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Short Review

Ginsenosides: the need to move forward from bench to clinical trials

Seung Eun Yu^{1,☆}, Benjamin Mwesige^{2,☆}, Young-Su Yi^{3,**}, Byong Chul Yoo^{1,2,*}¹ Biomarker Branch, Research Institute, National Cancer Center, Gyeonggi, Republic of Korea² Department of Cancer Biomedical Science, Graduate School of Cancer Science and Policy, National Cancer Center, Gyeonggi, Republic of Korea³ Department of Pharmaceutical and Biomedical Engineering, Cheongju University, Cheongju, Republic of Korea

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ABSTRACT

Panax ginseng, known as Koran ginseng, one of the most commonly used traditional plants, has been demonstrated to show a wide range of pharmacological applications. Ginsenosides are the major active ingredients found in ginseng and are responsible for the biological and pharmacological activities, such as antioxidation, antiinflammation, vasorelaxation, and anticancer actions. Existing studies have mostly focused on identifying and purifying single ginsenosides and investigating pharmacological activities and molecular mechanisms in cells and animal models. However, ginsenoside studies based on clinical trials have been very limited. Therefore, this review aimed to discuss the currently available clinical trials on ginsenosides and provide insights and future directions for developing ginsenosides as efficacious and safe drugs for human disease.

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1. Introduction

Korean ginseng (*Panax ginseng* Meyer) has long been used in several eastern Asian countries, such as China, Japan, and Korea, as a traditional tonic for longevity. In traditional medicine, ginseng was simply prepared in water as a drink. A number of clinical studies on ginseng have been conducted to characterize its pharmacological properties, including improving physical performance and sexual function and treating diabetes, hypertension, inflammatory diseases, and cancer [1]. The mechanism of ginseng's functions had not been known until ginsenosides were purified as the major active components of ginseng. Since this discovery, many efforts have been made to focus on evaluating their pharmacological functions and demonstrating the molecular mechanisms of each ginsenoside. The therapeutic potential of ginseng has been studied extensively, and ginsenosides have been reported to modulate various physiological activities [2] and treat many chronic diseases. One of the major advantages of ginsenosides is their ability to interact with various target molecules in the cells, leading to combined beneficial effects [3]. Despite the

remarkable achievements in diagnosis and treatment, current clinical therapies using conventional chemotherapeutic agents and pharmaceutical drugs are often toxic and have limited effectiveness, suggesting a high demand for novel, more effective, and less toxic therapeutic agents. Therefore, much attention has been paid to the exploration of novel drugs isolated from natural resources with low adverse effects and high efficacy for the treatment of human diseases. Complementary alternative medicine is a diverse type of medical systems, practices, and products [4]. Among the complementary alternative medicines, ginseng has been extensively used in Asian and, currently, in Western medicines, with a history stretching back more than 5,000 years [5]. Extensive studies have identified ginsenosides as the major pharmacological ingredient in ginseng and confirmed that ginsenosides play pivotal roles in preventing and treating various human diseases [6–10]. However, most of the promising studies reporting the pharmacological effects of ginsenosides on human diseases are *in vitro* cell-based and animal studies; therefore, this review discusses the recent studies on ginsenosides in clinical trials.

* Corresponding author. Biomarker Branch, Research Institute, National Cancer Center, Republic of Korea; Department of Cancer Biomedical Science, National Cancer Center Graduate School of Cancer Science and Policy, National Cancer Center, Goyang-si, Gyeonggi-do, 10408, Republic of Korea.

** Corresponding author. Department of Pharmaceutical and Biomedical Engineering, Cheongju University, Chungcheongbuk-do 28503, Republic of Korea.

E-mail addresses: ysyi@cju.ac.kr (Y.-S. Yi), yoo_akh@ncc.re.kr (B.C. Yoo).

☆ These authors contributed equally to this work.

