^+ channel opener) or nifedipine (Ca^{2+} channel blocker). Insulin secretion stimulating activity of compound K was also confirmed with an oral glucose tolerance test in ICR and *db/db* mice. From these studies, we concluded that compound K lowered the plasma glucose level by stimulating insulin secretion and this action was presumably associated with an ATP-sensitive K^+ channel [80].

Second, Wang *et al*. [32] demonstrated the hypoglycemic activity of ginseng glycopeptide possibly through stimulation of β-adrenoceptor and increase of various rate-limiting enzyme activities related to tricyclic acid cycle. Our group also reported that ginseng radix can ameliorate hyperglycemia possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase, and ginseng rootle can do it through the up-regulation of adipocytic peroxisome proliferator-activated receptor γ (PPAR-γ) expression as well as inhibiting intestinal glucose absorption in KKAy mice [88]. One of the most efficient ways to modulate glucose metabolism in diabetic patients would be a perturbation on hepatic glucose production. Recently, ginsenoside Rb_2, Re and Rg_1 were reported to suppress the hepatic gluconeogenesis in H4IIE and HepG2 cells, respectively, via activation of AMP-activated protein kinase (AMPK) [41,49,50].

Third, enhancement of glucose uptake through glucose transporter 4 (GLUT4) overexpression was documented to occur by treatment with either *P. notoginseng* [37], Rg_3 [43,44], Re [49] and 20(S)-PPT [51] in adipocytes or skeletal muscle cells. PPT increased expression of GLUT4 through increasing PPAR-γ transactivation activity in the 3T3-L1 adipocytes [51]. Recently, Lee *et al*. [64] reported that KRG at a dose of 200 mg/kg/d for 40-week-period improves insulin sensitivity in Otsuka Long-Evans Tokushima fatty rats by increasing expression of peroxisome proliferator–activated receptor-γ coactivator–1α, nuclear respiratory factor–1, cytochrome c, cytochrome c oxidase-4, and GLUT4.

Lots of medicinal plants including *P. ginseng* show anti-diabetic effect as well as controlling inflammation.

Table 2. Effects of ginseng on different molecular targets related to diabetes in cell line studies

Material	Cell line	Molecular mechanism	Reference
American ginseng			
Root	HIT-T15	Insulin secretion ↑ (EC50=178.9 mg/mL)	[33]
	INS-1	Insulin production/secretion ↑, UCP-2↓, ATP↑, Bcl2↑, caspase-9↓	[34]
Asian ginseng			
Root	MIN6N8	Cytokine-induced β-cell apoptosis ↓, NO & ROS production ↓, p53/p21↓, caspase ↓, PARP ↓	[35]
Root (KRG)	Rat pancreatic islets	Insulin secretion ↑ (glucose-independent manner)	[36]
Notoginseng			
Saponins	3T3-L1	Glucose uptake & glycogen synthesis ↑	[37]
Fermented ginseng (β-galactosidase treated)			
Root	RINm5F	iNOS, COX-2 & TNF-α ↓ NF-κB & MAPK (ERK and JNK) ↓	[38]
PPD type saponin			
Rb_1	3T3-L1	Glucose uptake ↑, GLUT1 & GLUT4 translocation ↑	[39]
	MIN6N8	Insulin secretion ↑	[40]
Rb_2	H4IIE	Hepatic gluconeogenesis ↓, LKB1, AMPK & SHP ↑, G6Pase & PEPCK ↓	[41]
Rc	C2C12	Glucose uptake↑, ROS ↑, AMPK ↑, p38↑	[42]
Rg_3	L6 myotubes	Glucose uptake ↑, IRS-1 & GLUT4 expression ↑	[43]
	C2C12	Glucose uptake ↑, CaMKK & AMPK ↑	[44]
	MIN6N8	Palmitate-induced apoptosis ↓, MAPK ↓	[45]
	3T3-L1	Glucose uptake ↑, GLUT4 ↑, IRS & PI3K ↑	[46]
Compound K	Caco-2	SGLT1↑, GLUT1, GLUT2 & GLUT3 ↑	[47]
PPD	RMC	Rb_1, Rb_2 & Rg_3 - fibronectin expression ↓ Re & Rd - fibronectin expression × Rb1 - MAPK and Akt phosphorylation ↑	[48]
PPT type saponin			
Re	3T3-L1	Glucose uptake ↑, GLUT4 ↑, IRS & PI3K ↑	[46]
	HepG2	Hepatic gluconeogenesis ↓, AMPK ↑, SREBP-1c ↓	[49]
Rg_1	MIN6N8	Insulin secretion ↑	[40]
	Caco-2	SGLT1 ↓, GLUT1, GLUT2 & GLUT3 ×	[47]
	HepG2	Hepatic gluconeogenesis ↓, AMPK ↑	[50]
PPT	3T3-L1	PPAR-γ ↑, aP2 ↑, LPL ↑, PEPCK ↓, GLUT4 ↑	[51]

