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Review article

Ginseng and obesity

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ABSTRACT

Although ginseng has been shown to have an antiobesity effect, antiobesity-related mechanisms are complex and have not been completely elucidated. In the present study, we evaluated ginseng's effects on food intake, the digestion, and absorption systems, as well as liver, adipose tissue, and skeletal muscle in order to identify the mechanisms involved. A review of previous *in vitro* and *in vivo* studies revealed that ginseng and ginsenosides can increase energy expenditure by stimulating the adenosine monophosphate-activated kinase pathway and can reduce energy intake. Moreover, in high fat diet-induced obese and diabetic individuals, ginseng has shown a two-way adjustment effect on adipogenesis. Nevertheless, most of the previous studies into antiobesity effects of ginseng have been animal based, and there is a paucity of evidence supporting the suggestion that ginseng can exert an antiobesity effect in humans.

1. Introduction

Obesity is a medical condition in which excess body fat accumulates to the extent that it may have a negative effect on health. Previous researchers have reported that obesity can increase the risk of various diseases, particularly type 2 diabetes [1]. Many factors such as diet, lifestyle, genetics, and gut microbiota may be associated with obesity; of those, excess food intake is considered a primary factor [2]. Apart from dieting and physical exercise, several drugs such as lorcaserin, orlistat, phentermine, and topiramate are available for the treatment of obesity. Unfortunately, drug treatment of obesity is often associated with side effects and a rebound weight gain after the cessation of drug use [3]. Complementary and alternative therapies, long used in the Eastern world, are currently receiving considerable attention and are eliciting widespread interest worldwide. Ginseng is an ancient herbal remedy that was recorded in *The Herbal Classic of the Divine Plowman*, the oldest comprehensive *materia medica*, which was scripted approximately 2000 yr ago. Contemporary science suggests that ginseng has various bioactivities. At present, research studies have also indicated that ginseng might exert a potential antiobesity effect. Ginsenosides are the main ginseng component that is responsible for its various activities. Dammarane-type ginsenosides can be divided into two groups: protopanaxadiol (PPD) and protopanaxatriol (PPT) types. Those groups are based on the number of hydroxyl groups that can be joined to sugar moieties via a dehydration reaction. Common PPD-type ginsenosides include ginsenosides Rb1, Rb2, Rc, Rd, Rg3, F2, Rh2, compound K (cK), and PPD, whereas common PPT-type ginsenosides include Re, Rf, Rg1, Rg2, F1, Rh1, and PPT. Ginsenosides can be degraded to a deglycosylated form by the actions of gut microbiota [4]. Generally, only the ginsenosides cK and Rh1 (or F1), the degraded forms of PPD and PPT types, respectively, can be absorbed into the circulatory system after oral intake [5]. This review is aimed at evaluating the antiobesity efficacy of ginseng and ginsenosides and delineating the mechanisms by which they function.

2. Effect on food intake

Hypothalamic inflammatory activation as a result of consuming a high fat diet (HFD) and obesity are thought to disturb anorexigenic and thermogenic signals and promote abnormal body weight control [6]. Under chronic inflammation in the hypothalamus of mice, as a response to HFD, mechanisms mediating a sustained cycle of appetite enhancement were observed [7]. Leptin is a hormone made by adipocytes, and it acts on receptors in the arcuate nucleus of the hypothalamus to regulate appetite in order to achieve energy homeostasis. Long-term HFD consumption in murine

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has been reported to evoke leptin resistance, which is characterized by an increased level of plasma leptin. Ginsenoside Rb1 was reported to decrease the expression levels of inflammatory markers such as p-IκB kinase, interleukin (IL)-6, and IL-1β, and negative regulators of leptin signaling such as suppressor of cytokine signaling 3 (SOCS3) and protein-tyrosine phosphatase 1B (PTP1B) in the hypothalamus and restore the anorexic effect of leptin in HFD-fed mice and leptin p-STAT3 signaling in the hypothalamus [8]. Administration of ginseng extracts has decreased plasma levels of leptin and neuropeptide Y and alleviated leptin resistance in HFD-fed murine [9]. In addition, it was reported that PPD-type ginsenosides inhibited expression of cholecystokinin (CCK), which acts as a hunger suppressant, in the hypothalamus of mice fed with HFD, whereas PPT-type ginsenosides increased the expression [10]. Through such actions, ginseng or ginsenosides may prevent excess energy intake and the onset of obesity. In support of this suggestion, a number of animal researchers have documented that ginseng administration can repress food intake in mice and rats [10–18].