2. Ginseng and ginsenosides

Ginseng belongs to the genus *Panax* in Araliaceae family with nine species, including Korean ginseng (*Panax ginseng*), South China ginseng (*Panax notoginseng*), and American ginseng (*Panax quinquefolius*), etc. [11]. *Panax* means “all-healing”, and people believed that it is a panacea promoting longevity [12]; the name “ginseng” arises from the Chinese character “rénshēn”, literally meaning “essence of men” [13]. Ginseng includes a variety of active ingredients, such as ginsenosides, polysaccharides, flavonoids, volatile oils, amino acids, and vitamins [14,15]. Among these, ginsenosides are steroidal saponins with a triterpenoid dammarane structure, having a 4-ring, steroid-like configuration with sugar moieties conjugated, and more than 40 different types of ginsenosides have been identified and isolated from ginseng roots [15]. Ginseng root contains 2–3% ginsenosides, and among these, Rb1, Rb2, Rg1, Rc, Rd, Re, and Rb0 are quantitatively the most abundant and critical ones [16]. Chemical structures of ginsenosides are generally divided into two groups: protopanaxadiol and protopanaxatriol [6,9]. Protopanaxadiols, including Rb1, Rb2, Rc, Rd, Rg3, and Rh3, have the sugar moieties attached to the 3-position of dammarane-type triterpene, whereas protopanaxatriols, including Re, Rf, Rg1, Rg2 and Rh1, have them attaching to the 6-position of dammarane-type triterpene [6,9]. There have been a large number of studies investigating the pharmacological effect of ginseng and ginsenosides and the underlying molecular mechanisms. Ginseng and ginsenosides have been reported to play critical roles in preventing and treating many human diseases, including cancers and neuronal, cardiovascular, inflammatory, and metabolic diseases [6–10]; furthermore, the molecular mechanisms of their pharmacological actions are due to the diverse biological activities of the natural products, such as proapoptosis, antiangiogenesis, stimulation of the central nervous system, antiinflammatory responses, protective effects on DNA, and chemoprophylaxis [6,9,17–21].

3. Clinical trials on ginsenosides

3.1. Ginsenoside Rb1 and compound K

Ginsenoside Rb1 (G-Rb1) is abundant in roots and is also present in the stem and leaves [22]. Many investigations have suggested that Rb1 and its major metabolite, compound K (CK), have diverse *in vitro* and *in vivo* effects, including neuroprotective, antiinflammatory, and antiobesity actions [9]. However, only a few clinical trials of Rb1 have been reported. First, Kim orally administered healthy human individuals with red ginseng extract, followed by collection of blood samples for the pharmacokinetic analysis of both G-Rb1 and CK, and reported that maximum plasma levels of CK were significantly higher than those of G-Rb1, suggesting the delayed absorbance of CK compared with G-Rb1, which provides evidence that intestinal microflora plays a pivotal role in transforming G-Rb1 to CK [23]. Chang et al investigated the effect of G-Rb1 on insulin secretion and plasma glucose levels in healthy human individuals. Interestingly, G-Rb1 exerted no effect on plasma glucose levels and insulin secretion [24] although G-Rb1 was reported to decrease blood glucose levels in obese mice [25] and to increase insulin secretion in cultured insulinoma cells [26]. Despite these studies, further study of G-Rb1 in human patients to examine the pharmacological effects on human diseases is required.

3.2. Ginsenoside Rb2

Various pharmacological properties of ginsenoside Rb2 (G-Rb2) have been reported, including anticancer, antiadipocytic,

antidiabetic, and antioxidative functions in cells and animal disease models [27–30]. The anticancer activity of G-Rb2 was further reported; in uterine endometrial cancer cells, G-Rb2 suppressed matrix metalloproteinase 2 expression and cellular invasion and also inhibited neovascularization and tumor growth in a melanoma animal model [31]. Antiadipocytic activity of G-Rb2 was also reported; G-Rb2 decreased cholesterol and triglyceride levels and increased mRNA expression of the sterol-regulated element-binding protein, which is a lipid metabolism regulator in 3T3-L1 adipocytes [28]. Moreover, G-Rb2 was reported to show antiosteoporosis activity and to improve bone microarchitecture and bone mineral density by decreasing and increasing malondialdehyde and glutathione levels, respectively, in ovariectomized mice [32]. Despite these many pharmacological and mechanism studies of G-Rb2 in cells and animal models, only one clinical study has demonstrated no effect of G-Rb2 on the motility of human sperm in semen samples collected from human patients [33].