AMPK, AMP-activated protein kinase; aP2, fatty acid binding protein; Bcl2, B-cell lymphoma 2; CaMKK, calcium/calmodulin-dependent protein kinase kinase; COX-2, cyclooxygenase-2; ERK1/2, extracellular signal-regulated kinase; GLUT, glucose transporter; iNOS, inducible nitric oxide synthase; IRS, insulin-receptor substrate; JNK, c-jun NH2-terminal kinase; KRG, Korean red ginseng; LKB1, liver kinase B1; LPL, lipoprotein lipase; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-κB; NO, nitrite oxide; PARP, poly (ADP-ribose) polymerase; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphatidylinositide 3 kinase; PPAR-γ, peroxisome proliferator-activated receptor γ; PPD, protopanaxadiol; PPT, protopanaxatriol; RMC, rat mesangial cell; ROS, reactive oxygen species; SGLT1, sodium-glucose cotransporter 1; SHP, small heterodimer partner; SREBP, sterol regulatory element-binding protein; TNF-α, tumor nuclear factor-α; UCP, uncoupling protein.

It has been postulated that diabetes is a manifestation of an ongoing chronic low-grade inflammation. Chronic subclinical inflammation is associated with insulin resistance, a situation of increased risk for developing diabetes [89]. Inflammatory processes seem to play an important role in the development of diabetes and its late complications [90]. Inflammatory cytokines, for example, TNF-α, IL-1β, IL-6, nitrite oxide, and so on, are released from macrophages or other tissues during a state of inflammation. These factors can activate the IκB kinase (IKK)/c-Jun NH2-terminal kinase (JNK) pathway, which results in the inhibition of insulin receptor substrate/phosphatidylinositide 3-kinase pathway and brings about insulin resistance. Therefore, slight or moderate anti-inflammatory effects of *P. ginseng* (or its active components) may be responsible for their hypoglycemic mechanisms. For example, Zhang *et al*. [87] examined the insulin signaling and anti-inflammatory effect of gin-

senoside Re in 3T3-L1 adipocytes and in high fat diet-fed rats to dissect its anti-hyperglycemic mechanism. The results show that Re reduces insulin resistance through inhibition of JNK and nuclear factor-kB. This may contribute new evidences indicating that slight or moderate regulatory modulation by Re on inflammation may be an effective tactic to prevent the development of insulin resistance. Recently, Lee *et al*. [41] also demonstrated that ginsenoside Rb_2 inhibits palmitate-induced gluconeogenesis in H4IIE cells (rat-derived hepatocytes) via AMPK-

