



Effect of *Panax notoginseng* Saponins and Major Anti-Obesity Components on Weight Loss

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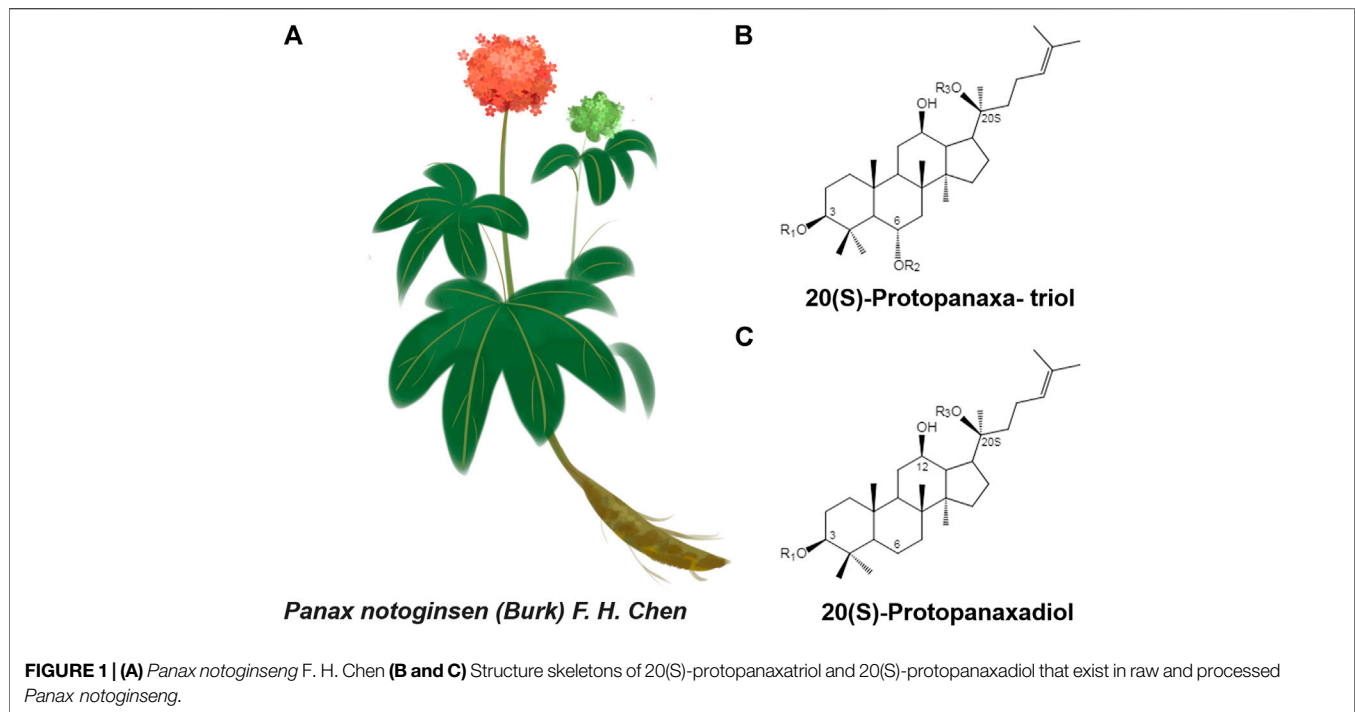
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The prevalence of individuals who are overweight or obese is rising rapidly globally. Currently, majority of drugs used to treat obesity are ineffective or are accompanied by obvious side effects; hence, the options are very limited. Therefore, it is necessary to find more effective and safer anti-obesity drugs. It has been proven *in vivo* and *in vitro* that the active ingredient notoginsenosides isolated from traditional Chinese medicine *Panax notoginseng* (Burk.) F. H. Chen exhibits anti-obesity effects. Notoginsenosides can treat obesity by reducing lipid synthesis, inhibiting adipogenesis, promoting white adipose tissue browning, increasing energy consumption, and improving insulin sensitivity. Although notoginsenosides are potential drugs for the treatment of obesity, their effects and mechanisms have not been analyzed in depth. In this review, the anti-obesity potential and mechanism of action of notoginsenosides were analyzed; thus laying emphasis on the timely prevention and treatment of obesity.