3.3. Ginsenoside Rg3

Ginsenoside Rg3 (G-Rg3) is highly enriched in Korean Red Ginseng [34] and exhibits various effects, including neuro-modulatory, cognition-enhancing, antiinflammatory, antioxidative, antiangiogenic, and anticancer chemotherapeutic activities [7,35–39]. Rg3 has enhanced anticancer activity compared with other ginsenosides and has the best proapoptosis effect [40]. Despite the useful antitumor effect of Rg3, only a few clinical studies have been demonstrated on ginsenoside Rg3. Many researchers have reported that combined chemotherapy with Rg3 improves the survival rate in cancer patients. For example, Sun et al and Lu et al reported that combined chemotherapy with Rg3 can improve the survival of cancer patients with advanced non-small cell lung cancer after surgery [41,42], suggesting that Rg3 in combination with current anticancer drugs could improve a short-term therapeutic efficacy of non-small cell lung cancer. Shenyi capsule is a G-Rg3 monomer preparation, and using combined use of Shenyi capsules with current chemotherapy, it improved the postoperative survival of patients, mainly by improving immune functions and inhibiting angiogenesis in gastric cancer patients [43]. Huang et al also evaluated the therapeutic effect of Shenyi (95% G-Rg3) in combination with gemcitabine and cisplatin in advanced esophageal cancer patients and compared this patient group with the control patient group with chemotherapy alone. Results showed no significant difference in the total response rate between the Shenyi-administered and placebo-administered groups; however, the vascular endothelial growth factor in the Shenyi-administered group was found to be lower than that in the placebo-administered groups [44], suggesting the inhibitory effect of G-Rg3 on angiogenic activity. Moreover, the one-year survival rate in the Shenyi-administered group was higher than that in the placebo-administered groups [44]. Another clinical study also demonstrated that G-Rg3 is an effective antitumor agent [45], but more qualified clinical studies are needed to confirm the pharmacological effect of G-Rg3.

3.4. Ginsenoside Rh2

Ginsenoside Rh2 (G-Rh2) originally isolated from ginseng root has been suggested to have anticancer properties [46] and is considered one of the critical ginsenosides for antidiabetic, anti-allergic, and antiinflammatory activities [47–49]. Recently, Qiu et al showed that G-Rh2 ameliorated Alzheimer's disease symptoms in mice by improving the learning and memory function in the diseased mice [50]. However, the poor oral bioavailability due to its low solubility in water greatly limits the use of G-Rh2 in clinical

studies [51]. Therefore, additional studies are required to increase the solubility of G-Rh2 for better efficacy in clinical applications for long-term use.

3.5. Ginsenoside Rh3

Ginsenosides are generally metabolized by the bacteria in the human intestine to deglycosylated forms, which could be easily absorbed in the bloodstream and act as a bioactive ingredient [52]. Ginsenoside Rh3 (G-Rh3) is a bacterial metabolite of ginsenoside Rg5 (G-Rg5) [53], and treatment of human retinal cells with G-Rh3 induced the nuclear factor (erythroid-derived 2)-2 activation [54]. Moreover, G-Rh3 was reported to protect against memory deficits in mice by suppressing acetylcholinesterase activity as well as by inducing hippocampal brain-derived neurotrophic factor expression and cyclic adenosine monophosphate (cAMP) response element-binding protein activation [55]. However, no clinical study of G-Rh3 has been reported so far.