Table 3. Effects of ginseng on diabetes-related parameters in animal studies

Material	Animal	Molecular mechanism	Reference
American ginseng			
Berry	*ob/ob* mice	Glucose & body weight ↓, improve glucose tolerance	[52]
	ob/ob mice	Glucose & body weight ↓, body temperature ↑, improve glucose tolerance	[53]
Leaf	*ob/ob* mice	Glucose & body weight ↓, improve glucose tolerance	[54]
Root	*db/db* mice	TNF-α-induced free fatty acid release↓, adiponectin secretion ↑	[55]
	STZ-induced SD rats	Serum urea, creatinine, glucose, C-peptide & NO↓, G6Pase & glycogen phosphorylase ↓	[56]
	ZDF rats	Body weight ↑, kidney weight ↓, cholesterol ↓	[57]
Asian ginseng			
Berry	*ob/ob* mice	Glucose↓, improve glucose tolerance	[58]
Leaf	HFD-induced mice	Body weight, glucose, insulin, TG, TC & leptin ↓, NEFA ↓, SREBP1, FAS, SCD1& GPAT ×, PPAR-α & CD36 ↑, PEPCK ↓	[59]
Leaf and root	*ob/ob* mice	Glucose↓	[60]
Root	*db/db* mice	Glucose, insulin & HbA1c ↓, adiponectin & leptin ↑, TG & NEFA↓, AMPK ↑, SREBP1, FAS & SCD1↓, PPAR-α ↑, CD36 ↑, PEPCK ↓	[61]
	db/db mice	Glucose↓, insulin ↑, HbA1c ↓, adiponectin & leptin ↑, TG & NEFA↓, AMPK ↑, SREBP1, FAS & SCD1↓, PPAR-α ↑, CD36 ↑, PEPCK ↓	[62]
	db/db mice	Glucose, TG & HbA1c↓, PPAR-α & PPAR-g↑, LPL ↓	[63]
	OLETF rats	Glucose ↓, insulin ↑, HbA1c ↓, TC, TG & LDL-C↓, hsCRP ↓, AST ↑, AMPK ↑, PGC-1α ↑, MEF-2 ↑, GLUT4 ↑, NRF-1↑, cytochrome c↑, cytochrome c oxidase-4↑, UCP-1↑	[64]
Root (KRG)	STZ-induced mice	Glucose ↓, improve glucose tolerance	[65]
	STZ-induced rats	Glucose ↓, renal index ↓, creatinine clearance rate ↓, urinary albumin ↓, TGF-β↓, Smad ↑	[66]
	C57BL/6J and KK-Ay mice	Glucose, insulin & insulin resistant ↓, leptin ↓, improved glucose tolerance, food intake ↓, epididymal fat weight↓	[67]
Fermented ginseng			
Vinegar-treated root	HFD-fed mice	Insulin resistance↓, epididimal fat size↓, glucose, insulin, TG, TC, LDL-C & NEFA ↓, HDL-C ↑	[43]
	OLETF rats	IRS protein level ↑	[68]
β-galactosidase treated root	*db/db* mice	Glucose & HbA1c ↓, insulin ↑, leptin ↑, adiponectin ↓, TG & NEFA ↓	[69]
	STZ-induced rats	Glucose & insulin ↓, iNOS, COX-2 & NF-κB ↓, JNK and ERK1/2 phosphorylation ↓	[70]
Heat-treated root	OLETF rats	Glucose, TG & TC ↓, TBA-reactive substance ↓, urinary protein ↓, iNOS ↓, CML ↓	[71]
	STZ-induced rats	Glucose ↓, glycosylated protein ↓, urinary protein ↓, urea nitrogen ↓, creatinine ↓, AGEs ↓, TBA-reactive substance ↓, iNOS, COX-2 & NF-κB ↓, CML & RAGE ↓	[72]
	STZ-induced rats	Glucose ↓, glycosylated protein ↓, urinary protein ↓, NF-κB, COX-2 & iNOS ↓, CML & RAGE↓	[73]
	STZ-induced rats	Glucose ↓, glycosylated protein ↑, urinary protein ↓, creatinine clearance rate ↑, AGE ↓	[74]
Pectinase-treated root	HFD-fed mice	Glucose ↓, insulin ↓, improved glucose tolerance AMPK & GLUT4 ↑	[75]
Wild ginseng			
Root	HFD-fed mice	Body weight gain ↓, glucose & insulin ↓, TG, LDL-C & NEFA ↓, HDL-C ↑	[76]
PPD type saponin			
Rg_3	OLETF rats	Glucose, TG & TC ↓, TBA-reactive substance ↓, urinary protein ↓, iNOS ↓, CML ↓	[71]
	STZ-induced rats	Water intake and urine volume ↓, glucose ↓ glycosylated protein ↓, TBA-reactive substance ↓ iNOS, COX-2 & NF-κB ↓, 3-Nitrotyrosine ↓ NMDA-NR1 ↓, CML & RAGE ↓	[77]
Rh_2	Wistar rats	Glucose ↓, insulin & C-peptide ↑	[78]
	STZ-induced rats	Glucose ↓, β-endrophin secretion ↑, GLUT4 ↑	[79]

