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Ginseng and obesity: observations and understanding in cultured cells, animals and humans

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Abbreviations

ACC, acetyl-coA carboxylase

AMPK, AMP-activated protein kinase

C/EBPs, CCAAT/enhancer binding proteins

CVD, cardiovascular disease

EGCG, epigallocatechin-3-gallate

FABP4, fatty acid binding protein 4

FAS, fatty acid synthase

FGF-2, fibroblast growth factor-2

GLUT4, glucose transporter 4

MMPs, matrix metalloproteinases

NPY, neuropeptide Y

PGC-1α, PPAR-γ coactivator-1α

PPARs, peroxisome proliferator-activated receptors

PPD, protopanaxadiols

PPT, protopanaxatriols

T2D, type 2 diabetes

VEGF-A, vascular endothelial growth factor -A

Abstract

Ginseng, a traditional medical herb, has been reported having beneficial effects in fatigue, heart diseases, diabetes, immune function and erectile dysfunction. In recent years, increasing investigations have been conducted on ginseng in preventing and treating of obesity, one of the major worldwide escalating public health concerns. However, the effect and the relevant mechanisms behind how ginseng works as an anti-obesity treatment are still controversial. In this review, we briefly discussed the chemical structures, metabolism and pharmacokinetics of ginseng and its major bioactive components ginsenosides. The major focus is on the anti-obesity effects and the physiological, cellular and molecular mechanisms of ginseng and its ginsenosides in cultured cells, animal models and humans. We particularly compared the ginsenosides profiles, the anti-obesity effects and the mechanisms between Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinqefolius*), the two major ginseng species having opposite medical effects in traditional Chinese medicine. Our unpublished data on the ginseng anti-obesity in cultured cells and mice were also included. We further addressed the current problems and future directions of the ginseng anti-obesity research.

Keywords: ginseng; ginsenosides; anti-obesity effects; mechanisms; adipocytes; animals; humans

1. Introduction

The first written record of Ginseng for therapeutic use was about 2,000 years ago in Asia [1]. The name ginseng is derived from the Chinese term referring to the "man-like" shape of the root, and they were believed to be beneficial for human health. In 1761 with the help of Native Americans, Lafitau J. F. discovered the first American ginseng speices in North America [2]. In 1843, the Russian botanist Carl A. Meyer gave ginseng the botanical name "Panax", which means "all-healing" in Greek [3]. According to the cultivation distribution, the Asian ginseng (*Panax ginseng* C.A. Meyer) and American ginseng (*Panax quinquefolius*) are the two major classes of the well-known ginseng. Other types of ginseng include: Japanese ginseng (*Panax japonicas*), notoginseng (*Panax notoginseng*), Nepal ginseng (*Panax pseudoginseng*), Vietnamese ginseng (*Panax vietnamensis*), Dwarf ginseng (*Panax trifolius*), and Siberian ginseng (*Eleutherococcus senticosus*). Within all the *Panax* species, the American ginseng and Asian ginseng are the closest related [4], and Siberian ginseng is distantly related to *Panax* family and is considered to be an entirely different plant species. Although the roots of the ginseng plant are typical used in Chinese medicine [5-7], the leaves and berries of the plant are also a source of medicine, [8, 9]. China, South Korea, Canada, and USA are the major ginseng producers and their total production of fresh ginseng is about 99% of 80,080 tons, the total ginseng production around the world [10]. Ginseng is distributed to more than 35 countries in various forms such as fresh ginseng, dried ginseng, boiled and dried ginseng, red ginseng and the related products. Ginseng is consumed as food, dietary supplements, and used as therapeutic medical supplies. The world ginseng market including ginseng root and the processed products, was estimated to be worth $2,084 million in 2013 [10]. American ginseng (mainly produced in

Ontario, Canada and Wisconsin, USA) is the fifth most commonly used natural product in USA [11].

Obesity, a condition of excessive fat accumulation in the body to the extent that health and well-being are adversely affected (body weight index (BMI) >30), has reached its epidemic proportions. According to the World Health Organization database [12], worldwide obesity rates (11% of men and 15% of women aged 18 years and older) in 2014 were two times the rates in 1980. It is estimated that if recent trends continue, up to 57.8% of the world's adult population will be either overweight or obese by 2030 [13]. As stated by the most recent obesity data, the prevalence of obesity in the United States is very high, with 34.9% of adults and 17% of children being obese in 2012 [14], and future predictions indicate about 42% of the US population will be obese by 2030 and this will cost an additional $549.5 billion each year on medical expenditures [15]. Obesity increases the risks of various chronic diseases including type 2 diabetes (T2D) [16], hypertension [17], heart disease [18], stroke [19], musculoskeletal diseases [20] and certain types of cancers [21].

Changing lifestyle such as increasing physical activity and reducing energy intake have successfully reduced body weight in humans [22-24]; however, alternative methods are required to control body weight, because increasing physical activity and limiting energy intake are extremely difficult for many people. Natural plants-derived compounds are recently considered as an excellent alternative strategy for developing safe and cost-effective anti-obesity agents because of the potential hazardous side effect and high cost of the current anti-obesity drugs [25]. Indeed, a number of plants-derived compounds such as soy bean genistein [26], green tea

epigallocatechin-3-gallate (EGCG) [27, 28], and grape isolate resveratrol [29] have been reported having anti-obesity effects. Various health benefits of ginseng has been reported for neurological disorders [30-32], cardiovascular disease [33, 34], type 2 diabetes [35], immune function [36, 37], erectile dysfunction [8, 38, 39] and obesity [40-42]. Although the potential anti-obesity effect of Asian ginseng have been investigated in mice [40], adipocytes [41] and humans [43] in Asia in the last several decades, the anti-obesity effect and mechanism of ginseng are still not fully understood, especially in humans. Moreover, high-quality studies of the effects of ginseng in the United States are rare [44], particularly whether and how American ginseng prevents obesity is almost blank.

This review focuses on the anti-obesity effect of ginseng and its bioactive compounds as well as the relevant physiological, cellular and molecular mechanisms in cultured cells, animal models and humans. We particularly compared the ginsenosides profiles, the anti-obesity effects and the relevant mechanisms between Asian ginseng and American ginseng. These two major ginseng species have opposite therapeutic effects in traditional Chinese medicine. The current problems and future directions on the anti-obesity effect of ginseng were also discussed.