3.6. Ginsenoside Rc

Ginsenoside Rc (G-Rc) was found in tea [56] and has been reported to have various biological activities, such as inhibiting photaging, oxidative stress, formalin-induced nociception, and inflammatory responses as well as increasing the life span of *Caenorhabditis elegans* [57–61]. Moreover, G-Rc was reported to have a potential antidiabetic activity by enhancing glucose uptake in C2C12 myotubes [62]. Despite these pharmacological and mechanism studies of G-Rc in cells and animal models, only one clinical study demonstrated that G-Rc enhanced the motility and progression of sperm in semen samples collected from human patients [33].

3.7. Ginsenoside Rg1

Ginsenoside Rg1 (G-Rg1) appears to be most abundant in Korean ginseng (*Panax ginseng*) [63] and has been demonstrated to

have antiaging and antineurodegenerative activities [64,65]. G-Rg1 was reported to improve memory impairment, to ameliorate behavioral abnormalities, and to modulate the hippocampal proteomic change in the mouse model of Alzheimer's disease [66], suggesting that Rg1 might be considered as a potential drug candidate to improve the behavioral deficits in Alzheimer's disease. However, the evidence that G-Rg1 plays a critical role in neurodegenerative diseases such as Alzheimer's disease is insufficient; in addition, there is a dearth of clinical trials investigating the effect of G-Rg1 in combination with other neuroprotective drugs, which needs to be explored in future clinical studies.

3.8. Ginsenoside Rg2

Ginsenoside Rg2 (G-Rg2) is found to be more abundant in the stems and leaves of ginseng [67], and a number of studies have demonstrated that G-Rg2 has *in vitro* and *in vivo* pharmacological properties, such as neuroprotective and antidiabetic activities [68,69]. The capacity of G-Rg2 regulating the expression of apoptosis-related proteins suggests that G-Rg2 might be a potential treatment for vascular dementia and other ischemic insults [70]. Despite these *in vitro* and animal studies regarding the pharmacological activity of G-Rg2, no clinical study of G-Rg2 has yet been reported, indicating the high demand for clinical studies of G-Rg2 to treat human diseases.

3.9. Ginsenoside Rh1

Ginsenoside Rh1 (G-Rh1) has been demonstrated to have anti-inflammatory action in colitis in mice [71] and antioxidative activities in rat primary astrocytes [72]. Moreover, G-Rh1 was reported to exhibit neuroprotective effects on cognitive deficits in mice [73]. Despite these *in vivo* animal studies, no clinical study of G-Rh1 has been reported, and further clinical trials using G-Rh1 are highly recommended to provide more reliable evidence for its pharmacological activity.