3. Effect on digestion and absorption systems

Liu et al [19] reported that PPD-type ginsenosides such as Rb1, Rb2, Rc, and Rd significantly suppress pancreatic lipase activity, whereas PPT-type ginsenosides Re and Rg1 do not, results that support the research results reported by Liu et al [20]. In addition, an extract of ginseng root, mainly containing PPD-type ginsenosides [21], was shown to exert similar activities [19,22]. Pancreatic lipase inhibitors can prevent obesity by increasing fat excretion into feces, and it has been reported that supplementation of ginseng extract increases fecal weight and fecal lipid content in mice [12,23]. Therefore, ginseng may decrease energy harvest of an organism by inhibiting pancreatic lipase activity. Although PPD-type ginsenosides may be more efficient than PPT-type ginsenosides in inhibiting pancreatic lipase activity, the PPT-type ginsenoside Rg1 was shown to suppress the expression of sodium-dependent glucose transporter 1 (SGLT1), thereby decreasing glucose absorption across Caco-2 cell monolayer, whereas cK, a PPD-type ginsenoside, increased the expression of SGLT1 and the uptake of glucose [24]. Subsequent research has revealed that ginsenoside Rg1 can inhibit SGLT1 expression by reducing the binding of cAMP response element-binding protein (CREB) to the cAMP response element that is associated with an inactive chromatin status [25].

4. Effect on liver

The enzyme adenosine monophosphate-activated kinase (AMPK) acts as a metabolic master switch regulating cellular energy homeostasis, and activation of AMPK stimulates fatty acid oxidation, ketogenesis, biogenesis of mitochondria, and uptake of glucose, but inhibits cholesterogenesis, lipogenesis, and triglyceride (TAG) synthesis [26].

Numerous *in vitro* research reports have documented that ginseng and ginsenosides can activate the AMPK pathway resulting in increased levels of p-AMPK and phospho-acetyl-CoA carboxylase in hepatocyte HepG2 cells [27–35] (Table 1). By activating this pathway, ginseng and ginsenosides can, *in vitro*, suppress the expression of fatty acid synthase (FAS), 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), phosphoenolpyruvate carboxykinase (PEPCK), and glucose 6-phosphatase (G6Pase)—thereby inhibiting TAG synthesis [27,28,31], cholesterogenesis [28,33], and gluconeogenesis [29,30,34].

Consistent with the results of *in vitro* studies, various *in vivo* animal studies have indicated that ginseng or ginsenosides activate the AMPK pathway in liver in an HFD-fed model [29,65]. HFD-fed mice supplemented with a ginseng extract showed a low liver weight [66,67], which might be attributed to a decrease in the deposition of hepatic lipid. In support of that suggestion, several researchers have reported that ginseng supplementation can decrease hepatic lipid content and ameliorate liver steatosis [11,12,17,18,23,66–68] (Table 2).

Peroxisome proliferator-activated receptor (PPAR)-α can be activated downstream by AMPK and can facilitate fatty acid export from hepatocytes and oxidation [76]. It has been reported that a fermented ginseng extract can increase the expression of PPAR-α in HepG2 cells [27]. Furthermore, ginseng extract and its main ginsenoside, Rb1, were reported to exert such an effect *in vivo* [18,73]. An HFD increases PPAR-γ protein expression and decreases expression of CREB in the nuclei of hepatocytes—results that have been associated with HFD-induced liver steatosis [77]. Ginsenoside PPT, the final metabolite of PPT-type ginsenosides, has been shown to work as a PPAR-γ antagonist and represses fat deposition in the liver of HFD-induced obese C57BL/6 mice [13].

Nonalcoholic fatty liver disease (NAFLD), the most common liver disorder in developed countries, occurs when fat is deposited in the liver owing to causes other than excessive alcohol use and up to 80% of evaluated obese individuals have been shown to have NAFLD [78]. NAFLD is strongly associated with hepatic insulin resistance and type 2 diabetes [79]. On an HFD, lipotoxicity can result in increased activity levels of aspartate transaminase and alanine transaminase (ALT), which are commonly measured clinical biomarkers of liver health. Mice fed with HFD supplemented with ginseng have shown a low activity level of these two enzymes [67]. Thus, ginseng might alleviate lipotoxicity, hepatic steatosis, and insulin resistance by activating the AMPK pathway.

In enterohepatic circulation, bile synthesized in the liver from cholesterol is released to the intestine where a portion of the bile acids is degraded by intestinal bacteria exerting bile acid hydrolase activity and excreted with feces [80]. Cholesterol is used to neosynthesize bile acids in a homeostatic response, resulting in a lowering of cholesterol levels in liver and plasma. Cytochrome P450 7A1 (CYP7A1) and cytochrome P450 8B1 (CYP8B1) are enzymes involved in bile acid synthesis, and multidrug resistance-associated protein (MRP) 2 is a transporter that facilitates biliary efflux from hepatocytes. It has been shown that red ginseng extract and ginsenosides can increase the expression of CYP7A1, CYP8B1, and MRP2 *in vitro* and *in vivo* [81,82]. Ginsenoside Rb1 can decrease the cholesterol content in the liver of HFD-fed mice by suppressing HMGCR [83], and ginsenoside Rb2 can upregulate the expression of the low density lipoprotein receptor (LDL-R), which mediates the clearance of cholesterol from plasma to hepatocytes [55,84]. Qureshi et al [68] and Muwalla and Abuirmeileh [85] showed that dietary supplementation of ginseng can suppress avian hepatic cholesterogenesis and decrease plasma LDL cholesterol. Taken together, it may be concluded that ginseng inhibits cholesterogenesis in the liver and facilitates cholesterol clearance in plasma, bile acid synthesis from cholesterol, and biliary efflux from hepatocytes. Through such effects, the levels of cholesterol in liver and plasma are reduced.