2. Ginseng and ginsenosides

2.1 Ginsenosides: major therapeutic constituents of ginseng

Ginseng contains a varieties of bioactive compounds such as ginseng saponins, peptides, polysaccharide, fatty acids, vitamins, alkaloids, lignans, and flavonoids [45]. Saponins, the major pharmacological compounds in ginseng, were named in 1957 by Brekhamn, and the structure was then identified and named as ginsenoside by Shebta [46, 47]. Over 100 ginsenosides have

been identified since the first description [48]. As shown in **Fig. 1**, the major ginsenosides are protopanaxadiols (PPD) including Ra1, Ra2, Ra3, Rc, Rd, 20(S)-Rg3, Rb2, quinoquenosides (Q)-R1, Rs1, Rs2; malonyls (MA)-Rb1, MA-Rb2, MA-Rc, MA-Rd and Rg3; protopanaxatriols (PPT) including Re, Rf, Rg1, Rg2, Rh1, 20-glucopyranosyl (Glc)-Rf, r-R1, 20R-Rg2 and 20R-Rh1; oleanolic acid (Ro) and ocotillol (F11, R15) [37]. The amphiphilic nature of ginsenoside is influenced by the polarity of the different sugar moieties attached to the ring structure [49] (**Fig. 1**). The basic ginsenoside structure contains a steroidal core (17 carbons in a four-ring structure), with various sugar moieties (e.g. glucose, rhamnose, xylose, arabinose). Ginsenosides are named as 'Rx', where the 'R' stands for the root and the 'x' describes the chromatographic polarity in an alphabetical order. There are two major groups of ginsenosides based on the functional group on the C6 position: PPD and PPT. PPD has a hydrogen atom at C6 and PPT contains a C6 sugar side-chain. The different ginsenosides structures may lead to different biological activities. For example, the ginsenoside Rg1 and Re may be useful as non-peptide-based angiotherapeutic agents for tissue regeneration; however, the coexisting ginsenoside Rb1 has anti-angiogenic properties and the ratio of the concentrations of the two ginsenosides can alter angiogenic properties [50].

The quantity and composition of ginsenosides in ginseng plants are significantly influenced by species, age, part of the plant, cultivation method, harvesting season, preservation method and geographical distribution [51]. For example, ginsenosides Ra, Rb, Rc are mainly from roots; ginsenosides Rh6, Ki, Km are usually from leaves; floralginsengosides H, A, C, J are from flower buds [48]; and Re and Rd are significantly higher in berry than that from roots [52]. The total contents of ginsenosides in these five parts of American ginseng follow this order: leaves (165 mg/g) > root-hair (69 mg/g) > rhizome (51 mg/g) > roots (49 mg/g) > stem (20 mg/g) [53].

In contrast to the main constituent ginsenosides Re (20 mg/g) and Rb1(19 mg/g) of American ginseng roots [53], the main constituent of American ginseng berry juice is ginsenoside Rb3 (2.90 mg/g) [54]. Moreover, the contents of ginsenoside Re and Rb1 in roots increase gradually from 1-year-old to 5-year-old [53]. Wild samples of American ginseng contain higher levels of notoginsenosides R1 and Rw2 and lower levels of the ginsenosides Rd, Rd isomer and 20 (S)-Rg3 than these constituents in cultivated samples [55]. In fact, the steaming process (95-100ºC for 2-3 hours before drying) may lead to a significant increase in the bioactive components (20 (S)-, 20 (R)-Rg3, Rk3, Rh4, Rk1, Rg5 and benzopyrene) by hydrolysis, dehydration and isomerization at C-3, C-6 or C-20 [56]. These increased ginsenosides are the major differences among white ginseng (manufactured by dehydration of fresh ginseng using sunlight), red ginseng (produced by steaming fresh ginseng at 95-100ºC for a reasonable time) and black ginseng (produced by nine-time repetitive steaming white ginseng at 95-100ºC for 3 hours) [57]. Although the profiles of the compositions are similar between Asian ginseng and American ginseng, it has been reported that the crude saponins were within 4.8-5.2% in Asian ginseng, 7.0-7.3% in American ginseng [58], and there are some minor ginsenosides composition differences among them [59]. Particularly, ginsenoside Rf is unique to Asian ginseng while F11 is found exclusively in American ginseng [60], and these ginsenosides have been used to identify whether a ginseng is Asian ginseng or American ginseng [49]. Indeed, pseudoginsenoside F11 is abundant (>1 mg/g) in American ginseng, but occurs at only trace levels (<0.001 mg/g) in Asian ginseng. In contrast, ginsenoside Rf is abundant (>0.2 mg/g) in Asian ginseng but absent in American ginseng [49, 60]. The weight ratio of ginsenoside Rb1/ginsenoside Rg1 is usually 1–3 for Asian ginseng, whereas a value of 10 or greater is characteristic of American ginseng [55, 61, 62] (**Table 1**). Sanqi contains a substantial amount (>10 mg/g) of the PPT-type notoginsenoside

R1, which is also different from Asian and American ginsengs [63]. These differences may contribute to the different theraputic effects between Asian and American ginsengs.