Keywords: anti-obesity, adipogenesis, lipolysis, browning of white adipose tissue, insulin sensitivity

INTRODUCTION

Individuals with excess fat accumulation that can impair health are called overweight or obese. According to the World Health Organization, an adult with a body mass index (BMI) ≥ 25 is overweight and ≥ 30 is obese. The global prevalence of obesity almost tripled between 1975 and 2016, with 39% of adults classified as overweight and 13% as obese (Collaboration, 2017). Obesity often increases the risk of lifestyle diseases, such as cardiovascular disease, diabetes, and cancer. Although a healthier lifestyle, such as healthy food and regular exercise can prevent obesity and promote weight loss; but, in the long run, lifestyle, environmental, and genetic factors can easily lead to obesity again (Dulloo and Montani, 2015). Therefore, drug therapy combined with exercise and diet management is extremely beneficial for individuals who struggle with weight loss. However, currently, there are very few drugs available for obesity treatment. Currently, only Orlistat, Lorcaserin, and Qsymia (Fentiemine/Topiramate sustained-release tablets) have been approved by the FDA for use for long-term weight control. Orlistat is an intestinal lipase inhibitor; by inhibiting the hydrolysis of triglycerides, Orlistat reduces the absorption of fat from food to achieve weight loss. However, long-term use of the drug can lead to deficiency of fat-soluble vitamins and cause gastrointestinal disorders (Filippatos et al., 2008; Halpern and Halpern, 2015). Lorcaserin, which can reduce appetite, acts on the 5-HT_{2C} receptor as a sympathetic nerve agent, but its long-term use has put individuals



at risk for valvular heart disease and cancer (Greenway et al., 2016). Qsymia is a central nervous system weight-loss drug that has precipitated adverse effects, such as headache, insomnia, constipation, and dizziness (Siebenhofer et al., 2016; Halpern and Mancini, 2017). In addition, many weight-loss medications have been withdrawn due to strong side effects, such as Flaviprolamine (heart disease), Amirese (obstructive pulmonary hypertension), Phentamine (insomnia, fatal pulmonary hypertension), and Rimonabant (psychiatric reactions, depression and anxiety, suicide risk) (Cheung et al., 2013). Therefore, the development of safe and effective new anti-obesity drugs has great clinical significance and economic value.

Panax notoginseng (Burk.) F. H. Chen (Sanqi in Chinese) is a valuable traditional Chinese medicine, belonging to the genus Araliaceae, that was first recorded in Shennong Ben Cao *Jing*. Its dried roots promote blood circulation, stop bleeding, reduce swelling, and relieve pain. With developments in traditional medicine, a more systematic study of *Panax notoginseng* has been carried out using modern physics, chemical technology, and modern medical theories. More than 80 types of monomeric saponins, flavonoids, and notoginseng phytoconstituents with unique pharmacological activities were isolated from different parts of *P. notoginseng*, among which *P. notoginseng* saponins (PNS) are the main active components. The PNS are divided into two groups, 20(S)-protopanaxatriol or 20(S)-protopanaxadiol (Qiao et al., 2018) (Figure 1). These components have a variety of pharmacological activities, such as anti-oxidation (Hu et al., 2018; Hu et al., 2019), anti-depression (Xiang et al., 2011; Cui et al., 2012; Zhang et al., 2018), treatment of cardiovascular diseases (Zhou et al., 2018; Liu X. W. et al., 2019) and treatment of diabetes (Guo et al., 2019; Wang et al., 2019).

Recent studies have found that PNS or monomer notoginsenosides have regulatory effects on obesity and lipid metabolism in addition to the treatment of type 2 diabetes and atherosclerosis (Fan et al., 2012; Peng et al., 2019). When the type 2 diabetes model KK-Ay mice were treated with PNS, it was found that PNS decreased the fasting blood glucose level of diabetic mice accompanied with significant weight loss (Yang et al., 2009). Further studies showed that PNS could downregulate SREBP1, SCD1, and FAS through the AMPK signaling pathway, inhibit adipogenesis, and reduce white adipose tissue weight, thereby reducing the weight of diabetic mice (Wang et al., 2020). In high-fat diet-induced atherosclerosis models, treatment with the PNS/monomer notoginsenosides significantly reduced lipid levels (Jia et al., 2010; Fan et al., 2012; Liu C. et al., 2019). In addition, PNS can inhibit lipase protein expression in non-alcoholic fatty liver disease (NAFLD), reduce lipolysis in white adipose tissue, and thus alleviate lipid accumulation in the liver (Ding et al., 2015). In addition, PNS, notoginsenosides R1, ginsenoside Rg1, and ginsenoside Rb1 can significantly reduce the content of SREBP2 and HMG-CoA, directly inhibit the synthesis of cholesterol, and protect the liver (Chen et al., 2016).