Table 3. (Continued)

Material	Animal	Molecular mechanism	Reference
Compound K	*db/db* mice	Glucose, insulin & TG ↓ GLUT4 & PPAR- γ expression ↑	[80]
	db/db mice	Glucose, insulin, HbA1c, adiponectin, TG & NEFA ↓, insulin secretion ↑	[81]
	db/db mice	Glucose, TG, TC & NEFA ↓, insulin ↑, AMPK ↑, SREBP1, FAS, SCD1 & GPAT ↓, CD36, PPAR-α & GLTU4 ↑	[82]
	db/db mice	Glucose ↓, insulin ↑, HbA1c ↓, adiponectin ↓, TG, TC & LDL-C ↓, HDL-C ↑	[83]
PPT type saponin			
Re	STZ-induced rats	When Re-treated diabetic rats were compared to the untreated control rats, a protein peak was detected to have significant alteration corresponding to Re treatment. This specific protein was a C-reactive protein , indicating that Re may improve diabetes by alleviation of inflammation.	[84,85]
	ob/ob mice	EC70=10.3 mg/kg, glucose & insulin ↓ Improved glucose tolerance Body weight & body temperature ×	[86]
	HFD-fed rat	JNK & NF-κB ↓, insulin resistance ↓	[87]

AGEs, advanced glycation end products; AMPK, AMP-activated protein kinase; AST, aspartate transaminase; CML, Nε-Carboxymethyl lysine; COX-2, cyclooxygenase-2; ERK1/2, extracellular signal-regulated kinase; FAS, fatty acid synthase; FPG, fasting plasma glucose; G6Pase, glucose-6-phosphatase; GLUT, glucose transporter; GPAT, glycerol-3-phosphate acyltransferase; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; iNOS, inducible nitric oxide synthase; IRS, insulin-receptor substrate; JNK, c-Jun NH2-Terminal kinase; KRG, Korean red ginseng; LDL-C, low-density lipoprotein cholesterol; MEF-2, myocyte enhancer factor-2; NEFA, non-esterified fatty acid; NF-κB, nuclear factor-κB; NO, nitrite oxide; NMDA-NR1, N-methyl-D-aspartate receptor NR1, NRF-1, nuclear respiratory factor-1; OLETF, Otsuka Long-Evans Tokushima fatty; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor- γ coactivator-1 α; PPAR-γ, peroxisome proliferator-activated receptor γ; PPD, protopanaxadiol; PPT, protopanaxatriol; RAGE, receptor for AGEs; SCD1, stearoyl-CoA desaturase-1; SREBP, sterol regulatory element-binding protein; TBA, thiobarbituric acid; TC, total cholesterol; TG, triglyceride; TGF-β, transforming growth factor-β; TNF-α, tumor nuclear factor- α; UCP, uncoupling protein.