Table 1: Comparison of typical ginsenoside compositions between Asian ginseng and American ginseng

Chemical composition	Asian ginseng	American ginseng
Crude saponins	4.8-5.2%	7.0-7.3%
Major ginsenosides	Rb2,Rc, Rb1, Rg1, Rf	Rb1, Re, Rd, F11
PPD-group to PPT-group	<2.0	>2.0
Rb1:Rg1	<5.0	>5.0
F11	<0.001 mg/g	>1 mg/g
Rf	>0.2 mg/g	<0.001 mg/g

2.2 Metabolism and Pharmacokinetics

The absorption of ginsenosides from intestine to blood is poor (0.1% to 9.3%) after oral intake of ginsenosides or crude extracts [64, 65]. The major reasons are the physicochemical trait including large molecular mass (>500 Da), high hydrogen-bonding capacity (>12) and high molecular flexibility (>10). These oral intake ginsenosides are decomposed to smaller or water soluble molecules by acid, enzymes and bacteria in the digestive system. For instance, ginsenoside Re is converted to ginsenoside Rg2, 20(S)-ginsenoside Rh1, 20(R)-ginsenoside Rh1, ginsenoside F1, 3-oxo-ginsenoside Rh1 and PPT in rats [66]. Rb1, Rb2, Rc are transformed by intestinal bacteria to compound K, the main bacteria metabolite and is then absorbed into the blood [67, 68]. Ginsenoside Rg1 is easily hydrated to the same prospogenins in rat stomach, but Rb1 and Rb2 are little decomposed in rat stomach [69]. PPD-type ginsenosides are mainly metabolized to PPT (M4) by intestinal bacteria and absorbed into lymphatic vessels, and then

esterified with fatty acids and accumulated in the liver [70]. The decomposed products are more permeable than natural ginsenosides, for instance, the time to reach maximum concentration in blood only needs 2 hours after oral compound K intake but needs 8 hours after Rb1 oral intake [71] because compound K is the decomposed product of Rb1. The intestinal absorption of compound K [72] and 20(S)-protopanaxadiol [73] is dose-dependent and can reach 35% in rats. Ginsenoside Rg3 is mostly produced from PPD ginsenosides, such as Rb1, Rb2, Rc, and Rd by attacking the C-20 glycosidic bond through acid treatment or heat processing, and the optimum condition producing ginsenoside Rg3 from ginsenoside Rb1 is heat at 180^{o}C for 30 minutes [74]. The maximum plasma concentrations of ginsenoside Rg3 and its main metabolite ginsenoside Rh2 can reach 10.2 μM and 0.48 μM respectively in 2 hours after oral ginsenoside Rg3 (50 mg/kg) intake in normal rats [75].

Circulating ginsenosides are distributed to various tissues. The levels of ginsenosides in different tissues are type dependent. For instance, C5 min values of ginsenoside Rb1 after i.v. administration (5 μmol/kg) [76] are in the rank order of plasma (50 μM) > liver (22 μM) > kidney (19 μM) > heart (16 μM) > lung (12 μM) > bladder (5.1 μM) > spleen (4.7 μM) > testicle (3.8 μM) > large intestine (3.2 μM) > small intestine (2.7 μM) > stomach (2.2 μM) >adipose tissue (1.9 μM) > brain (0.8 μM). However, liver has the higher level of ginsenosides Rg1 (70 μM in liver versus 11 μM in plasma) [76], compound K (276 μM in liver versus 29 μM in plasma) [76] and ginsenosides Rh2 [73]. Most ginsenosides including Rg1, Rg2, Rf, Re, F1, Rh1, 20gRf, notoginsenoside R1, ginsenosides Rh2, Rg3, compound K, and ginsenoside F2 are rapidly eliminated from blood by biliary excretion (t ½ values <3.2 h), but ginsenosides Ra3, Rb1, Rc and Rd have slow biliary excretion (t ½ values are 7.5-20 h) in rats [76]. Although renal

excretion of most ginsenosides in rats is slow and minimal comparing to the rapid and extensive biliary excretion, renal excretion of notoginsenoside R1, Rf and Rg1 is rapid. It is known that approximately 40% and 20% of i.v-administered doses of ginsenosides Rb1 and Rg1, respectively, were excreted unchanged in rat urine [76]. Moreover, ginsenoside Rh1 and F1 can reach the systemic circulation by administrated with "Ginsana extract" [68]. A recent study shows that the maximum concentrations of ginsenosides Rg3 and ginsenoside Rh2 in normal rats were higher than those in the tumor-bearing rats after oral administration of Rg3, and the clearance of Rg3 in tumor-bearing rats was higher than that in normal rats [75].

2.3 *Ginseng and health*

Asian ginseng was first used as a medical herb in China about 5000 years ago [1], and the therapeutic benefits of ginseng has been summarized in a book named "*Shennong Ben Cao Jing"* (a classic work on plants and their uses, named in attribution to Shennong) [77]. Because its strength-giving properties and rejuvenating powers, the *Yellow Emperor's Canon of Medicine* (*Huangdi Neijing*) states that: "Ginseng strengthens the soul, brightens the eyes, opens the heart, expels evil, benefits understanding and if taken for prolonged periods of time will invigorate the body and prolongs one's life" [78]. In North America, ginseng was considered a botanical resource of importance for the Native American apothecary [79].

Asian ginseng and American ginseng have opposite medical effects in traditional Chinese medicine [80, 81]. Asian ginseng has a warm heat, excitation medicinal nature and function in Qi (refers to life energy or vital energy) supplement, Yang (refers to aspects or manifestations of Qi that are relatively immaterial, amorphous, expanding, hollow, light, ascending, hot, dry, warming, bright, aggressive, and active) returning. On the other hand, American ginseng is cool in nature,

normally it uses for patient with heat pattern, such as hypertension [80]. Asian ginseng can treat collapse due to Qi deficiency, fatigue, poor appetite, diarrhea, breath shortness, feeble pulse, spontaneous perspiration, febrile diseases, amnesia, insomnia and impotence [80]. American ginseng is used in Yin (refers to aspects or manifestations of Qi that are relatively material, substantial, condensing, solid, heavy, descending, cold, moist, cooling, dark, passive and quiescent) enrichment, and to treat diseases such as cough, blood sputum, dysphoria, fatigue and thirst [81]. Although Asian and American ginsengs have similar profiles of active ingredients, the different percentage of crude saponins (4.8-5.2% in Asian ginseng versus 7.0-7.3% in American ginseng) [58] and the specific ginsenoside (Rf only in Asian ginseng, F11 only in American ginseng) [60] may contribute to the different functions of these two ginsengs (**Table 1**). Therefore, it is very important to compare the medical effects using modern scientific approaches.