Table 1
Summary of the clinical trials using ginsenosides

Ginsenosides	Participants	Study design	Clinical outcome	Ref.
G-Rb1	10 healthy volunteers	Pharmacokinetics of G-Rb1 and its major metabolite CK after oral administration	Seven times shorter CK half-life than G-Rb1 half-life in plasma	[23]
	12 healthy gymnasts	Improvement of glycemic status of patients during resistance training	No significant effect of G-Rb1 on the circulating glucose and insulin levels	[24]
G-Rb2	20 patients with sperm motility between 20% and 40% of normal	G-Rb2 (0.1, 0.01, and 0.001 mg/mL) administration in patients	No effects of G-Rb2 on inferior human sperm motility <i>in vitro</i>	[33]
G-Rg3	115 patients with advanced NSCLC	Combined administration of G-Rg3 with vinorelbine plus cisplatin to stage III–IV NSCLC patients	1) Improved response rate 2) Improved survival time: 9.7 mo (mean) and 8.0 mo (median) in the placebo group; 15.3 mo (mean) and 10.0 mo (median) in the test group	[41]
	133 patients with NSCLC	Combined administration of G-Rg3 with chemotherapy to NSCLC patients	Rg3 in combination with chemotherapy improved the life span of NSCLC patients after surgery	[42]
	71 postoperative patients	Combined administration of G-Rg3 with mitomycin C plus tegafur to postoperative patients	The combined administration of G-Rg3 with chemotherapy decreased the serum VEGF level and improved the survival rate in advanced gastric cancer patients	[43]
	60 patients with advanced esophageal cancer	Combined administration of G-Rg3 with gemcitabine plus cisplatin to advanced esophageal cancer patients	The anticancer effect of combined administration of G-Rg3 with chemotherapy was better than chemotherapy alone	[44]
	124 patients with advanced NSCLC and EGFR-active mutation	Combined administration of G-Rg3 with EGFR-TKI to advanced NSCLC patients	Clinical benefit of combined administration of G-Rg3 with EGFR-TKI compared with EGFR-TKI alone in NSCLC patients harboring EGFR-active mutation	[45]
G-Rc	20 patients with sperm motility between 20% and 40% of normal	G-Rc (0.1, 0.01, and 0.001 mg/mL) administration in patients	G-Rc (0.01 and 0.001 mg/mL) enhanced the motility and progression of sperm	[33]

CK, compound K; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

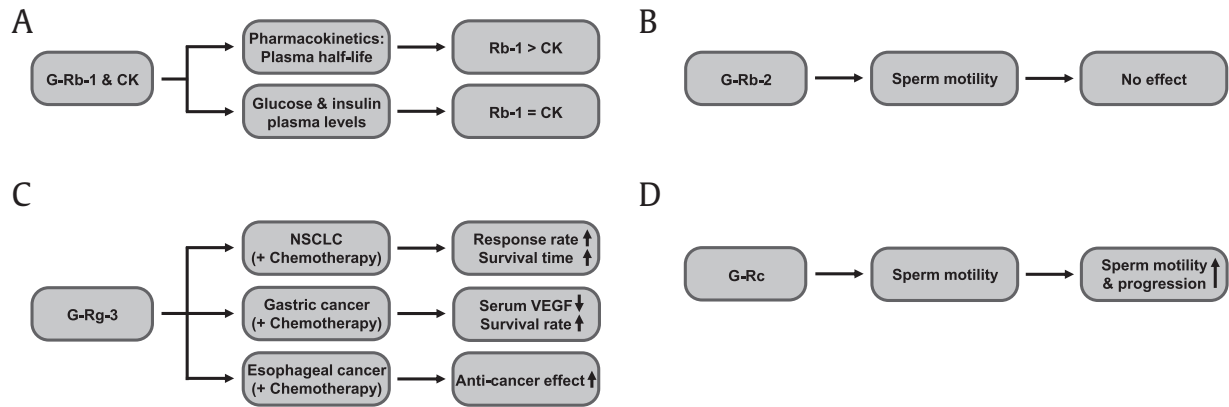


Fig. 1. Conceptual summary of clinical studies using ginsenosides. (A) The effects of G-Rb1 and CK on their plasma half-life and the plasma levels of glucose and insulin in healthy humans. (B) The effect of G-Rb2 on the sperm motility in the patients with reduced sperm motility. (C) The anticancer effect of G-Rg3 and chemotherapy on NSCLC, gastric cancer, and esophageal cancer patients. (D) The effect of G-Rc on the sperm motility in the patients with reduced sperm motility. CK, compound K; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor.

The clinical studies on ginsenosides discussed in this chapter are summarized in Table 1 and conceptually described in Fig. 1.