However, so far, pharmacological studies of PNS and monomer notoginsenosides have mostly focused on cardiovascular system diseases, central nervous system diseases, and anticancer activities. There is a lack of systematic evaluation of their role in regulating lipid metabolism and their anti-obesity effects. This review summarizes the anti-obesity effects and mechanisms of PNS, provides research potential for the clinical treatment of obesity and the development of safe and effective anti-obesity drugs.

TABLE 1 | Effect of notoginsenosides on adipogenesis.

Durg	Type	Effect	Mechanism	References
Ginsenoside Rb1	<i>In vivo</i>	Anti-obesity, improved insulin sensitivity	Elevated activation of hepatic AMP-activated protein kinase (AMPK) and phosphorylated acetyl-CoA carboxylase	Shen et al. (2013)
Ginsenoside Rb2	<i>In vitro</i>	Decreased TAG levels	Stimulated the expression of SREBP and leptin mRNA	Kim E. J. et al. (2009)
Ginsenoside Rc	<i>In vitro</i>	Decreased the number of adipocytes, reduced lipid accumulation in maturing preadipocytes	Down-regulated the expression of PPAR γ and C/EBP α	Yang and Kim (2015)
Ginsenoside Rg3	<i>In vitro</i> and <i>vivo</i>	Reduced serum levels of triglyceride, total cholesterol, and LDL-cholesterol; reduced lipid accumulation in adipocytes and suppressed adipogenesis; reduced epididymal white adipose tissue size; improved insulin sensitivity	Increased AMPK activation and suppressed adipogenesis by decreasing the mRNA expression of C/EBP α , PPAR γ , SREBP1, Pgc-1 α , FAS, AP2, and SIRT1 and by increasing that of CPT1 and HSL.	Hwang et al. (2009); Lee et al. (2012); Lee et al. (2017); Zhang et al. (2017); Lee H. S. et al. (2019); Kim et al. (2020)
Ginsenoside F2	<i>In vitro</i>	Reduced lipid accumulation	Reduced the gene expression of PPAR γ and perilipin	Siraj et al. (2015)
Ginsenoside CK	<i>In vitro</i>	Enhanced glucose uptake; inhibited triglyceride accumulation	Activation of AMPK and PI3K signaling pathways; induced GLUT4 expression at both the mRNA and protein levels	Huang et al. (2010)
Ginsenoside Rg1	<i>In vitro</i> and <i>vivo</i>	Decreased body weight, total cholesterol, and total triglyceride levels; inhibited lipogenesis, and decreased intracellular lipid content, adipocyte size, and adipose weight	Induced AMPK activation; increased CHOP10 and reduced the C/EBP β transcriptional activity; reduced fat and cholesterol anabolism genes such as SREBP-1c, ACC, ATP-CL, ACS; promoted the expression of PPAR- α , CPT1A, CPT2, and CYP-7A	Xie et al. (2015); Koh et al. (2017); Liu et al. (2018); Lee J. H. et al. (2019); Hou et al. (2020)
Ginsenoside Rg2	<i>In vitro</i> and <i>vivo</i>	Inhibited adipocyte differentiation and decreased body weight, reversed hepatic steatosis, and improved glucose tolerance and insulin sensitivity	Induced activation of AMPK and SIRT1 signaling pathway; decreased the expression levels of PPAR γ , C/EBP α , and SREBP1-c, and then regulated target genes such as ACC and FAS	Liu H. et al. (2019); Cheng et al. (2020)
Ginsenoside Rh1	<i>In vitro</i> and <i>vivo</i>	Suppressed body and epididymal fat weight gains and plasma triglyceride level; inhibited adipogenesis	Decreased the expressions of PPAR- γ , C/EBP- α , FAS, and FABP	Gu et al. (2013)