Various health benefits of ginseng and its ginsenosides have been reported in neurological disorders [30-32], cardiovascular disease (CVD) [31, 32], T2D [33], immune function [34, 35] and erectile dysfunction [8, 38, 39]. For instance, ginsenoside compound K, F1, Rh1 and Rh2 can inhibit Aβ aggregation, inflammation and decrease oxidative stress [82]. Ginsenoside Rb1 enhances neurotrophin expression and induces differentiation of midbrain dopaminergic neurons, which may contribute to the benefits of ginseng in treating Alzheimer's disease [83]. Ginsenoside Rb1 also inhibits cardiac hypertrophy [84] and reduces blood pressure [85] in rats . Moreover, total ginsenosides and panaxtrol saponins can effectively increase the concentrations of spleen NK cells, adrenocorticotrophic hormone and thyoid stimulating hormone in rats [37]. Oral administration Asian ginseng berry extract improves men's sexual function [8].

3. Anti-obesity effects and mechanisms

3.1 Obesity development and regulations

Obesity is a complex multifactorial chronic condition that develops from an interaction of genotype and the environment (imbalance between energy intake and expenditure), and is characterized by increased fat accumulation in adipose tissue [86]. Less physical activity, immoderately food intake and impaired energy homeostasis are all contributing to high prevalence of obesity. When an individual is in energy balance, metabolizable energy intake equals total energy expenditure, and body weight is relatively constant over a given time frame. A continued imbalance (energy intake> energy expenditure) leads to weight gain and develop obesity, which is characterized by increased fat accumulation in adipose tissue [86]. This energy imbalance comes from a combination of the individual behavior, genetic and social factors. Individual behaviors include dietary patterns, physical activity, medication use and other exposures. The social factors include the food and physical activity environment, education, knowledge as well as food marketing and promotion. Adipose tissue is the largest endocrine organ in the body that secretes numerous cytokines and adipokines into the circulation, which may significantly change the immune system and cause various chronic diseases [87] such as heart disease [88], diabetes [89] and cancer [90]. The increased adipose tissue mass comes from the increased number (hyperplasia) and the increased size (hypertrophy) of adipocytes [91].

Hyperplasia is the process of the proliferation and differentiation of pre-adipocytes to adipocytes, whereas mature adipocytes are generally incapable of division [92]. In fact, childhood-onset obesity is characterized by a combination of both hyperplasia and hypertrophy.

However, the number of fat cells increases when the existing fat cells reach a critical size in adult individuals, which is supported by obese individuals having larger and more fat cells, but overweight individuals having larger fat cells without fat cell number increase compared to lean individuals [93]. Moreover, approximately 10% of fat cells turnover annually in both lean and obesity adults, but obese adults recruit more adipocytes than lean adult [94], this is further supported by the adipocyte number increases in response to a high-fat diet in adult rats [95]. Therefore, pre-adipocytes differentiation, adipogenesis, plays a key role in the adult obesity development.

The adipogenesis and lipogenesis (the process of fatty acid, triglyceride synthesis and fat drop packaging) are regulated by transcriptional cascades, which is accompanied by a dramatic changes of expressions of peroxisome proliferator-activated receptor-γ (PPAR-γ) and CCAAT/enhancer binding protein (C/EBP), fatty acid binding protein 4 (FABP4), acetyl-coA carboxylase (ACC), fatty acid synthase (FAS), perilipin and adiponectin [96]. Adipogenic induction rapidly induces expressions of C/EBP-β and C/EBP-δ at early clonal expansion and growth arrest. Increased C/EBP-β and C/EBP-δ target downstream key adipogenic transcriptional regulators C/EBP-α, PPAR-γ and the regulator of lipogenic genes sterol-regulatory-element-binding protein 1 (SREBP1). PPAR-γ activates the promoter of the gene encoding C/EBP-α and vice versa, creating a positive-feedback loop. Increased C/EBP-α and PPAR-γ induce the expression of genes that are involved in insulin sensitivity, lipogenesis and lipolysis, including those encoding glucose transporter GLUT4, FABP4, lipoprotein lipase, perilipin and the secreted factors adiponectin and leptin [97].

Numerous epidemiological and experimental studies show that long-term exposure to a high-fat diet can increase the body weight and obesity in human and animals [98-100]. Over-

consumption of high-fat, energy-dense foods, and sedentary lifestyle results in the energy imbalance and leads to obesity [101]. Indeed, increasing physical activity and reducing energy intake have successfully reduced body weight [22-24]. For example, Hagan et al reported both males and females participated in a 12 weeks of diet plus exercise significantly reduced body weight [102]. In fact, increasing physical activity and reducing energy intake have been recommended to prevent obesity in the American Dietary Guideline [103]. Therefore, changing lifestyle such as increasing physical activity and limiting energy intake can reduce body weight and prevent obesity.

Alternative methods are still required to control body weight, however, given that increasing physical activity and limiting energy intake are extremely difficult for many people. Natural plants-derived compounds are recently considered as an excellent alternative strategy for developing, safe and cost-effective anti-obesity agents because of the potential hazardous side effect and high cost of the current anti-obesity drugs [25]. A number of studies have been carried out to investigate the anti-obesity effect of several plants extract compound like curcumin, capsaicin, gingerol, EGCG, resveratrol, genistein and quercetin [25]. For instance, in 3T3-L1 cells, genistein decreased lipid accumulation and the expression adipocyte specific genes PPAR-γ and C/EBP-α [104]. As a matter of fact, dietary EGCG (0.32%) intake for 17 weeks showed decreased body weight, liver triglyceride, blood glucose and plasma cholesterol levels in male (ob/ob) mice [105]. Therefore, natural compounds from plants have potential in obesity prevention.

3.2 Anti-obesity effects and the mechanisms of ginseng

The potential anti-obesity benefits of ginseng have been investigated in Asia including China and South Korea in the last several decades [40-42]. Ginseng and its ginsenosides may play a role in energy intake and metabolism including appetite, food absorption, gut microbiota, adipogenesis and angiogenesis, fat oxidation and energy expenditure in cultured adipocytes, animals and humans.