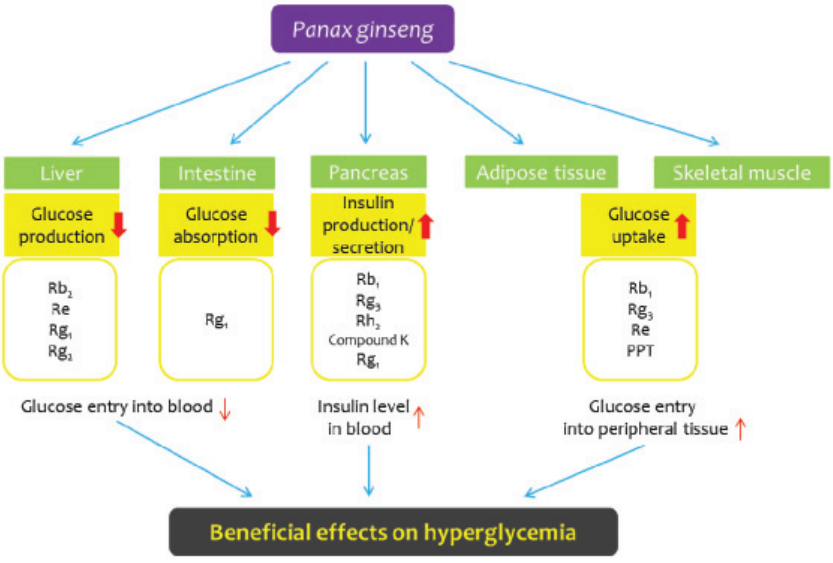

Fig. 1. Pharmacological effects of *Panax ginseng* on various organs related to diabetes. Ginsenosides known to work on each organ are listed underneath. PPT, protopanaxatriol.

induced orphan nuclear receptor small heterodimer partner by relieving endoplasmic reticulum stress, which is induced by palmitate through JNK activation. Taken together, proposed action mechanisms of *P. ginseng* and ginsenosides as a potential anti-diabetic agent can be summarized in Fig. 1.

Recent trends in drug prescription for type 2 diabetics have seen a move away from agents that stimulate insulin secretion, such as the sulfonylureas, toward agents that increase insulin sensitivity, such as biguanides (metformin) and thiazolidinediones (pioglitazone). An exciting recent development has been a finding that both of these latter classes of drug activate the AMPK [91,92]. As research on AMPK has progressed, it became increasingly clear that AMPK activators might be useful as drugs to treat insulin resistance or type 2 diabetes. First, AMPK