EFFECTS ON ADIPOGENESIS AND LIPOLYSIS

Adipogenesis

Due to the long-term imbalance of energy intake and consumption by the body, excess energy is stored in white adipocytes in the form of triglycerides (Kopelman, 2000). This process is accompanied by the proliferation and differentiation of preadipocytes and cell hypertrophy, resulting from increased lipid storage that eventually leads to the proliferation of adipose tissue volume, presenting as obesity (Arner and Spalding, 2010). In mammalian cells, peroxisome proliferator-activated receptor (PPAR) and CCAAT/enhancer binding protein (C/EBP) are considered to be key early regulators of adipogenesis (Wu et al., 1999; Rosen et al., 2000; Lefterova and Lazar, 2009), whereas SREBP1 and cAMP response element binding protein (CREB) regulate adipose tissue differentiation and metabolism by influencing PPAR (Kim and Spiegelman, 1996; Fajas et al., 1999; Reusch et al., 2000). Additionally, proteins, such as glucose transporter 4 (GLUT4), lipoprotein lipase (LPL), SCD, and FAS, are also involved in adipogenesis and lipid storage (Moseti et al., 2016).

The experimental results (Table 1) of *in vivo* and *in vitro* studies showed that many kinds of notoginseng monomer saponins, such as ginsenosides RC, Rg3, and Rg2, can inhibit the proliferation and differentiation of adipocytes, reduce the number of adipocytes, and inhibit the accumulation of lipids in adipocytes by reducing the expression levels of PPAR γ , C/EBPs, SREBP, and FAS, to achieve anti-obesity effects. The combination of various saponins, such as ginsenosides Rb1, Rg1, and notoginsenosides R1, can also reduce the synthesis of lipids and cholesterol through SREBP-1C, acetyl-CoA carboxylase (ACC), acetyl-coa synthetase (ACS), and other proteins (Xie et al., 2015). In addition, the AMPK pathway acts as a central regulator of cellular energy sensors, organelle biogenesis, cell metabolism, cell proliferation, and differentiation (Hardie, 2011). Current studies have shown that activation of AMPK signaling increases energy consumption and reduces lipid accumulation and adipogenesis (Fernandez-Veledo et al., 2013; Desjardins and Steinberg, 2018). Ginsenosides Rb1, Rg3, CK, and Rg1, can improve insulin sensitivity and inhibit the occurrence of obesity by activating the AMPK pathway. The *in vitro* and *in vivo* anti-obesity effect and mechanism of some notoginsenosides have been discussed at present as some drugs are still lacking *in vivo* experimental verification, and the mechanism of action needs to be further explored.

Lipolysis

In obesity, excess circulating fatty acids in plasma may accumulate ectopically in insulin-sensitive tissues and impair insulin action. Increased basal lipolysis may also change the secretion status of adipose tissues, affect the insulin sensitivity of the whole body, and exacerbate the inflammation of adipose tissue (Morigny et al., 2016). Therefore, in addition to inhibiting the proliferation and differentiation of adipocytes, regulating adipolysis is also crucial for the management of obesity.

In the experimental studies reported so far, the regulation of notoginsenosides on adipolysis involves several different mechanisms; Ginsenosides, Rg1, Rg2, and Rh1, regulate PPAR, C/EBP, and AMPK signaling pathways, while inhibiting adipogenesis, reduce lipid synthesis and inhibit lipolysis, thereby reducing circulating blood lipid levels and improving insulin sensitivity (Masuno et al., 1996; Lee K. et al., 2019). Interestingly, Hyun Sook Lee et al. found that ginsenoside Rg3 can directly increase the expression of lipolysis-related genes in the white adipose of obese mice that were fed a high-fat diet and promote lipolysis by upregulating crucial genes *CPT1* and *HSL* (Rupasinghe et al., 2016; Dankel et al., 2019; Lee H. S. et al., 2019). However, there are also reports on Ginsenoside Rb1-induced beta three adrenergic receptor-dependent lipolysis and thermogenesis. Ginsenoside Rb1 treatment can increase the protein expression of lipase and thermogenic factor UCP1, increase the level of lipolysis, and reduce the size of adipocytes, and meanwhile increase the thermogenic capacity of obese mice, thereby consuming free fatty acids (Lim et al., 2019). In addition, 20(S)-ginsenoside Rg3 can exert a similar effect to Orlistat by regulating pancreatic lipase. Experiments have shown that 20(S)-ginsenoside Rg3, which is a potential drug for the treatment of obesity, can inhibit pancreatic lipase activity, reduce the decomposition and absorption of lipids in food, and inhibit lipid accumulation during the differentiation of 3T3-L1 adipogenic cells through AMPK and PPAR-signaling pathways. (Fei et al., 2016).