3.2.1 Ginseng affects appetite, food absorption and gut microbiota

Leptin and ghrelin are two hormones that regulate appetite and energy balance. Leptin suppresses appetite and food intake while ghrelin increases appetite and food intake via receptors in the hypothalamus [106]. Leptin is released by adipose tissue [107], and signals are sent to the brain, relaying information about the status of the body's energy storage. Then, food intake is decreased and energy expenditure is increased to manage the body weight [108, 109]. Obese individuals have impaired energy homeostasis, and they usually have a very high plasma leptin concentrations [110]. However, hyperleptinemia may not reduce appetite or increase energy expenditure, which is termed "leptin resistance" in obese individuals [110]. Similarly, circulating level of adiponectin, a hormone produced by fat tissue and highly associated with diabetes and cardiovascular dysfunction, is lower in obese people than that of normal weight individuals [111]. Interestingly, ginseng and ginsenoside intake affects the plasma levels of leptin, adiponectin and ghrelin. For instance, high-fat-increased leptin levels , bodyweight and fat pads were reduced in obese mice by Korean ginseng whole extract at 8-18 g/kg intake for 8 weeks [112] or 5, 10, 30 g/kg diet for 13 weeks [113] as well as in rats at 0.2 g g/kg diet for 12 weeks [114]. While white Korean ginseng increased plasma adiponectin level in mice [112, 113], red Korean ginseng extract did not work in rats [114]. Similarly, Rb1 (intraperitoneal injections, 14 mg/kg, daily for

21 days) reversed high-fat-induced body weight, fat content and leptin levels in C57BL/6 mice [115]. Another study found that Rb1 (intraperitoneal injections, 2.5, 5, 10, 20 mg/kg, daily for 4 weeks) dose-dependently reversed high-fat-induced body weight, plasma adiponectin and neuropeptide Y (NPY) expression in high-fat-induced obese rats [116]. Surprisingly, whole Korean ginseng extracts did not significantly reduce food intake either in mice [112] or rats [114], but Rb1 injection reduced food intake [115, 116]. A recent study showed that Chinese ginseng extract (0.5g/kd diet, 15 weeks) reduced concentrations of plasma insulin and leptin, but had no effect on plasma adiponectin level as well as NPY expression in high fat diet-fed mice [117]. Ghrelin is primarily (60% to 70%) secreted into the blood stream by gastric X/A-like cells in the submucosal region, with a secondary contribution from the small intestine and other tissues such as endothelial cells. Interestingly, ginsenoside Rb1 increased ghrelin levels both in mice and endothelial cells [118]. However, Korean red ginseng extract (200 mg/kg, i.p. 3 weeks) reduced food intakes both in normal and high-fat diet intake and decreased levels of leptin and NPY in high-fat diet fed rats [119]. Therefore, the effect of ginseng on appetite and the relevant hormones is still controversial.

Increasing evidence shows that ginseng suppresses food digestion and absorption. Amino acid derivatives such as arginyl-fructose and arginyl-fructosyl-glucose, which are produced during the heat process of raw ginseng to red ginseng, inhibit carbohydrate absorption in the gastrointestinal system and therefore reduce blood glucose in rats [120]. Similarly, black ginseng ethanol extract (10, 30, 50 g/kg diet for 12 weeks) reduced fat digestion and absorption, which is supported by the increased fecal weight and fecal fat excretion compared to the high-fat diet control mice [121]. The lack of absorption of both carbohydrate and fat may result from the

inhibition of pancreatic lipase by ginseng intake [120-122]. However, Rb1 (intraperitoneal injections, 20 mg/kg, daily for 4 weeks) did not affect lipid absorption while reducing weight gain and fat content in high-fat-induced obese rats [116]. In addition, American ginseng leaves extract did not inhibit pancreatic lipase in vitro although the extract reduced fat pad in high-fat-induced mice [123].

The remarkable influences of gut microbiota on energy utilization and storage have been well established in humans [124]. Asian ginseng extract (4 g/tablet, 2 tablets/day, for 8 weeks) intake exerted a weight loss effect and affected gut microbiota profile (significantly reduced Proteobacteria) in obese women [43]. Moreover, the activity of transforming ginsenoside Rb1 to compound K is variable between individuals, depending on the composition of gut microbiota [125]. In humans, Rh2 was mainly transformed by intestinal bacteria from Rg3, and Rg3 usually was metabolized in the stomach from Rb1 and Rb2, which is the major naturally occurring ginsenosides in fresh ginseng [126, 127]. This data indicates that the interactions between ginsenosides and gut microbiota may contribute to the anti-obesity effect of ginseng although more animal and human studies are needed.

3.2.2 Ginseng inhibits adipogenesis and angiogenesis

Excess energy (fat, carbohydrate and protein) intake is stored as fat in the body. This fat storage process includes hypertrophy and hyperplasia as aforementioned, is strictly regulated by PPAR-γ/ C/EBP-α signaling pathway and characterized by increasing proteins including FABP4, ACC, FAS and perilipin. Ginseng whole extract and various ginsenosides have been reported in suppressing this process. Ginsenoside Rb1, Rg1, Re and Rd (at 20 μM) [128], Rh2 (at 20 and 40

μM) [129], Rg3 (at 20 and 40 μM) [130], Rd (at 80 μM) [131], Rh1 (at 50 and 100 μM) [132], compound K (5 μM) [133] inhibit the differentiation process in 3T3-L1 cells. However, Rh2 promotes adipogenesis at low concentrations (0.01- 1μM) by activating glucocorticoid receptor in 3T3-L1 cells [134]. In animal models, Korean ginseng whole extract reduced bodyweight and fat pads in obese mice at 8-18 g/kg diet for 8 weeks [112] or 5, 10, 30 g/kg diet for 13 weeks [113] as well as in rats by 0.2 g g/kg diet for 12 weeks [114]. High hydrostatic pressure extract of fresh ginseng is more efficient in inhibiting fat accumulation than that of water extract of red ginseng in 3T3-L1 cells [135]. Oil extract of ginseng (1 g/kg of body weight) also showed anti-obesity effect in mice [136]. Both American ginseng berry juice (oral gavage, once a day, 0.6 mL/kg for 10 days) [54] and Asian ginseng berry extract (intraperitoneal injection, 150 mg/kg body wt, 12 days) [137] reduced bodyweight gain in mice. Interestingly, the body weight was not significantly changed by ginseng root extract (150 mg/kg body wt, 12 days) , but the same dosage of ginseng berry extract (150 mg/kg body wt, 12 days) significantly decreased body weight in ob/ob mice [52], which may result from significantly higher Re and Rd contents in berry than that from roots [52]. Intraperitoneal injected Rb1 significantly reduced body weight gain, fat mass accumulation and improved glucose tolerance in high-fat-induced obese rats (20 mg/kg, daily for 4 weeks) [116] and mice (14 mg/kg, daily for 21 days) [115], but there is no report of oral intake of Rb1 in preventing obesity in animals. Oral administration of ginsenoside Rh1 (20 mg/kg/day, 4 weeks) suppressed body and epididymal fat weight gains and plasma triglyceride level in mice [138]. Similarly, oral intake of compound K (400 mg/kg, 6 times/week) significantly reversed high-fat-increased body weight, liver weight and subcutaneous fat weight in mice [139]. Dietary intake of Chinese ginseng extract (0.5g/kd diet, 15 weeks) reduced body fat mass gain, improved glucose tolerance and whole body insulin sensitivity, and prevented

