J Ginseng Res 45 (2021) 199–210

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Review Article

Pharmacological potential of ginseng and its major component ginsenosides

Zubair Ahmed Ratan [1], Mohammad Faisal Haidere [2], Yo Han Hong [3], Sang Hee Park [4], Jeong-Oog Lee [5], Jongsung Lee [3,4,**], Jae Youl Cho [3,4,6,*]

[1] Department of Biomedical Engineering, Khulna University of Engineering and Technology, Khulna, 9203, Bangladesh
[2] Department of Public Health and Informatics, Bangabandhu Sheikh Mujib Medical University, Dhaka, 1000, Bangladesh
[3] Department of Integrative Biotechnology, Sungkyunkwan University, Suwon, 16419, Republic of Korea
[4] Department of Biocosmetics, Sungkyunkwan University, Suwon, 16419, Republic of Korea
[5] Department of Aerospace Information Engineering, Bio-Inspired Aerospace Information Laboratory, Konkuk University, Seoul, Republic of Korea
[6] Research Institute of Biomolecule Control and Biomedical Institute for Convergence at SKKU (BICS), Suwon, 16419, Republic of Korea

ARTICLE INFO

Article history:
Received 31 December 2019
Accepted 25 February 2020
Available online 25 March 2020

Keywords:
Efficacy
Ginsenosides
Health care
Panax ginseng
Pharmacology

ABSTRACT

Ginseng has been used as a traditional herb in Asian countries for thousands of years. It contains a large number of active ingredients including steroidal saponins, protopanaxadiols, and protopanaxatriols, collectively known as ginsenosides. In the last few decades, the antioxidative and anticancer effects of ginseng, in addition to its effects on improving immunity, energy and sexuality, and combating cardiovascular diseases, diabetes mellitus, and neurological diseases, have been studied in both basic and clinical research. Ginseng could be a valuable resource for future drug development; however, further higher quality evidence is required. Moreover, ginseng may have drug interactions although the available evidence suggests it is a relatively safe product. This article reviews the bioactive compounds, global distribution, and therapeutic potential of plants in the genus Panax.

1. Introduction

Ginseng, called the king of all herbs, has been used as a traditional medicine for the treatment of diseases for thousands of years in East Asian countries. In the last three decades, it has become one of the most popular herbs worldwide [1]. It is used in agricultural products, dietary and health supplements, and medicines in different countries. The signature bioactive ingredients of ginseng are ginsenosides, which are triterpene saponins. However, the therapeutic effects of ginseng are not solely dependent on ginsenosides. Recently, the active ingredient gintonin was identified [2–4]. Nevertheless, most pharmacological and medical studies of ginseng have focused primarily on ginsenosides. To date, nearly 200 ginsenosides have been reported; some of these, such as Rb1, Rb2, Rc, Rd, Re, and Rg1, are considered major ginsenosides [5–8]. These compounds have multifaceted pharmacological activities because of their steroidal structure. They can interact with membrane-bound ion channels, cell membranes, and extracellular and intracellular receptors, and as a result cause alterations at the transcriptional level [9,10]. They show various antiinflammatory, antioxidant, antibacterial, antiviral, and antifungal activities. Moreover, they have been demonstrated to have therapeutic potential in hypertension, stress, and different neurological disorders such as Alzheimer's disease (AD), Parkinson disease (PD), and Huntington disease. Numerous molecular targets for ginseng have been identified in recent years [6,11–15]. Plants are an important natural resource for the development of drugs. Different pathological conditions can be treated by plant-derived medicines. A number of modern drugs originate from traditional medications [16]. Ginseng has been used in clinical settings all over the world [17] and may provide the basis for the development of novel therapeutic agents. The objective of this article is to review the state of ginseng research and to evaluate the use of its bioactive compounds as therapeutic agents. The medicinal and pharmacological

* Corresponding author. Department of Integrative Biotechnology, Sungkyunkwan, 2066 Seobu-Ro, Suwon, 16419, Republic of Korea.
** Corresponding author. Department of Integrative Biotechnology, Sungkyunkwan University, 2066 Seobu-Ro, Suwon, 16419, Republic of Korea.
E-mail addresses: ratandmck62@gmail.com (Z.A. Ratan), mfaisal.dhaka@gmail.com (M.F. Haidere), ghddygks13@naver.com (Y.H. Hong), 84701@naver.com (S.H. Park), ljo7@konkuk.ac.kr (J.-O. Lee), bioneer@skku.edu (J. Lee), jaecho@skku.edu (J.Y. Cho).

https://doi.org/10.1016/j.jgr.2020.02.004
p1226-8453 e2093-4947/$ – see front matter

potential of ginseng and ginsenosides in different diseases is discussed based on documentation of their therapeutic applications in various in vitro and in vivo models. We performed a literature search of PubMed, PubMed Central, and Google Scholar of articles published from 2000 to 2019. The number of publications increased dramatically after 2006–2007, and most of these studies were conducted in China and South Korea.