EFFECTS ON BODY ENERGY CONSUMPTION

Promote White Adipose Tissue Browning

There are two main types of adipocytes in mammals: white adipose tissue (WAT), which is the major tissue for energy storage, and brown adipose tissue (BAT), which is the major tissue for energy consumption. WAT converts the excess energy of the body into triglycerides and stores them in cells, whereas BAT contains a large number of mitochondria, among which high levels of UCP1 consume bioenergy and emit energy in non-tremor thermogenesis to maintain human body temperature and energy consumption (Contreras et al., 2016; Lee J. H. et al., 2019). More recently, a third type of adipocyte, called beige adipocytes, has been identified in WAT that is similar to classic brown adipocytes but with comparatively higher levels of UCP1 (Giordano et al., 2014). Biogenesis of beige adipocytes in WAT can be induced by cold exposure and drug or hormone

stimulation (de Jong et al., 2017). In the past few years, the development and transcriptional regulation of beige fat has received much attention. It has been found that genetically and pharmacologically inducing beige adipocytes can protect mice from obesity and insulin resistance induced by a high-fat diet, as well as effectively increase energy expenditure and improve metabolic disorders. Recent studies have also identified several major transcriptional regulators of the development and function of beige adipocytes, including PPARs, PGC1, FOXC2, and, PRDM16 (Su et al., 2018; Lizcano, 2019).

At present, many studies have shown that ginsenoside Rb1 induces browning of adipocytes through AMPK-mediated pathways thereby exerting anti-obesity effects (Mu et al., 2015; Park S. J. et al., 2019; Lim et al., 2019). *In vitro*, 10 μ M ginsenoside Rb1 treatment increased glucose uptake in 3T3-L1 cells and promoted mRNA expression of brown fat marker proteins UCP-1, PGC-1 α , and PRDM16. In addition, ginsenoside Rb1 also increased PPAR γ expression (Mu et al., 2015; Park S. J. et al., 2019), and browning was eliminated with PPAR γ antagonist GW9692 (Mu et al., 2015). *In vivo*, db/db mice were intraperitoneally injected with ginsenoside Rb1, the amount of WAT in the groin decreased, and respiration and heat production increased. After pre-treatment with β 3AR antagonist L748337, ginsenoside Rb1 lost its ability to promote browning and thermogenesis (Lim et al., 2019). In addition, other studies have found that ginsenosides Rb2, Rg1, and Rg3 induced AMPK phosphorylation, stimulated the expression of UCP1, and increased thermogenesis and mitochondrial gene expression to induce BAT activation and white adipocyte browning (Lee K. et al., 2019; Hong et al., 2019; Kim et al., 2020). Ginsenoside Rd enhances thermal gene expression in brown adipose tissue through the PKA signaling pathway and increases browning of white adipose tissue induced by cold exposure (Yao et al., 2020).

As shown in **Table 1**, many panax notoginseng monomer saponins can affect body adipogenesis by regulating PPARs and AMPK. PPARs are a group of nuclear transcription factors; there are three types of PPAR: PPAR α , δ , and γ . PPAR γ is a core transcription factor required for white adipogenesis (Rosen and Spiegelman, 2014). When PPAR γ binds to PRDM16, PPAR γ stimulates the expression of selective genes in brown and beige adipocytes and inhibits white adipocyte specific genes (Ohno et al., 2012; Qiang et al., 2012). PPAR α and PPAR δ stimulate fatty acid oxidation and mitochondrial respiration, promoting white adipose tissue browning (Wang et al., 2003; Hondares et al., 2011; Mottillo et al., 2012; Barquissau et al., 2016). In addition, studies have shown that activation of AMPK can increase the activity and energy expenditure of BAT and beige adipocytes and targeting AMPK may have therapeutic potential for treating obesity and related diseases (Fernandez-Marcos and Auwerx, 2011; van Dam et al., 2015). Therefore, in addition to the observed inhibition of adipogenesis and weight loss by AMPK and PPARs, we can also explore whether this component can resist obesity by promoting browning of white adipose tissue and increasing body energy consumption.