5. Effect on adipose tissue

There are several reports showing that ginseng can reduce adipocyte size and fat storage in mice and rats fed with HFD [9,20,69,70]. In fact, ginseng or ginsenosides also activate the AMPK pathway in fat cells. Ginsenosides Rg1, Rg3, Rh2, and cK increase the level of p-AMPK and inhibit TAG synthesis in 3T3-L1 cells [40,43,45]. PPAR-γ stimulates lipid uptake, fatty acid storage, and adipogenesis in fat cells, and PPAR-γ knockout mice fail to generate adipose tissue when fed with HFD [86]. It has also been reported that ginsenosides Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, and cK

Table 1
Effects of ginseng on different targets related to obesity in cell line studies

Material	Cell line	Mechanism	Ref.
Rb1	3T3-L1	Insulin-induced GPDH↑	[36]
Rb1, Rd, Rh2		Insulin-induced adipogenesis↑	
Re, Rg1, Ro		No effect	
Rb2, Ro, Re, Rg1, Rh1	3T3-L1	LPL↑	[37]
Rb1	3T3-L1	PPAR-γ↑, C/EBPα↑, aP2↑, GLUT4↑ adipogenesis↑	[38]
PPT	3T3-L1	PPAR-γ↑, aP2↑, LPL↑, GLUT4↑, PEPCK↑, adipogenesis↑	[39]
PPT	3T3-L1 (rosiglitazone)	PPAR-γ↓, aP2↓, C/EBPα↓, FAS↓, CD36↓, LPL↓	[13]
Rh2	3T3-L1	PPAR-γ↓, p-AMPK↑, ROS↑, UCP2↑, CPT1↑, adipogenesis↓	[40]
Rb2, Rc, Rd, Re, Rb1, Rg1	3T3-L1	TAG↓, cAMP↓ glucose uptake↑ cAMP↑, PKA↑, PPAR-γ↓, C/EBPα↓, aP2↓, TAG↓, glucose uptake↑	[41]
Rb1	3T3-L1	GLUT1 and GLUT4 translocation↑, IRS1↑, p-Akt↑, PI3K↑ Glucose uptake↑	[42]
Rg3	3T3-L1	PPAR-γ↓, AMPK↑, adipogenesis↓(rosiglitazone-treated)	[43]
Rb2	3T3-L1	In high cholesterol and high fatty acids conditions, SREBP1↑, FAS↑, leptin↑, cholesterol ↓, TAG↓	[44]
Rg1	3T3-L1	GLUT4↑, p-Akt↑, p-AMPK↑, p-ACC↑, glucose uptake↑, TAG↑	[45]
cK		GLUT4↑, p-Akt↑, p-AMPK↑, p-ACC↑, glucose uptake↑, TAG↓	
Rh2	3T3-L1	Activation of glucocorticoid receptor↑, adipogenesis↑	[46]
Rg3, less polar ginsenosides	3T3-L1	Lipid accumulation↓	[47]
Re	3T3-L1	TNF-α↓, LPL↑, leptin↓, resistin↓	[48]
Re, Rc	3T3-L1	Leptin↓, HSL↑, resistin↓,	[49]
American ginseng	3T3-L1	Adiponectin↑, TAG↓	[50]
Ginseng extract	3T3-L1	Adiponectin↑, TAG↓	[51]
Re, Rg3	3T3-L1	GLUT4↑, IRS1↑, PI3K↑, glucose uptake↑	[52]
cK	3T3-L1	PPAR-↓, aP2↓, C/EBPα↓, VEGF-A↓, FGF2↓, MMP2↓, MMP9↓, TSP1↑, TIMP1↑, TIMP2↑, adipogenesis↓	[53]
Ginseng extract, Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3	3T3-L1	PPAR-γ↓, aP2↓, C/EBPα↓, MMP2↓, MMP9↓, TIMP1↑, TIMP2↑, adipogenesis↓	[54]
Rb2	HepG2	SREBP1↑, LDL-R↑	[55]
Rg1	HepG2	p-AMPK↑, p-ACC↑, G6Pase↓, PEPCK↓, gluconeogenesis↓	[30]
Fermented ginseng	HepG2	PPAR-α↑, p-AMPK↑, p-ACC↑, FAS↓, TAG↓	[27]
Korean Red Ginseng	HepG2	p-AMPK↑, p-ACC↑, FAS↓, SCD↓, TAG↓	[31]
Korean Red Ginseng	HepG2	p-AMPK↑, p-ACC↑	[32]
	L6 myotubule	p-AMPK↑, p-ACC↑	
Rg3	HepG2	SREBP2↓, HMGCR↓, cholesterol↓, TAG↓, AMPK↑	[33]
Re	HepG2	p-AMPK↑, p-ACC↑, G6Pase↓, PEPCK↓, SREBP1↓, FAS↓, gluconeogenesis↓	[29]
Rg1	HepG2	p-Akt↑, p-AMPK↑, p-ACC↑, gluconeogenesis↓, glycogen synthesis↓, lipids↓	[34]
Korean Red Ginseng	HepG2	FAS↓, HMGCR↓, TAG↓, cholesterol↓	[28]
ginseng	HepG2	p-AMPK↑, FAS↓, HMGCR↓, TAG↓, TC↓	[35]
Rc	C2C12	p-AMPK↑, p-ACC↑, glucose uptake↑	[56]
Rg1	C2C12	AMPK↑, p-AMPK↑, GLUT4↑, glucose uptake↑	[57]
Korean Red Ginseng	C2C12	p-AMPK↑, p-ACC↑, fatty acid oxidation↑	[58]
Ginseng extracts	C2C12	Glucose uptake↑	[59]
Re, Rc	C2C12	p-AMPK↑, glucose uptake↑	[60]
20(R)Rg3	C2C12	p-AMPK↑, p-ACC↑, glucose uptake↑	[61]
Rg3, Rh2	C2C12	AMPK↑, glucose uptake↑	[62]
Rb1	C2C12	AdipoR1↑, AdipoR2↑, GLUT4↑,	[63]
Rg3	C2C12	IRS1↑, p-Akt↑, ATP↑, PGC1-α↑, NRF1↑	[64]
black ginseng	C2C12	p-IRS1↑, p-LKB1↑, p-AMPK↑, p-mTOR↑	[14]