2. Main body

2.1. What is ginseng?

Many commercially available products are labeled 'ginseng' or 'ginseng-derived'. However, many of these are not derived from ginseng. Authentic ginseng products or plants have distinguishable compounds. Saponins and sapogenins or ginsenosides are signature compounds of the genus Panax, known popularly as ginseng after the scientific name of Asian or Chinese ginseng, *Panax ginseng* [18]. To the best of our knowledge, there are 8–13 species within the genus Panax, and three of these species are widely used as major sources of medicinal constituents: *P. ginseng*, commonly known as Asian or Chinese ginseng; *P. quinquefolius* or American ginseng; and *P. notoginseng*, commonly named sanchi (Table S1) [19,20].

2.2. Bioactive components of ginseng

The genus Panax in the family Araliaceae occurs primarily in the northern hemisphere and is cultivated in 35 countries across the globe (Fig. 1) [21]. The constituents and chemical contents in ginseng depend upon geographical location, climate, part of the plant, and method of extraction. For example, *P. notoginseng* or sanchi contains more total ginsenosides than *P. quinquefolius* (American ginseng) and *P. ginseng* (Asian ginseng). Ginsenoside Rb2 is abundant in *P. ginseng*, whereas in the other two species it is found only in trace amounts. Signature compounds of *P. notoginseng* and *P. quinquefolius* are notoginsenoside R1 and pseudoginsenoside F11, respectively. Ginsenoside Rf, in contrast, is found in widely geographically distributed ginseng species [22]. There are three main types of chemical constituents in this genus: ginsenosides/saponins, nonsaponins, and miscellaneous, and these can be further subcategorized (Fig. 2). In addition, at least 289 saponins were reported from 11 species of this genus by the end of 2012. The most common subtype of ginsenoside/saponins (126 reported compounds) has C-17 side chains. In addition, 66 20(S)-/20(R)-protopanaxadiol, 50 20(S)- or 20(R)-protopanaxatriol, 19 oleanolic acid, 15 ocotillo, and 13 miscellaneous saponin compounds have been reported [5,23].

2.3. Pharmacokinetics of ginseng

Various in vivo and clinical studies have identified the pharmacokinetics of various ginseng saponin compounds. However, the pharmacokinetic activities of ginseng and ginsenosides are still not clearly understood because of their heterogeneous and diversified chemical structures [22]. Studies have revealed that absorption of ginseng saponins is low when they are administered orally; they have low membrane permeability and are extensively metabolized in the gastrointestinal tract. Ginsenosides Rg1, Re, and Rh1 and R1 saponins show better bioavailability than ginsenosides Ra3, Rb1, Rd, Rg3, and Rh2 saponins. In humans, the half-lives (T1/2) of saponins are usually less than 24 hours [24–26]. Possible drug interactions have been reported between *P. ginseng* and warfarin, phenelzine, and alcohol.