hypertension in HF diet-induced obese mice [117]. In humans, Asian ginseng extract (4 g/tablet, 2 tablets/day, for 8 weeks) intake exerted a weight loss effect in obese women [43]. However, there is no report that ginsenoside Rg3, Rh2, Rg1, Rd and Re reduce body weight and fat accumulation in animals. Studies of the anti-adipogenic effect of American ginseng extract in cells are still lacking and there is only one study using American ginseng berry extract in ob/ob mice. Most anti-adipogenic effect of these ginsenosides Rb1, Rg1, Re and Rd [128], Rh2 [129], Rg3 [130], Rd [131], Rh1 [132], compound K [133] as well as Korean ginseng whole extract [135] and Chinese ginseng extract [117] in cells and animals is accompanied by the suppression of PPAR-γ and C/EBP-α expressions, the master regulators of adipogenesis. Our unpublished data show that Rg3, Rh2, compound K and whole extracts of both Asian ginseng and American ginseng inhibited adipogenesis in 3T3-L1 cells, human primary preadipocytes and mice via regulating PPAR-γ and C/EBP-α expressions. Additionally, ginsenosides Rf [140], F2 [141] and Rh1 [142] may directly bind the active site of PPAR-γ and then down-regulate PPAR-γ and perilipin protein expressions.

Each adipocyte is nourished by an extensive capillary network, and growing numbers of adipocyte requires more blood vessels. This process of new blood vessel formation is called angiogenesis, which is regulated by critical factors such as vascular endothelial growth factor -A (VEGF-A), fibroblast growth factor-2 (FGF-2)-2 and matrix metalloproteinases (MMPs). Interestingly, VEGF-A, MMP-2 and MMP-9 mRNA expressions were inhibited by ginsenosides Rb1, Rb2, Rd, Rf, Rg1, Rg2 (10 μM), and Re (0.1 μM) as well as whole red ginseng extract (10 μg/ml) in 3T3-L1 cells [143, 144]. Compound K also inhibited angiogenesis and MMPs activities in 3T3-L1 cells [133]. Expressions of VEGF-A, FGF-2, MMP-2 and MMP-9 were also

reduced by Korean red ginseng extract (0.5% or 5% w/w, 8 weeks) [145] or (5% w/w, 13 week s) [143] in db/db mice.

3.2.3 Ginseng promotes fat oxidation, energy expenditure and browning in mature adipocytes

AMP-activated protein kinase (AMPK), a key regulator of energy dynamics, produces ATP and enhances oxidative metabolism and mitochondrial biogenesis and lipolysis [146-148]. Overexpression of AMPK in mice induces the expression of genes controlling lipid oxidation in mitochondria [149, 150]. Hence, the activation of AMPK provides an energy expenditure pathway for obesity prevention. Ginseng [151-153] and its ginsenosides such as Rg3 [130, 154, 155], Rg1 [156], Rh2 [129], Rb2 [157], Rc [158], Rd [131] and compound K [159] activate the AMPK pathway in cells including HepG2 cells [160], C2C12 cells [151, 158], H4IIE cells [157], HIT-T15 cells [154] and 3T3-L1 cells [130, 157, 161] as well as C57BL/KsJ *db/db* mice [153] and Otsuka Long-Evans Tokushima rats [151]. Rb1 (intraperitoneal injections, 20 mg/kg, daily for 4 weeks) intake increased energy expenditure in high-fat-induced obese rats [116]. Red ginseng extract (2 mg /ml of drinking water, 15 weeks) significantly enhanced energy expenditures by modulating PKA dependent lipid mobilization in fat tissue [162]. Dietary intake of Chinese ginseng extract (0.5g/kd diet, 15 weeks) increased body temperature and fatty acid oxidation in the liver, although energy expenditure, respiration rate, and locomotive activity were not significantly altered in high fat diet-induced obese mice [117].

PPAR-α, one member of the PPAR family, has a crucial role in controlling fatty acid oxidation [163]. Activation of PPAR-α by fatty acids promotes hepatic fatty acid oxidation to

generate ketone bodies [164, 165]. Korean red ginseng enhanced the fatty acid oxidation and energy expenditures via activation of PPAR-α in rats (200mg/kg to 10 week-old, for 32 weeks) [166], db/db mice (0.5% w/w diet for 12 weeks) [167] and HepG2 cells [168]. Similarly, overexpression of PPAR-γ coactivator-1α (PGC-1α), a mediator of the transcriptional outputs and controlling cellular energy expenditure [169], increased energy expenditure [170, 171]. Exposure of 3T3-L1 mature adipocytes to 10 μM ginsenoside Rb1 increased mitochondria respiration and energy metabolism via enhancing the PGC-1α expression [172]. Additionally, treatment with Korean red ginseng (5% w/w ginseng for 13 weeks) promoted fatty acid oxidation and energy expenditure, which were accompanied by the up-regulation of PGC-1α mRNA level in female db/db mice [143]. Moreover, Ginsenosides from leaves of ginseng and ginseng extract are also reported to activate SIRT1 gene expression [173-175], which activates PGC-1α and thereby increases fatty acid transport, binding and activation and β-oxidation as well as energy expenditure [176].

