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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

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