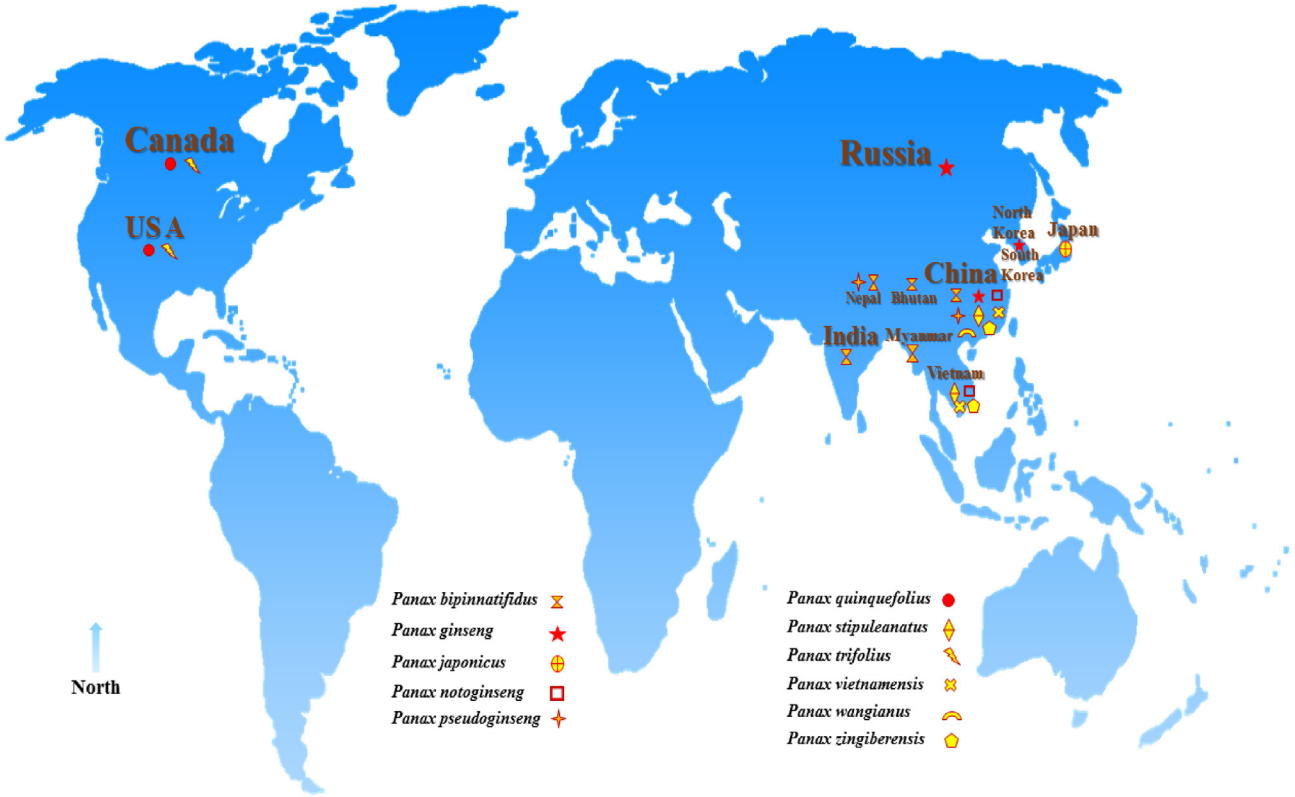

Fig. 1. Global distribution of *Panax* L. The genus Panax in the family Araliaceae occurs primarily in the northern hemisphere and is cultivated in 35 countries across the globe (Fig. 1).

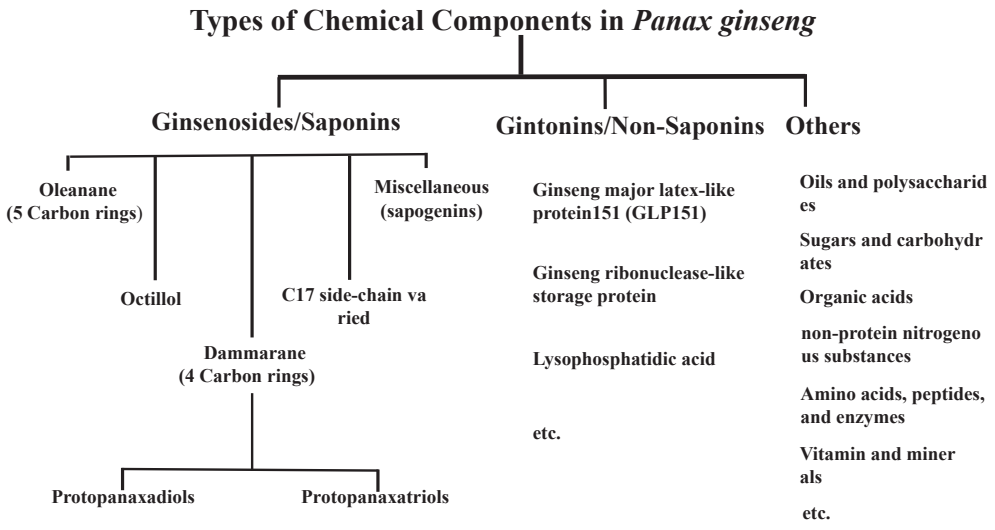

Fig. 2. Types of chemical components in *Panax ginseng*.

2.4. Potential pharmacological uses of ginseng

2.4.1. Antioxidant activity

Free radicals, reactive oxygen species (ROS), and reactive nitrogen species originate from both exogenous and endogenous sources. Major exogenous sources are pollution, alcohol, tobacco consumption, smoking, heavy metals, transition metals, industrial solvents, pesticides, and certain drugs such as halothane, paracetamol, and radiation. Endogenous sources include mitochondria, peroxisomes, the endoplasmic reticulum, and phagocytic cells [28]. Different studies have reported that atherosclerosis, asthma, cancer, degenerative eye disease, diabetes, inflammatory joint disease, senile dementia, and many other conditions are closely related to free radicals [29,30]. Scientists are always in search of substances that are potential antioxidants (Table S2). Studies have shown that ethanol and methanol extracts of ginseng leaves have the potential to scavenge free radicals (Fig. 3). Ethanol extracts have shown the highest 2,2-diphenyl-1-picrylhydrazyl radical, ferrous ion chelating, and hydroxyl radical scavenging activities [31–33]. Furthermore, levels of glutathione peroxidase and superoxide dismutase-like antioxidant enzymes are increased by ginseng [34]. The antioxidant activity of ginseng has also been demonstrated clinically. In a double-blind, randomized controlled clinical trial, Yang and his team investigated the antioxidant role of *P. ginseng* in healthy volunteers; they found that administration of Korean ginseng led to a significant decrease in the level of serum ROS and methane dicarboxylic aldehyde activity [35].