4. Clinical trials on ginseng

Although a large number of studies have successfully demonstrated both *in vitro* and *in vivo* pharmacological effects of ginseng in a variety of diseases, including cancers, inflammatory diseases, cardiovascular diseases, metabolic diseases, and hepatotoxicity, the efficacy of ginseng in human patients has not been clearly established, and there are insufficient reliable clinical data, meaning that the quality of most clinical studies using ginseng is relatively poor. However, several studies have demonstrated the effects of ginseng in humans. Choi et al investigated the anti-hyperglycemic effect of the *Panax ginseng* berry in healthy human individuals and reported that ginseng berries did not have an antihyperglycemic effect but showed potential to improve glucose metabolism in humans [74]. Hwang et al investigated the antiaging effect of a mixture of *Panax ginseng* and *Crataegus pinnatifida* in healthy human skin and reported that this mixture exerted an antiaging effect by suppressing wrinkle formation and increasing moisture in human skin [75]. Lee and Ji investigated the effect of fermented red ginseng on the depression in postmenopausal women and reported that fermented red ginseng ameliorated cognitive depression [76]. Lee et al also examined the effect of *Panax ginseng* on the cognitive performance of patients with

Alzheimer's disease. The study reported that *Panax ginseng* improved the cognitive performance of patients with Alzheimer's disease and that discontinuing ginseng consumption exacerbated the cognitive performance of the patients [77]. Moreover, Choi et al demonstrated the effect of Korean Red Ginseng on the erectile dysfunction in patients and showed that Korean Red Ginseng improved disease symptoms [78]. Despite the small number of clinical studies, these studies demonstrated the clinical efficacy of ginseng for human diseases. The clinical studies on ginseng discussed in this chapter are summarized in Table 2 and conceptually described in Fig. 2.

5. Why are clinical studies of ginseng and ginsenosides so few?

The importance of ginseng and ginsenosides as natural remedies has long been recognized based on their versatile efficacies that have been proven in *in vitro* cells and *in vivo* animal models. Although many ginsenosides have showed clear anticancer activities in cancer cells and animal tumor models, it is required to examine their comparable effects in human patients. However, the use of ginsenosides has been limited to cells and animal models due to their low bioavailability, such as poor water solubility and biomembrane permeability, instability in gastrointestinal tract, and high metabolic rate in the body. Therefore, a number of efforts have been made on solving these problems by

Table 2
Summary of the clinical trials using ginseng

Ginseng	Participants	Study design	Clinical outcome	Ref.
<i>Panax ginseng</i> berry extract	72 healthy volunteers	Administration of ginseng berry extract in participants with a fasting glucose level between 100 mg/dL and 140 mg/dL	Ginseng berry extract improved glucose metabolism	[74]
<i>Panax ginseng</i> mixture	20 healthy female volunteers (aged 30–65 yr) with crow's feet wrinkles	Administration of a mixture of <i>Panax ginseng</i> and <i>Crataegus pinnatifida</i>	<i>Panax ginseng</i> mixture decreased wrinkle formation and increased moisture in the human skin	[75]
FRG	93 postmenopausal female volunteers (aged 50–73 yr)	Administration of FRG	FRG ameliorated cognitive depression that occurred via the energy factor	[76]
<i>Panax ginseng</i>	97 Alzheimer's disease patients	Administration of <i>Panax ginseng</i>	<i>Panax ginseng</i> enhanced cognitive performance of Alzheimer's disease patients	[77]
Korean Red Ginseng	90 patients with erectile dysfunction	Administration of Korean Red Ginseng	Clinical efficacy on Korean Red Ginseng on erectile dysfunction	[78]

FRG, fermented red ginseng.