Mitochondrial Protective Effect

Mitochondria are essential organelles for energy metabolism. Adipocyte mitochondria play a substantial regulatory role between whole-body energy balance, muscle and adipose tissue differentiation, and insulin sensitivity and glucose metabolism (Bhatti et al., 2017). Various studies have shown that mitochondrial function and biogenesis are impaired in type 2 diabetes, obesity, and insulin-resistant adipose tissue (Bhatti et al., 2017; Dai and Jiang, 2019). The main function of mitochondria in adipocytes is to produce ATP to support a variety of key metabolic pathways for lipid clearance, including triglyceride synthesis, glucometosis, and fatty acid oxidation. In addition, in response to cold exposure, drugs or adrenal hormones, activation of mitochondria in brown and beige adipocytes accelerates energy consumption by increasing the expression of mitochondrial UCP1 (Harms and Seale, 2013). Fatty acid oxidation and reduced energy consumption, caused by mitochondrial dysfunction in the brown adipocytes of individuals with obesity and metabolic diseases, indicate the role of mitochondrial function in anti-obesity effects (Bournat and Brown, 2010).

Excessive reactive oxygen species (ROS) production in adipose tissue of obese mice and significantly decreased mitochondrial mtDNA and respiratory protein expression, resulting in mitochondrial dysfunction (Furukawa et al., 2004; Sparks et al., 2005). Ginsenosides Rb2, F1, and Rc enhanced the deacetylation activity of SIRT1 and inhibited the formation of intracellular ROS. In addition, by increasing mitochondrial DNA content, cell oxygen consumption was restored, and mitochondrial damage induced by oxidative stress was reduced, showing the protective effect of mitochondrial function (Wang et al., 2016). Ginsenosides Rd and Re reduce oxidative stress, improve mitochondrial integrity and function, and inhibit intracellular ROS production and lipid peroxidation caused by rotenone (Gonzalez-Burgos et al., 2017). Ginsenosides Rg3 and Rg1 can regulate mitochondrial autophagy and biogenesis by activating the AMPK signaling pathway, thus improving mitochondrial dysfunction (Xing et al., 2017; Lee K. et al., 2019). Thus, notoginsenosides may protect mitochondrial function by regulating mitochondrial energy metabolism, oxidative stress, biogenesis, autophagy, and enhance energy consumption in obese patients. In addition, it has been reported that inhibition of fatty acid oxidation and maintenance of mitochondrial energy metabolism are essential for the survival of brown and beige adipocytes during dormancy (Kutyavin and Chawla, 2019). Therefore, the mitochondrial protective effect of notoginsenosides may affect the thermogenic function maintenance of BAT and beige adipocytes in a thermally neutral environment, which needs further experimental investigation.

EFFECTS ON INSULIN SENSITIVITY

Obesity and Insulin Resistance

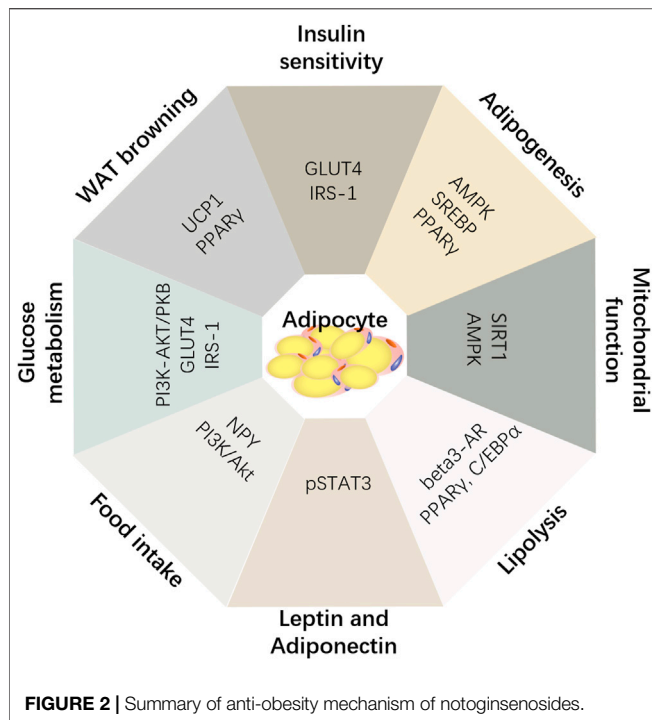
It has been shown that obesity-induced adipose tissue metabolic disorders cause primary insulin resistance in insulin-sensitive