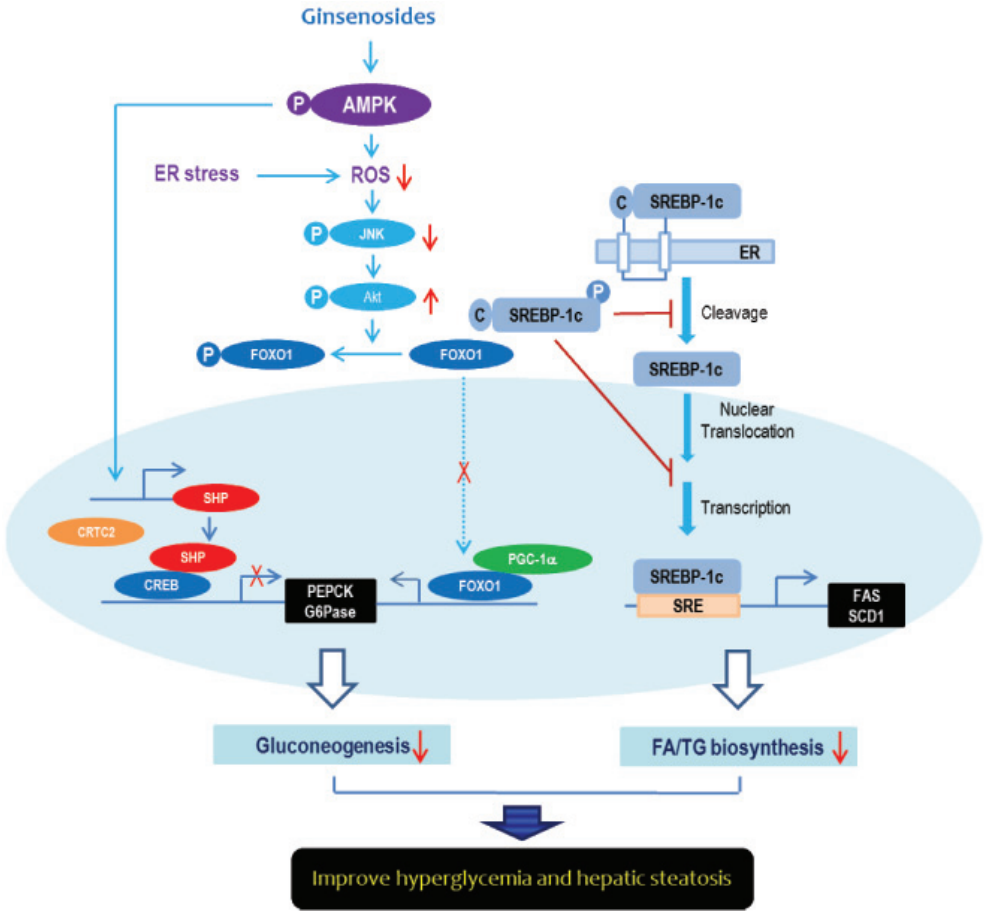

Fig. 2. Proposed model for ginsenosides to suppress hepatic gluconeogenesis and steatosis through induction of small heterodimer partner (SHP) gene expression, reduction of reactive oxygen species (ROS) production, or phosphorylation of sterol regulatory element-binding protein (SREBP)-1c via AMP-activated protein kinase (AMPK) signaling pathway. Lee *et al*. [95] demonstrated that SHP decreases cAMP response element binding (CREB)-dependent induction of gluconeogenic gene expression and hepatic glucose production via disruption of CREB·CREB-regulated transcription co-activator 2 (CRTC2) complex due to direct interaction with CREB. AMPK is also known to suppress mitochondrial ROS production by oxidative stress via inducing antioxidant enzymes such as manganese superoxide dismutase, which leads to inactivation of c-Jun NH2-Terminal kinase (JNK), activation of Akt and consequently inhibition of hepatic glucose production. Recently, Li *et al*. [97] also demonstrated that AMPK interacts with and directly phosphorylates SREBP, which is necessary for inhibition of proteolytic processing and transcriptional activity of SREBP-1c in response to ginsenosides. ER, endoplasmic reticulum; FAS, fatty acid synthase; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1 α; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase-1; FA, fatty acid; TG, triglyceride.

acutely increases glucose uptake into adipose tissue or skeletal muscle via a mechanism that remains functional in insulin-resistant individuals and also increases GLUT4 expression [93] so that insulin would promote glucose uptake even with no change in insulin sensitivity. Second, AMPK promotes glucose metabolism by increasing mitochondrial biogenesis, which is relevant because people at risk of developing type 2 diabetes appear to have a deficit in mitochondrial function [94]. Third, AMPK could increase insulin sensitivity by promoting fat oxidation and reducing triglyceride storage; an excess amount of muscle triglyceride is associated with insulin resistance [94]. Finally, an important source of the high glucose concentrations in type 2 diabetes patients is elevated hepatic glucose production, which AMPK inhibits by down-regulating gluconeogenic genes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Up to now, about fifteen articles were published to demonstrate that pharmacological and therapeutic effects of ginsenosides are associated with AMPK. Ginsenosides as an AMPK activator can ameliorate metabolic diseases such as diabetes (Rb_2, Rc, Rg_3, compound K, Rg_1, Rg_2, Re), obesity (Rg_3 and Rh_2), nonalcoholic fatty liver disease (compound K), and cancer (Rg_3 and compound K). Along with other researchers, our group is working on AMPK signaling pathway as a molecular target of ginseng and specific ginsenosides since 2007, and several ginsenosides including Rg_3 [44], compound K [81,82], Re

[49], Rg_1 [50] and Rg_2 [96] are shown to activate AMPK signaling pathway and possess beneficial effects on type 2 diabetes, obesity and nonalcoholic fatty liver disease. At present, we do not know exactly how ginseng or specific ginsenoside activates AMPK signaling pathway, so further studies are needed to investigate whether AMPK is a direct molecular target for ginseng and specific ginsenoside. Unlike 5-aminoimidazole-4-carboxamide riboside, a well-known direct AMPK activator, ginsenosides seem not to be a direct AMPK activator. We are now working on the hypothesis that ginsenosides, as an uncoupler like carbonylcyanide-p-trifluoromethoxyphenylhydrazone (FCCP) and 2,4-dinitrophenol, may cause a decrease in ATP biosynthesis in mitochondria, resulting change in AMP:ATP ratio, which provides a possible mechanism for its activation of AMPK. Taken together, our results regarding AMPK signaling pathway as a molecular target, we propose the action mechanism of ginsenosides to suppress hepatic gluconeogenesis and steatosis via activation of AMPK signaling pathway (Fig. 2).