AMPK, adenosine monophosphate-activated kinase; aP2, adipocyte protein 2; CPT, carnitine palmitoyltransferase; FAS, fatty acid synthase; FGF2, fibroblast growth factor 2; G6Pase, glucose 6-phosphatase; GPDH, glycerol-3-phosphate dehydrogenase; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HSL, hormone sensitive lipase; IRS1, insulin receptor substrate 1; LKB1, liver kinase B1; LPL, lipoprotein lipase; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NRF1, nuclear respiratory factor 1; p-ACC, phospho-acetyl-CoA carboxylase; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphatidylinositide 3-kinases; PKA, protein kinase A; PPAR-γ, peroxisome proliferator-activated receptor-gamma; ROS, reactive oxygen species; SCD, stearoyl-CoA desaturase; SREBP, sterol regulatory element-binding protein; TAG, triglyceride; TC, total cholesterol; TNF, tumor necrosis factor; TSP1, thrombospondin 1; UCP, uncoupling protein; VEGF-A, vascular endothelial growth factor A.

suppressed PPAR-γ and CCAAT-enhancer-binding protein (C/EBP)α, thereby inhibiting adipogenesis in 3T3-L1 cells [43,44,47,53,54]. With regard to the effects of ginsenosides Rb1, Rd, Rh1, and PPT on adipogenesis *in vitro*, the results of previous studies have been inconsistent [13,36,38–41,46,54], which might be attributed to those studies' distinct experimental conditions and the differentiation phases of the preadipocytes in those studies. HFD model studies have indicated that ginseng represses differentiation of fat cells in adipose tissue of mice and rats and produces an antiobesity effect [9,23,72], whereas *ob*/*ob* and *db*/*db* diabetic mouse studies have shown that ginseng treatment stimulates the expression of PPAR-γ, adipogenesis, and exerts insulin-like effects [73,75]. Lipoprotein lipase (LPL) releases free fatty acids from circulating TAG-rich lipoprotein and mediates the clearance of blood fats. Moreover, ginsenosides Ro, Rb2, Re, Rg1, and Rh1 increase insulin-induced expression of LPL [37], whereas the results from PPT-type ginsenosides were contradictory [13,39]. Ginseng treatment downregulates the expression of LPL in HFD-fed mice [9], but upregulates it in diabetic ob/ob or db/db mice [73,75]. Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, Rg3, and cK have been shown to stimulate glucose uptake in 3T3-L1 cells [41,42,45,52]. Taken together, these results suggest that ginseng and ginsenosides may have biphasic modulation effects on PPAR-γ, LPL, and adipogenesis and can have an effect on the maintenance of glucose homeostasis.