Browning of white adipocyte tissue plays a potential role in sliming of obesity, increasing energy expenditure and reducing insulin resistance. Interestingly, ginsenoside Rb1 (10 μM) increased basal glucose uptake and promoted browning process in 3T3-L1 mature adipocytes, which were evidenced by significant increases in mRNA expressions of uncoupling protein, PGC-1α and homologous domain containing 16 (PRDM16) through activating PPAR-γ [177].

4. Current problems and future direction

4.1 Anti-adipogenic effect of American ginseng studies is very limited

Although the anti-obesity effect of ginseng may come from both American ginseng and Asian ginseng, most anti-obesity studies using whole extract/juice in cultured cells, animals and humans are from Asian ginseng, and there are only two studies using American ginseng extract berry juice [54] and leaves [123] in mice. We did not find reports on the anti-adipogenic effect of American ginseng whole extract either in cultured cells or in humans. Interestingly, the exclusive American ginseng pseudoginsenoside F11 did not inhibit, but promote the fat accumulation in 3T3-L1 cells [178], although more independent studies are needed to confirm this result. While the reasons of lacking studies on the anti-obesity effect of American ginseng remain, we noticed that the most studies on ginseng beneficial effects were conducted in Asian countries including China and Korean; there are very few investigators in USA focusing on this field [44].

4.2 Comparison between American ginseng and Asian ginseng on obesity is lacking

American ginseng and Asian ginseng have opposite medical effects in traditional Chinese medicine [80, 81] with quite different ginsenosides profiles [55, 61, 62] (**Table 1**) as aforementioned, it is of importance to compare the anti-obesity effect between these two ginseng, particularly whole extract. However, most ginseng whole extract anti-obesity studies in cultured cells, animals and humans are using Asian ginseng, and there are only two studies using American ginseng extract berry juice [54] and leaves [123] in mice, and studies of the anti-adipogenic effect of American ginseng whole extract in cultured cells and humans are still lacking. Our preliminary study (not published data) showed that Asian ginseng significantly inhibited fat accumulation in 3T3-L1 cells but American ginseng has no effect at the same concentration (1mg/mL), which may partly result from the increased fat accumulation via

activating PPAR-γ in 3T3-L1 cells by pseudoginsenoside F11[178], one of the major ginsenosides in American ginseng but is not detectable in Asian ginseng. The different anti-obesity effect between American ginseng and Asian ginseng may also result from the different profiles of other ginsenosides including Rg1, Re, Rf, Rc, Rb2 and Rd [55, 61, 62].

4.2 Clinical trials of anti-obesity effect of ginseng and ginsenosides are very limited

There is only one study showing that Asian ginseng extract (4 g/tablet, 2 tablets/day, for 8 weeks) intake exerted a weight loss effect in obese women [43]. However, Korean red ginseng powder (6 g /person/ per day, 12 weeks) did not change the body weight, percent body fat and insulin in healthy overweight and obese adults [179]. Similarly, 30 days of treatment with ginseng root extract (8 g/day) or ginsenoside Re (250–500 mg/day) did not affect the body weight, percent body fat and insulin in overweight and obese subjects with impaired glucose tolerance or diabetes [180]. To our knowledge, there is no study using single ginsenoside (except Re) in humans. American ginseng extract or whole plant/berry has not been investigated in the anti-obesity in humans. In addition, there is no report using human primary cells investigating the anti-obesity effect of ginseng and ginsenosides. This is very important because human primary pre-adipocytes are more sensitive and need lower concentrations of chemicals in inhibiting adipogenesis according to our and others [181] recent studies. This lower concentration requirement may narrow down the gap of the high concentration demands in animal cell lines such as 3T3-L1 cells and human ginseng consumption. Therefore, more clinical trials are needed to confirm the anti-obesity effect of individual ginsenoside or whole ginseng extract in cultured cells and animal models.

4.3 Standardized ginseng production is extremely needed

While increasing studies show the ginseng anti-obesity effect in cultured cells, animal and humans, the results of these studies, particularly in humans are still controversial. These controversial results at least partly come from the variety of the quality of ginseng, especially the whole extract and juice. The quantity and composition of ginsenosides in ginseng plants are dramatically influenced by species, age, and part of the plant, cultivation methods, harvesting season, preservation methods and geographical distribution [48, 49, 51, 52, 55-60]. However, almost all ginsenosides or extracts in these studies were prepared in the individual labs or from different companies, it is almost impossible to keep the quality at the same level, particularly the whole extract. Although few studies are trying to standardize the process [182], and a standardized ginseng extract G115 has been investigated [183-186], a comprehensive standardized ginseng extract producing procedure covering all major factors including species, age, part of the plant, cultivation method, harvesting season, preservation method and geographical distribution is required. This procedure will fundamentally contribute to the beneficial effects of ginseng research and finally human health.

5. Conclusions

Ginseng is a traditional medical herb and has been investigated in the theraputic benefits in human health conditions including CVD, T2D, fatigue, erectile dysfunction and obesity. These ginseng beneficial effects come from its various ginsenosides, and the level and composition of these ginsenosides are significantly depending on the species, age, and part of the plant, cultivation methods, harvesting season, preservation methods and geographical distribution of

ginseng. Ginseng and its ginsenosides may affect appetite, food digestion and absorption, inhibit fat tissue formation, promote energy expenditure and lipid oxidation and finally prevent/reduce obesity in cultured cells, animals and humans. Inhibition of PPAR-γ/C/EBP-α by ginseng contributes to its anti-adipogenic effect, and regulation of AMPK and PPAR-α by ginseng may involve ginseng-increased lipid oxidation and energy expenditure (See schemed mechanisms summary in **Fig. 2**). Most of these ginseng anti-obesity studies were using Asian ginseng and were conducted by investigators in Asian countries like China and Korean, there are very limited anti-obesity studies focusing on American ginseng. The comparison studies on the anti-obesity effect between Asian ginseng and American ginseng, particularly using whole root extract are lacking. These comparison studies are very important because these two ginsengs have opposite medical effects in traditional Chinese medicine, and the different ginsenosides profiles in these two ginsengs. In addition, more clinical trials and a standardized procedure of ginseng producing are needed to confirm the ginseng anti-obesity effect and finally prevent/reduce obesity by ginseng consumption in humans.