The prevalence of obesity in a modern society has increased dramatically over the past few years and has reached epidemic proportions. Obesity is a major risk factor for type 2 diabetes, cardiovascular problems, and some forms of cancer. Although efforts to address the environmental and genetic factors responsible for the 'epidemic' must continue, and because currently available anti-obese and anti-diabetic drugs have limited efficacy and/or safety concerns, developing safe and effective medicinal agents, particularly with the dual properties of controlling body weight and reducing blood glucose, offers exciting possibilities for developing successful therapies. In this context, it would be more desirable if *P. ginseng* or its active constituents show both anti-obese and anti-hyperglycemic effects. For example, Attele *et al*. [58] evaluated anti-hyperglycemic and anti-obese effects of *P. ginseng* berry extract and ginsenoside Re in C57BL/6J *ob/ob* mice. Intraperitoneal injection of berry extract significantly improved glucose tolerance and caused to reduce body weight, and ginsenoside Re was known to be responsible for anti-hyperglycemic action of *P. ginseng* berry extract. Recently, Xiong *et al*. [98] identified ginsenoside Rb_1 as anti-obese and anti-hyperglycemic agent. Acute administration of Rb_1 suppressed food intake, probably mediated by stimulation of c-fos gene. Four-week administration of Rb_1 significantly reduced food intake, body weight gain, and body fat content and increased energy expenditure in high fat diet-induced obese rats. Rb_1 also markedly decreased fasting blood glucose and improved glucose tolerance, suggesting that although Rb_1's anti-hyperglycemic effect is partially attributable to reduced food intake and body weight, there may be additional effects of Rb_1 on glucose homeostasis.

CONCLUSION

Data from animal and *in vitro* studies have shown that ginseng extract and specific ginsenosides have beneficial effects on glucose and lipid metabolism. However, the results from clinical studies for ginseng root or ginsenoside Re are unclear because of confounding factors that could have influenced the outcomes, such as changes in body weight and physical activity, changes in diabetic medications, large drop-out rates, and poor systemic bioavailability. Although some ginsenosides including Re have claimed anti-hyperglycemic and/or diabetes-related activities, it remains unclear which species and batches of ginseng have anti-hyperglycemic efficacy and which saponin or non-saponin components confer this efficacy. Therefore, there are some points to be duly considered for usage of ginseng (or its active constituents) as a dietary supplement for diabetes mellitus: 1) standardization, 2) pharmacokinetic and pharmacodynamic studies at the molecular levels, and 3) double-blind and placebo-controlled large scale clinical studies. Although most of preclinical studies have mainly focused on ginsenosides as active constituents of *P. ginseng* for diabetes, researches directed at the identification of active components are still needed to support efficacy claims for ginseng. Another concern is the claim of poor systemic bioavailability of ginseng and ginsenoside Re, which is recently reported by Reeds *et al*. [27]. They did not observe any beneficial effects of KRG and ginsenoside Re on pancreatic β-cell function and insulin resistance. They concluded that poor systemic bioavailability might be responsible for the lack of a therapeutic effect, since ginsenosides Re, Rb_1, and Rb_2 were not detectable in plasma after treatment with ginseng root or ginsenoside Re. Liu *et al*. [99], however, have detected simultaneously ginsenoside Re and its probable metabolites (Rg_1, Rf_1, Rh_1, and PPT) in plasma after Re administration in healthy volunteer. Therefore, in-depth pharmacokinetic studies of ginseng and specific ginsenosides are to be performed to examine the presence of active metabolites. Along with these pharmacokinetic and pharmacodynamics studies, standardization for ginseng preparation is also imperative to support therapeutic implications. While more studies are warranted to further understand these contradictions, ginseng holds promise as a therapeutic agent for diabetes prevention and treatment.

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