Adiponectin, exclusively secreted from adipose tissue, is a protein hormone that modulates fatty acid oxidation and glucose

Table 2
Effects of ginseng on different targets related to obesity in animal studies

Material		Animal	Mechanism	Ref.
Ginseng extracts	Orally, 4 wk	chickens	BW gain↓, serum TC↓, LDL-C↓, TAG↓, liver HMGCR↓, CYP7A1↓, FAS↓	[68]
Korean Red Ginseng	i.p., 3 wk	HFD rats	Food intake↓, BW gain↓, fat storage↓, leptin↓, NPY↓	[69]
Wild ginseng extract	8 wk	HFD mice	BW gain↓, serum FBG↓, IR↓, TAG↓, TC↓, HDL-C↑, LDL-C↓, NEFA↓, adipocyte size↓, adipose tissue GLUT4↓	[70]
Mix of PPD type ginsenosides	Orally, 8 wk	HFD mice	BW gain↓, liver weight↓, adipose tissue weight↓, serum TAG↓, TC↓, LDL-C↓, liver TAG↓, TC↓	[20]
Ginseng extract	Orally, 8 wk	HFD mice	BW gain↓, weight of WAT↓, serum TAG↓, leptin↓, adipocyte size↓, PPAR-γ↓, SREBP1↓, FAS↓, LPL↓, DGAT1↓	[9]
Vinegar processed Ginseng extracts	Orally, 8 wk	HFD mice	Food intake↓, BW gain↓, FBG↓, insulin↓, HOMA-IR↓, liver weight↓, fat weight↓, serum TAG↓, TC↓, LDL-C↓, NEFA↓, HDL-C↑, blood pressure↓, adipocyte size↓	[11]
Ginseng saponin	Orally, 3 wk	HFD mice	BW gain↓, serum TAG↓	[22]
PPD type PPT type	i.p., 3 wk	HFD rats	Food intake↓, BW gain↓, fat storage↓, serum TAG↓, TC↓, HDL-C↑, leptin↓, NPY↓, CCK↑(PPD), CCK↓(PPT)	[10]
Korean Red Ginseng	Orally, 13 wk	HFD mice	BW gain↓, liver weight↓, fat storage↓, serum TC↓, LDL-C↓, leptin↓, insulin↓, adiponectin↑	[66]
Korean Red Ginseng	Orally, 8 wk	HFD mice	Food intake↓, BW gain↓, fat storage↓, adipocyte size↓, blood vessel density↓, MMP2↓, MMP9↓, VEGF-A↓, FGF2↓, TSP1↑, TIMP1↑, TIMP2↑	[15]
Ginseng radix	Orally, 8 wk	HFD mice	BW gain↓, FBG↓, insulin↓, HOMA-IR↓, muscle p-AMPK↑, p-ACC↑, GLUT4↑,	[65]
Ginsenoside Re	Orally, 3 wk	HFD mice	FBG↓, insulin↓, HOMA-IR↓, NEFA↓, Liver p-AMPK↑, p-ACC↑, SREBP1↓, FAS↓, GPAT↓, PEPCK↓, G6Pase↓.	[29]
Korean Red Ginseng	Orally, 12 wk	HFD rats	BW gain↓, fat storage↓, adiponectin↑, leptin↓, muscle p-IRS1↑, p-Akt↑, p-GSK↑, GLUT4↑	[71]
Black ginseng	Orally, 12 wk	HFD mice	Food intake↓, BW gain↓, fat storage↓, fecal weight↑, fecal lipid↑, liver lipid↓	[12]
Fermented Korean Red Ginseng	Orally, 12 wk	HFD mice	BW gain↓, adipocyte size↓, serum TC↓, TAG↓, LDL-C↓, hepatocyte size↓, liver steatosis↓, AST, ALT↓	[67]
Ginsenoside Rh1	Orally, 4 wk	HFD mice	BW gain↓, adipocyte size↓, PPAR-γ↓, aP2↓, C/EBPα↓, FAS↓, TNF-α↓, IL-1β↓, IL-6↓, CD68↓, F4/80↓,	[72]
Ginseng extract	Orally, 14 wk	HFD rats	BW gain↓, epididymal fat↓, serum TAG↓, leptin↓, liver TAG↓, fecal TAG↑, adipose tissue PPAR-γ↓, aP2↓, TNF-α↓, IL-6↓, MCP-1↓	[23]
Ginseng radix	Orally, 5 wk	HFD mice	Food intake↓, BW gain↓, epididymal fat↓, adipocyte size↓, FBG↓, insulin↓, HOMA-IR↓, serum TAG↓, TC↓, NEFA↓, muscle p-AMPK↑, p-ACC↑, GLUT4↑	[16]
PPT	Orally, 4 wk	HFD mice	Food intake↓, BW gain↓, FBG↓, serum TAG↓, TC↓, LDL-C↓, NEFA↓, insulin↓, leptin↓, adiponectin↑, IL-1β↓, IL-6↓, AST↓, ALT↓, Liver TAG↓ TC↓, FAS↓, body temperature↑, adipose UCP1↑, UCP2↑, UCP3↑, TNF-α↓, IL-6↓, IL-1β↓	[13]
Rb1	i.p., 12 wk	HFD rats	Food intake↓, liver TAG↓, p-AMPK↑, CPT1↑, β-oxidation↑, SREBP1↓, FAS↓, SCD1↓, PGC1α↑, PPAR-α↑, Acox1↑	[18]
Korean Red Ginseng	Orally, 12 wk	db/db mice	BW gain↓, FBG↓, insulin↓, HbA1c↓, serum TAG↓, liver PPAR-α↑, adipose tissue PPAR-γ↑, LPL↑	[73]
Ginseng berry Ginseng root	i.p., 12 d	ob/ob mice	Food intake↓, BW gain↓, FBG↓, body temperature↑; BW gain↓, FBG↓	[74]
Wild ginseng	Orally, 4 wk	ob/ob mice	BW gain↓, FBG↓, adipose tissue PPAR-γ↑, LPL↑, GLUT4↑, Liver GLUT4↑, IR↑, muscle LPL↑, GLUT4↑, IR↑	[75]
Ginseng	Orally, 13 wk	db/db mice	Food intake↓, BW gain↓, adipocyte size↓, hepatic lipids↓, serum TAG↓, NEFA↓, FBG↓, insulin↓; adipose tissue blood vessel density↓, VEGF-A↓, FGF-2↓, UCP2↑, CPT-1↑	[17]