Disclosure statements

The authors have nothing to disclose.

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Figure legends

Fig. 1. Chemical structures and representative ginsenosides of four major ginsenoside types: protopanaxadiol (PPD), protopanaxatriol (PPT), ocotillol and oleaolic acid ginsenosides.

Fig.2. Hypothetical physiological, cellular and molecular mechanisms of the anti-obesity effect of ginseng and its ginsenosides. Ginseng and its ginsenosides may affect appetite, food digestion and absorption, inhibit fat tissue formation (adipogenesis and angiogenesis), promote energy expenditure and lipid oxidation and finally prevent/reduce obesity in cultured cells, animals and humans. Inhibitions of peroxisome proliferator-activated receptor gamma and CCAAT/enhancer binding protein alpha (PPAR-γ/C/EBP-α) and the downstream molecules including fatty acid binding protein 4 (FABP4), fatty acid synthase (FAS), vascular endothelial growth factor -A (VEGF-A), and matrix metalloproteinases (MMPs) by ginseng contribute to its anti-adipogenic effect, and regulations of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR-α) by ginseng may involve in the ginseng-increased lipid oxidation and energy expenditure.

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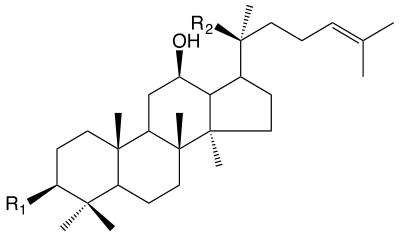
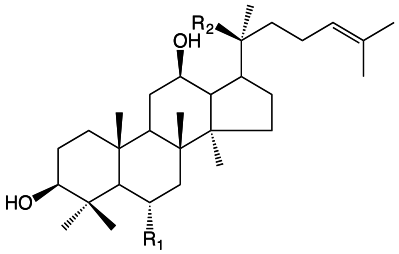
Figure 1



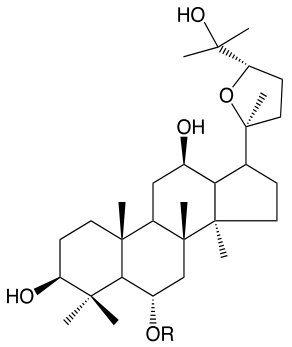
Ginsenoside PPD type

PPD type	R_1	R_2
Ginsenoside Ra_1	glc-glc-O-	xyl-ara(P)-glc-O-
Ginsenoside Rb_1	glc-glc-O-	glc-glc-O-
Ginsenoside Rc	glc-glc-O-	ara(f)-glc-O-
Ginsenoside Rd	glc-glc-O-	glc-O-
(20S)-ginsenoside Rg3	glc-glc-O-	OH
Ginsenoside Rh_2	glc-O-	OH
Ginsenoside Rs_1	ac-glc-glc-O-	ara(P)-glc-O-
Compound K	OH	glc-O-



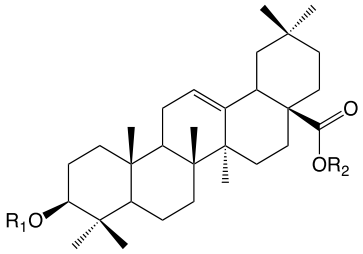
Ginsenoside PPT type

PPT type	R_1	R_2
Ginsenoside Re	rha-glc-O-	glc-O-
Ginsenoside Rf	glc-glc-O-	OH
Ginsenoside Rg_1	glc-O-	glc-O-
(20S)-ginsenoside Rg_2	rha-glc-O-	OH
Ginsenoside Rh_1	glc-O-	OH
20-glucoginsenoside Rf	glc-glc-O-	glc-O-
Notoginsenoside R_1	xyl-glc-O-	glc-O-
Notoginsenoside R_2	xyl-glc-O-	OH



Ginsenoside ocotillol type

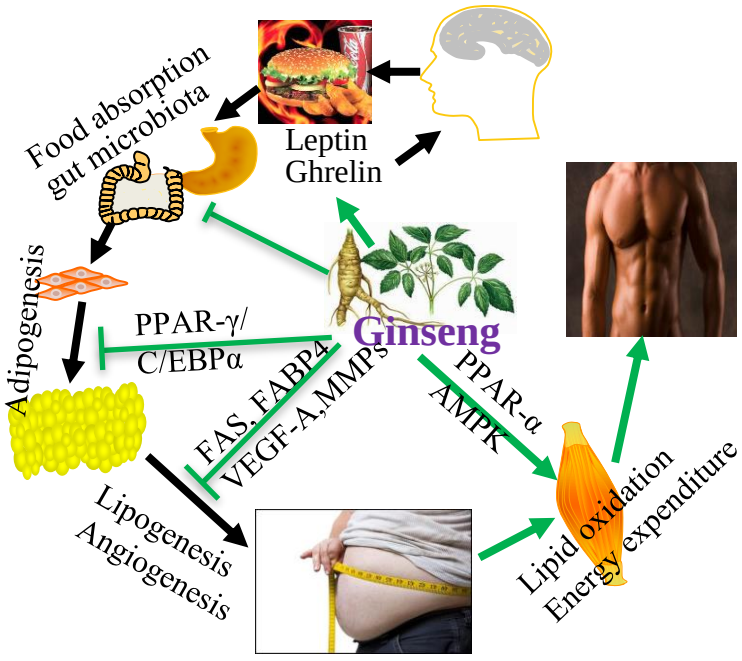
Ocotillol type	R
Majonoside R_2	xyl-glc-



Ginsenoside oleanolic acid type

Oleanic type	R_1	R_2
Ginsenoside Ro	glcA-glc-	glc-
Chikusetsusaponin IVa	glcA-	glc-
Chikusetsusaponin IV	ara(f)-glcA-	glc-

Figure 2


Food absorption
gut microbiota
Leptin
Ghrelin
Adipogenesis
PPAR-γ/
C/EBPα
Ginseng
FAS, FABP4
VEGF-A,MMPs
PPAR-α
AMPK
Lipogenesis
Angiogenesis
Lipid oxidation
Energy expenditure