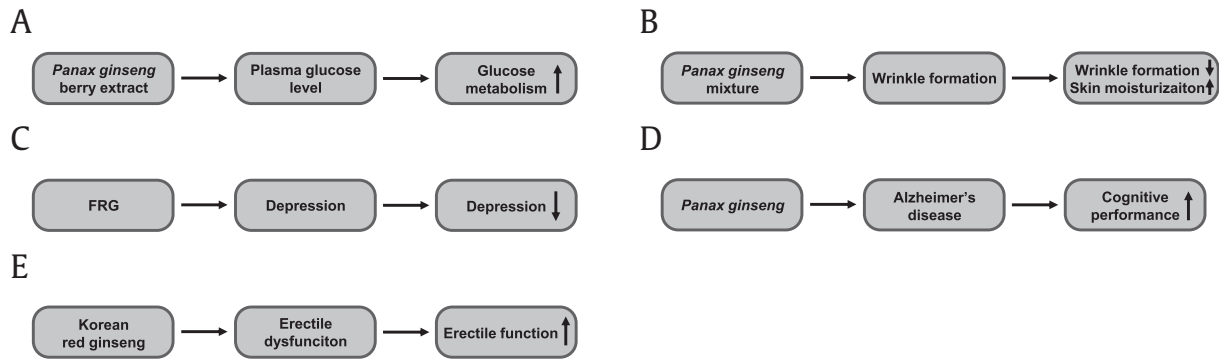


Fig. 2. Conceptual summary of clinical studies using ginseng. (A) The effect of *Panax ginseng* berry extract on the plasma glucose level in healthy humans. (B) The effect of *Panax ginseng* on wrinkle formation and skin moisturization. (C) The effect of FRG on the depression in postmenopausal patients. (D) The effect of *Panax ginseng* on the cognitive performance in patients with Alzheimer's disease. (E) The effect of Korean Red Ginseng on the erectile function in the patients with erectile dysfunction. FRG, fermented red ginseng.

developing effective delivery systems and a variety of administration routes to improve the bioavailability of ginsenosides, resulting in remarkable improvements in their bioavailability. Moreover, ginsenosides exhibit antioxidative, antiinflammatory, apoptotic, and immunostimulatory properties with diverse molecular mechanisms of action; with this said, it is often difficult to standardize the studies due to the diversity of ginsenosides in both chemical structure and biological activity. Therefore, further systemic studies using ginsenosides with improved bioavailability and a series of related compounds are required.

6. Conclusion and future perspectives

Panax ginseng is an herbal medicine traditionally used for a long time worldwide for a wide range of indications. Clinical trials using ginseng and ginsenosides and systematic reviews are now available, and although their conclusions vary, they are promising for some indications. The active ingredients have been mainly isolated and quantified in roots, extracts, and finished products of ginseng, and many studies have shown significant variations between finished preparations. Moreover, many European and American recommendations for using ginseng and its products involve dosages about 10 times less than those generally used in Asian countries. Recent emphasis on the standardized products, which may provide an impression that it is stronger than root powders or other ginseng extracts, might mask the fact that the ginseng products are often standardized to quite low dosages of active ingredients. Recent studies provide the support for using ginseng to treat hyperlipidemia, diabetes, heart failure, and hypertension with the administration doses used in Asian countries, but the evidence supporting performance-enhancing and energy-boosting effects is weak. In addition, there exists considerable confusion for the potential side effects of ginseng, but most of the warnings may not be justified.

Poor bioavailability of ginsenosides and their metabolites indicates that these compounds could not reach the intended biological system when orally administered. Ginsenoside studies could become physiologically relevant only when (a) a large amount of pure ginsenosides are available, (b) ginsenosides are stabilized to increase their stability and absorption in the gastrointestinal tract, and/or (c) special delivery strategies for ginsenosides to reach the treatment areas are established.

Most studies investigating the efficacy of ginseng and ginsenosides have been conducted in cell lines and animal models; relatively few have been undertaken in humans despite the fact that ginseng products have been widely believed and accepted to have therapeutic effects when used alone or in combination with other

therapeutic agents in the management of a wide range of chronic diseases. Therefore, active studies demonstrating the therapeutic effects of ginseng and ginsenosides are in high demand. Moreover, further studies using a single ginsenoside need to include the molecular and cellular mechanisms of action, specificity, and toxicity in animal models and humans. These studies could maximize the potential of ginsenosides as promising herbal medicines, thereby further contributing to the promotion of global health.

Conflicts of interest

The authors declare no conflicts of interest.

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