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REVIEWS: CURRENT TOPICS

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

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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 antiobesity 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 antiobesity 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 antiobesity effects and the mechanisms between Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*), the two major ginseng species having opposite medical effects in traditional Chinese medicine. Our unpublished data on the ginseng antiobesity in cultured cells and mice were also included. We further addressed the current problems and future directions of the ginseng antiobesity research.

Keywords: Ginseng; Ginsenosides; Antiobesity effects; Mechanisms; Adipocytes; Animals; Humans

1. Introduction

The first written record of ginseng for therapeutic use was about 2000 years ago in Asia [1]. The name ginseng is derived from the Chinese term referring to the "man-like" shape of the root, and it was believed to be beneficial for human health. In 1761 with the help of Native Americans, Lafitau J.F. discovered the first American ginseng species 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 the following: 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 the United States 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 $2084 million in 2013 [10]. American ginseng (mainly produced in Ontario, Canada and Wisconsin, USA) is the fifth most commonly used natural product in the United States [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 >30), has reached its epidemic proportions. According to the World Health Organization database [12], worldwide obesity rates (11% of men and 15% of women 18 years and older) in 2014 were two

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.

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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 that 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 has 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 antiobesity agents because of the potential hazardous side effect and high cost of the current antiobesity 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 antiobesity effects. Various health benefits of ginseng have been reported for neurological disorders [30–32], cardiovascular disease (CVD) [33,34], type 2 diabetes [35], immune function [36,37], erectile dysfunction [8,38,39] and obesity [40–42]. Although the potential antiobesity effect of Asian ginseng has been investigated in mice [40], adipocytes [41] and humans [43] in Asia in the last several decades, the antiobesity 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 antiobesity 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 antiobesity 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 antiobesity effect of ginseng were also discussed.

2. Ginseng and ginsenosides

2.1. Ginsenosides: major therapeutic constituents of ginseng

Ginseng contains a variety 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 (PPDs) 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 (PPTs) 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 ginsenoside 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 antiangiogenic 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 and Rc are mainly from roots; ginsenosides Rh6, Ki and Km are usually from leaves; floralginsengosides H, A, C and 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 (95–100°C for 2–3 h 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 95–100°C for a reasonable time) and black ginseng (produced by nine-time repetitive steaming white ginseng at 95–100°C for 3 h) [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 and 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 therapeutic effects between Asian and American ginsengs.

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