Acox1, peroxisomal acyl-coenzyme A oxidase 1; ALT, alanine transaminase; AMPK, adenosine monophosphate-activated kinase; aP2, adipocyte protein 2; AST, aspartate transaminase; BW, body weight; CCK, cholecystokinin; CPT, carnitine palmitoyltransferase; DGAT1, diglyceride acyltransferase; FAS, fatty acid synthase; FBG, fasting blood glucose; FGF2, fibroblast growth factor 2; GSK, glycogen synthase kinase; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein-cholesterol; HFD, high fat diet; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HOMA-IR, homeostatic model assessment-insulin resistance; i.p., intraperitonally; IR, insulin resistance; LDL-c, low density lipoprotein-cholesterol; MCP-1, monocyte chemoattractant protein-1; NEFA, nonesterified fatty acid; PAT, glycerol-3-phosphate *O*-acyltransferase; p-ACC, phospho-acetyl-CoA carboxylase; PPAR, peroxisome proliferator-activated receptor; PPD, protopanaxadiol; PPT, protopanaxatriol; SCD, stearoyl-CoA desaturase; TAG, triglyceride; TC, total cholesterol; TNF, tumor necrosis factor; UCP, uncoupling protein; VEGF-A, vascular endothelial growth factor A; WAT, white adipose tissue.

regulation, and adiponectin levels are inversely correlated with body fat percentage in adults. Ginseng was shown to significantly increase the secretion of adiponectin in 3T3-L1 cells and in mice fed with HFD [13,50,51,66,71]. Resistin is an adipose-derived hormone, and its function has been the subject of controversy with respect to its involvement in obesity. Serum resistin levels increase with increased adiposity and decline with decreased adiposity [87], and it has been shown that ginsenosides Rc and Re can repress resistin expression in 3T3-L1 cells [48,49].

Unlike other tissues, which stop growing in adulthood, adipose tissue can grow and regress throughout life. Adipose tissue is highly vascularized, and adipocytes are nourished by an extensive capillary network, which suggests that obesity might be blocked by angiogenesis inhibitors. Matrix metalloproteinases (MMPs) are thought to play a major role in adipogenesis and angiogenesis. *In vitro* studies have demonstrated that ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, and cK suppress the expression of angiogenic factors such as vascular endothelial growth factor A (VEGF-A), basic fibroblast growth factor 2 (FGF2), and MMPs, whereas they facilitate the expression of angiogenic inhibitors such as thrombospondin (TSP) 1, tissue inhibitors of metalloproteinase (TIMP) 1, and TIMP2 in 3T3-L1 cells [53,54]. Such effects of ginseng on adipose tissue differentiation were also observed in HFD-induced obese mouse studies [15,17].

Obesity is associated with hyperplasia and hypertrophy of adipose tissue and is likely to lead to a reduction of adipose tissue blood flow, which results in adipocyte hypoxia [88]. Adipose hypertrophy, the enlargement of adipocytes, can increase the distance from adipocytes to blood capillaries, resulting in adipocyte hypoxia. Increased necrosis-like adipocyte cell death due to hypoxia has

Table 3
Effects of ginseng on different targets related to obesity in human studies