tissues (Smith and Kahn, 2016; Czech, 2017). Lipid overload and lipid toxicity caused by obesity affect insulin sensitivity of various organs by interfering with the insulin signal transduction pathway (Chen et al., 2017; Engin, 2017). In contrast, fatty factors secreted by adipose tissue, such as monocyte chemoattractant protein-1/chemokine (C-C motif) ligand-2 (MCP-1/CCL2) and tumor necrosis factor- α (TNF α), regulate inflammatory responses in adipose tissue (Sartipy and Loskutoff, 2003). MCP-1/CCL2 acts as a chemoattractant that increases the macrophage content in adipose tissue in obese patients and causes chronic low-grade inflammation in adipose tissue (Weisberg et al., 2003; Curat et al., 2004). The chronic inflammatory state of obesity is associated with excessive production of TNF α , which downregulates PPAR γ expression (Zhang et al., 1996). The downregulation of PPAR γ protein expression leads to a decrease in adipogenesis, and the storage capacity of triglycerides in adipocytes is impaired, which increases the level of free FFA, resulting in a vicious circle (Abdullahi and Jeschke, 2016). In addition, inflammation may cause insulin resistance through the direct action of TNF α on muscle insulin signaling. In addition, the normal secretion of adipogenic factors, such as leptin and adiponectin, is also affected by adipose tissue metabolic disorders (Berg et al., 2002). Improving insulin resistance is important in the treatment of obesity and obesity-related lifestyle disorders.

Ginsenoside Rg3 was found to improve the pathological changes caused by obesity by downregulating STAT5-PPAR. Rg3-treated 3T3-L1 cells showed reduced lipid accumulation and total TG levels, and alleviated obesity-induced insulin resistance and lipid toxicity (Lee et al., 2017). By measuring the expression level of apoptosis-related protein and TUNEL staining, it was found that ginsenoside Rb2 improved the insulin resistance and apoptosis of 3T3-L1 adipocytes induced by TNF- α (Lin et al., 2020), and ginsenoside Rd reduced the BAX/BCL2 ratio and directly reduced the apoptosis of islet cells (Kaviani et al., 2019). In addition, it has been found that ginsenoside Rg3 can improve insulin signaling in obese patients by stimulating the expression of IRS-1 and GLUT4 (Kim M. et al., 2009), and ginsenosides Rb1, Rg1, Rg3, and Rh2 can enhance glucose-stimulated insulin secretion in islet cells (Park et al., 2008; Yuan et al., 2012). It can be seen that notoginsenosides can improve insulin sensitivity of the body by alleviating lipid toxicity, protecting adipocytes and islet cells, and enhancing insulin signal transduction. However, interestingly, Reeds et al. found that oral administration of ginseng and ginsenoside Re did not improve impaired glucose tolerance or obesity, and there were no significant changes in cell function or insulin sensitivity in obese subjects, which may be related to the low systemic bioavailability of saponins (Reeds et al., 2011). This question needs to be answered with quality evidence in subsequent experimental studies to confirm the ginsenoside efficacy.

Glucose Metabolism

Adipose tissue plays an important role in the control of systemic glucose homeostasis in both normal and diseased states. Insulin resistance associated with obesity indicates a decrease in the body's ability to activate the insulin signaling pathway, which



stimulates glucose uptake and metabolism (Villalobos-Labra et al., 2019). In the adipocytes of insulin-resistant obese patients, reduced levels of the insulin-regulated glucose transporter GLUT4 trigger hyperglycaemia (Brannmark et al., 2013) thus activating oxidative stress, inflammation, and endoplasmic reticulum stress responses (Mozzini et al., 2015; Mota et al., 2016).

Ginsenosides Rb2 and Rg3 were found to increase glucose uptake by the IRS-1-PI3K-Akt/PKB pathway in 3T3-L1 adipocytes (Lee et al., 2011; Dai et al., 2018). Ginsenosides Rb1, Re, CK, and Rg1 promote the absorption and utilization of glucose in adipocytes, liver, and muscle tissues and improve insulin resistance by activating AMPK pathways and increasing GLUT4 mRNA and protein levels (Huang et al., 2010; Shang et al., 2014; Li et al., 2018). Although adipose tissue absorbs less glucose than skeletal muscle, it accounts for only about 10% of the glucose load at mealtime. However, it has recently been found that GLUT4 expression and glucose metabolism in adipose cells can affect substrate metabolism and adipogenesis by changing endocrine functions, thus improving lipid metabolism disorders caused by obesity (Figure 2) (Semirale et al., 2011; Smith and Kahn, 2016).