Material	Participants	Mechanism	Ref.
50% alcohol ginseng extract 6 g/d, for 8 wk	Male college students $n = 8$	MDA↓, SOD↑, CAT↑, TC↓, HDL↑, LDL↓, TAG↓	[93]
Korean Red Ginseng extract, 3 g/d for 2 wk, 8 g/d for 2 wk; Ginsenoside Re, 0.25 g/d for 2 wk, 0.5 g/d for 2 wk	Obese adults placebo, $n = 5$; intervention, $n = 5$; Re, $n = 5$	No effect on weight, BMI, fat mass, glucose, insulin, HbA1c, TC, TAG, HDL, LDL no effect	[94]
Korean Red Ginseng extract 6 g/d for 8 wk	Obese females placebo, $n = 23$; intervention, $n = 22$	BW↓, BMI↓, WHR↓, food intake↓, Genotype: GNB3, CT: BMI↓, WHR↓, food intake↓, SBP↓; ADRB3, Trp64/Arg: BST ↓ Trp64/Trp: AST↓; ACE, II: BST↓, AST↓, No distinct effect compared to placebo	[95]
Korean Red Ginseng powder 6 g/d for 12 wk	Overweight or obese adults placebo, $n = 34$; intervention, $n = 34$	No effect on caloric intake, BMI, percent body fat Blood TC, TAG, LDL, HDL	[96]
Korean Red Ginseng 4.5 g/d for 12 wk	Adults with metabolic syndrome Placebo $n = 25$; Intervention, $n = 23$	No effect on waist circumference, blood pressure, TC, HDL, TAG, fasting plasma glucose, insulin, HOMA-IR	[97]
Panax ginseng extract 8 g/d for 8 wk	Obese females $n = 10$	Weight gain↓, BMI↓, no effect on waist circumference, body fat percentage, plasma HDL, TAG, TC and glucose. effects differed depending on the composition of gut microbiota prior to ginseng intake	[98]
Red ginseng 3 g/d for 4 wk	Males with metabolic syndrome Placebo, $n = 30$; Intervention, $n = 32$	Mitochondrial function↑, total testosterone↑ IGF-1↑, diastolic blood pressure↓	[99]

AST, aspartate transaminase; BMI, body mass index; CAT, catalase; HbA1c, hemoglobin A1c; HDL-c, high density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; IGF-1, insulin-like growth factor 1; LDL-c, low density lipoprotein-cholesterol; MDA, malondialdehyde; SBP, Systolic blood pressure ; SOD, superoxide dismutase; TAG, triglyceride; TC, total cholesterol; WHR, waist/hip ratio.

been reported to result in recruitment of macrophages to adipose tissue [89]. Macrophages surrounding dying or dead adipocytes form crown-like structures that can be identified by the absence of perilipin staining. Activated adipocytes and macrophages release proinflammatory cytokines such as IL-6 and TNF (tumor necrosis factor)-α, and they promote insulin resistance [90]. Kim [48] reported that the ginsenoside Re can repress the expression of TNF-α in 3T3-L1 cells. Moreover, ginsenoside Rh1 was shown to prevent macrophage infiltration and decrease the release of IL-6, TNF-α, and IL-1β in the adipose tissue of HFD-induced obese mice [72]. Extracts of ginseng have also been found to repress the secretion of TNF-α, IL-6, and monocyte chemoattractant protein (MCP)-1 in the adipose tissue of mice fed with HFD [23].

6. Effect on skeletal muscle

Skeletal muscle is the predominant tissue responsible for the oxidation of glucose and fatty acids and therefore is a potential target for antiobesity and antidiabetes therapies. AMPK is an important energy-sensing and signaling system in skeletal muscle, and once activated, it stimulates biogenesis of GLUT4 and mitochondria and facilitates glucose uptake and acute fatty acid oxidation via phosphorylation of ACC with a consequent decrease in malonyl-CoA [91]. Many *in vitro* studies have indicated that ginsenosides Rc, Re, Rg1, Rg3, and Rh2 and ginseng extracts can activate the AMPK signaling pathway in C2C12 myoblast cells [14,56–58,60–62]. In addition, it has been reported that ginseng radix can activate AMPK in skeletal muscle of mice fed with HFD [16,65]. In that manner, ginsenosides or ginseng can alleviate insulin resistance via increased phosphorylation of insulin receptor substrate (IRS) 1 and Akt and facilitate uptake of glucose to myocytes via the regulation of GLUT4 biogenesis [42,59,71]. Korean Red Ginseng was reported to promote mitochondrial biogenesis and fatty acid oxidation in skeletal muscle and cultured C2C12 cells with increased expressions of PPAR-γ coactivator-1α (PGC-1α), nuclear respiratory factor 1 (NRF1), cytochrome *c*, and cytochrome *c* oxidase [58,64,71]. Jung and Kang [92], assessing the rate of glucose transport in the epitorchealis muscle under submaximal insulin concentrations, did not detect incremental glucose uptake after ginseng treatment. However, the rats in their study were fed with HFD and treated with ginseng for only 2 wk; thus, their research design might be a reason for their contrasting results. AMPK can be regulated downstream by adiponectin, and ginsenoside Rb1 has been shown to stimulate adiponectin signaling in C2C12 muscle cells through upregulation of adiponectin receptor (AdipoR)1 and AdipoR2 proteins [63].

7. Human study

Only seven papers of human study associated with ginseng and obesity are available and reviewed (Table 3). Kim and Park [93] reported that serum levels of TC (total cholesterol), TAG, and LDL decrease while high density lipoprotein increases following the administration of ginseng extract for 8 wk. A limitation of their study is that it was not placebo-controlled. Reeds et al [94] reported that oral administration of ginsenoside Re or Korean Red Ginseng extract to obese adults failed to have an effect on body weight, body mass index (BMI), fat mass, and plasma lipid profile. Although the small number of study participants ($n = 5$) may be a limitation of that research, their data did not even detect a trend toward treatment-induced improvement. Kwon et al [95] also reported that the administration of Korean Red Ginseng extract to obese females at a dose of 6 g/d for 8 wk failed to show an effect different from that in their placebo group, with the exception of an improvement in the obesity-related quality of life scale. Similarly, Cho et al [96] reported that administration of Korean Red Ginseng powder to overweight or obese adults at a dose of 6 g/d for 12 wk did not have an effect on BMI, body fat, and plasma lipid profile. In addition, Park et al [97] reported that administration of Korean Red Ginseng to adults with metabolic syndrome at a dose of 4.5 g/d for 12 wk failed to have an effect on waist circumstance, lipid profile, and insulin resistance. In contrast, Song et al [98] reported that administration of ginseng extract to obese middle-aged females at a dose of 8 g/d for 8 wk did produce a weight loss effect; moreover, there were slight effects on gut microbiota with the antiobesity effects differing dependent on the composition of the gut

microbiota prior to ginseng administration. However, their research design was limited by the absence of a placebo control. In male participants with metabolic syndrome, Jung et al [99] reported that red ginseng improved mitochondrial function, increased levels of testosterone and IGF-1, and reduced both diastolic blood pressure and serum cortisol level compared to the results in their placebo group.

Notably, ginsenosides have a very low bioavailability after oral intake, and only the deglycosylated forms of ginsenosides can be absorbed into the circulatory system. The transformation of ginsenosides is largely dependent on intestinal bacteria, which release various glycosidases to hydrolyze the sugar moieties of ginsenosides. Intestinal microflora composition varies among individuals, and approximately 20% of people cannot partially or fully transform ginsenosides [100]. Moreover, the degree of transformation and concentration of ginsenosides may vary among ginseng products. In addition, the effects of ginseng might vary with individual genotypes [95]. These factors may, in part, lead to the differing results attained in the various human-based research carried out thus far. In addition, the length of the treatment periods has usually been 8 wk, regardless of whether the study is animal or human based. As the human life span is far longer than that of murine, such a short treatment period may be another reason for the apparent lack of antiobesity effects in human studies.

8. Conclusion

Ginseng or ginsenosides may help control appetite and prevent the overintake of food energy by attenuating the HFD-induced chronic inflammation of the hypothalamus, improving leptin resistance, and reducing the secretion of neuropeptide Y. Once food is consumed, PPD-type ginsenosides can inhibit the activity of pancreatic lipase and prevent digestion of TAG. Ginsenoside Rg1 suppresses the expression of SGLT1 and blocks the absorption of glucose. In this way, the energy harvested by an organism from the consumed lipids and carbohydrates can be reduced. Through the activation of AMPK, metabolism is switched from anabolism to catabolism. In liver, TAG synthesis, cholesterogenesis, and gluconeogenesis are downregulated through the suppression of FAS, HMGCR, PEPCK, and G6Pase. Moreover, PPAR-α is activated downstream by AMPK, and it stimulates oxidation and export of fatty acids. In this way, liver steatosis induced by an HFD may be improved. Furthermore, ginseng and ginsenosides stimulate the synthesis of bile acid from cholesterol, upregulate the expression of LDL receptor, and thereby mediate cholesterol clearance from blood and liver. Ginseng and ginsenosides also activate the AMPK pathway and inhibit TAG synthesis in adipose tissue. Results describing the effects of ginseng on adipogenesis via PPAR-γ and C/EBPα have so far been inconsistent. However, many researchers have reported that HFD-fed mice administrated with ginseng have low adipose tissue weights and small adipocytes. Ginseng and ginsenosides may have a dual regulatory effect on adipogenesis and maintain homeostasis of lipid metabolism. In addition, inflammation due to hypoxia in adipose tissue is ameliorated by ginseng. Ginseng and ginsenosides also stimulate the AMPK pathway in skeletal muscle. Glucose uptake and fatty acid oxidation are upregulated via stimulation of GLUT4 and mitochondria biogenesis. Ginseng may downregulate blood glucose and lipids by facilitating energy expenditure in muscle.

In summary, ginseng and ginsenosides not only modulate appetite and reduce energy input in the intestine, but also inhibit lipid synthesis and stimulate energy consumption in skeletal muscle and liver via the activated AMPK pathway. Therefore, to some extent, the antiobesity effect of ginseng may be explained by the principle of energy conservation. In addition, ginseng treatment can result in a two-way adjustment of adipogenesis under HFD-induced obese and diabetic conditions. Nevertheless, previous studies into the antiobesity effects of ginseng are mostly restricted to animals. There is limited evidence supporting the suggestion that ginseng exerts an antiobesity effect in humans. Additional study and verification through longitudinal human studies are required to elucidate the antiobesity effects of ginseng in humans.

Conflicts of interest

Geun Eog Ji is a professor of Seoul National University and also the president of Bifido Co., Ltd. Zhipeng declares no conflict of interest.

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