CONCLUSION

Obesity has become an epidemic worldwide due to genetics, or poor lifestyle habits, such as fatty diet and less exercise. According to statistics, obesity-related diabetes, cardiovascular disease, and cancer have shortened the life span of obese patients by 4–7 years (Bray et al., 2018). At present, most of the drugs and strategies to

manage obesity have obvious side effects or are not effective. Moreover, obesity can cause a variety of pathological changes, including hyperlipidemia, chronic inflammation, adipocyte dysfunction, glucose and lipid metabolism disorder, mitochondrial injury and insulin resistance, and other multi-factor interactions, making the treatment of obesity more difficult. For example, in response to increased lipid levels, mitochondrial function is downregulated and the expression of oxidative phosphorylation genes is reduced (Richardson et al., 2005; Koves et al., 2008). However, reduced mitochondrial function results in impaired ability to consume fatty acids through oxidative metabolism that may further exacerbate lipid toxicity and glucose lipid metabolism disorders, secondary inflammation, and insulin resistance (Morino et al., 2006).

P. notoginseng contains a variety of phytoconstituents, including notoginsenosides, ginsenosides, quercetin, and ginseng polysaccharides, that have been used as a rare traditional Chinese medicine for many centuries. There is much evidence to support the effect of notoginsenosides in the management of obesity and weight loss. As mentioned above, notoginseng saponins regulate adipogenesis and lipolysis through signaling pathways, such as AMPK and PPAR, reducing adipose tissue volume while avoiding the generation of lipid toxicity. In addition, notoginsenosides also alleviate the mitochondrial metabolic disorders associated with obesity and protect mitochondrial function through antioxidant stress. They promote browning of white adipose tissue by PPARs and PGC-1A, such that energy storage tissue can be transformed into energy consumption tissue, and increase the body's energy consumption to resist obesity. Furthermore, notoginsenosides can also improve glucose and lipid metabolism disorders caused by obesity. By improving the expression of GLUT4 protein and improving the insulin sensitivity of all organs and tissues, and promoting the uptake and utilization of glucose and free lipids in all organs, obesity can be managed from various aspects.

In addition, it has been reported that ginsenosides treat obesity in other ways. Ginsenoside Rb1 decreased pro-inflammatory cytokines, such as TNF- α , IL-6, and NF- κ B induced by a high-fat diet, and restored leptin signaling in the hypothalamus and pSTAT3 in high-fat mice (Wu et al., 2014; Wu et al., 2018). In addition, ginsenoside Rb1 can improve insulin sensitivity in obese and diabetic db/db mice by upregulating plasma adiponectin levels, reducing liver fat accumulation, and inhibiting adipocyte lipolysis (Yu et al., 2015). Interestingly, acute intraperitoneal injection of Rb1 activates the PI3K/Akt signaling pathway through the expression of c-FOS in brain regions involved in energy homeostasis, and inhibits the expression of NPY gene in the hypothalamus, thereby reducing appetite and food intake, body weight, and body fat content and increasing energy consumption (Xiong et al., 2010; Park H. J. et al., 2019). Xu et al. also found that PNS-induced regulation of intestinal flora in DIO mice can increase BAT thermogenesis and beige adipocyte reconstruction by activating the leptin-AMPK/STAT3 signaling pathway thus promoting energy consumption (Xu et al., 2020).

At present, it is difficult to achieve significant therapeutic effects in the treatment of complex diseases using a single target

strategy. Although the efficacy of some notoginsenosides needs to be further confirmed, and the detailed mechanism of notoginsenosides in the treatment of obesity needs to be further elucidated, notoginsenosides show the possibility of resisting obesity in many ways, providing new ideas and methods for the multi-target treatment of such complex diseases. In addition, the oral utilization rates of different *P. notoginseng* saponins were significantly different; oral utilization of PPD ginsenoside was significantly higher than that of PPT ginsenoside. However, in general, PNS has poor absorption, long elimination half-life, and low bioavailability. PNS is metabolized by bacteria and enzymes in the gastrointestinal tract with many glycosides (Han et al., 2006; Liu et al., 2009). At present, there is insufficient evidence to support the clinical application of notoginsenosides in the treatment of obesity. Clinical trials of the safety and efficacy of these compounds are needed to verify the effects of saponins observed *in vitro* and in animal models.

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AUTHOR CONTRIBUTIONS

BZ, GS and XS contributed to the conception of the review, XZ contributed significantly to the complete manuscript preparation, and BZ and CZ contributed to constructive discussions. All authors read and approved the review.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer PZ declared a shared affiliation with the authors to the handling editor at the time of the review.

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