2.4.2. Antiinflammatory activity

Inflammation is a normal response to infection that involves both the innate and adaptive immune systems. Heat, pain, redness, swelling, and loss of function are the cardinal features of inflammation [36]. A number of in vitro, in vivo, and clinical studies suggest that ginseng has some degree of antiinflammatory activity

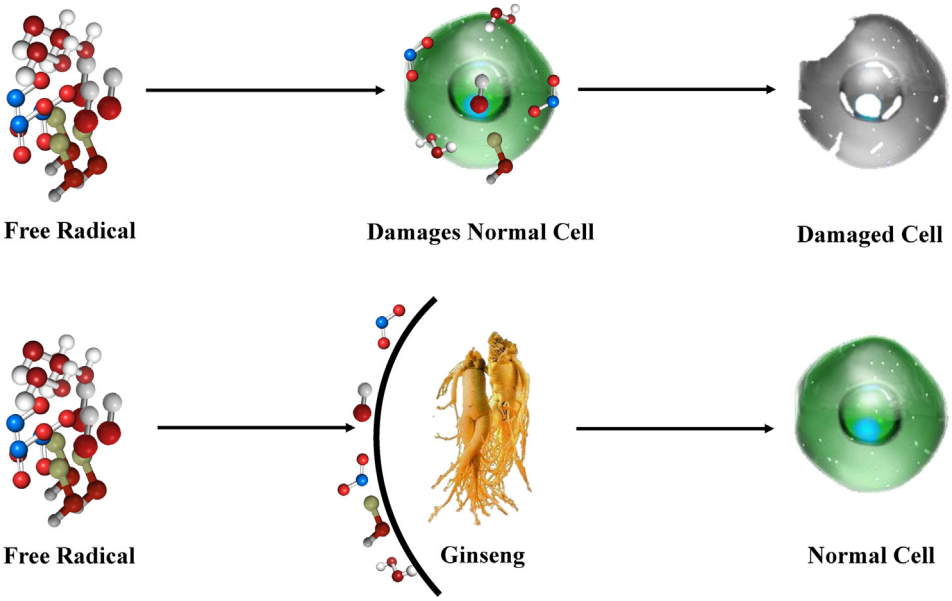

Fig. 3. Free radical scavenging activity of ginseng as an antioxidant.

(Table S3) [8,13,37–42]. Dong-Hyun Kim et al found that ginsenosides Re and Rp1 can suppress the NF-κB signaling pathway (Fig. 4) [27]. In another study, Yu et al revealed that ginsenoside Rc can inhibit the expression of macrophage-derived cytokines [1]. Moreover, it can suppress the activation of tumor necrosis factor receptor-associated factor family member-associated NF-kappa-B activator (TANK)-binding kinase-1/IκB kinase ε/interferon regulatory factor-3 and p38/ATF-2 signaling in activated RAW264.7 macrophages, human synovial cells, and HEK293 cells [1,10,33,43]. In 2006, Rhule et al examined the immunomodulatory effects of a *P. notoginseng* extract on cultured macrophages (RAW264.7 cells) [44] and found that it inhibited the lipopolysaccharide (LPS)-induced production of tumor necrosis factor (TNF)-α and interleukin (IL)-6 in a concentration-dependent pattern [44–46]. Interestingly, a clinical study reported that patients who took ginseng after curative surgery had up to a 35% higher chance of disease-free living for 5 years and up to a 38% higher survival rate than those patients who did not take it [47].

2.4.3. Antimicrobial activity

Antibiotic resistance is on the rise, and there is great need to develop new classes of antimicrobial agents [48]. In this context, novel antimicrobial agents, especially from an herbal source, would be well received (Fig. 5). A number of studies have reported that ginseng extract or its components individually or combined possess antiviral and/or antimicrobial properties (Tables S4 and S5). Korean Red Ginseng (KRG) extract blocked respiratory syncytial virus-induced inflammatory cytokines and increased the levels of IFN-γ, CD8+ T cells, and CD11c + dendritic cells and hence decreased lung disease in mice [49,50]. In another study, ginsenosides Rg1, Re, Rf, Rh1, Rg2(s), Rg2(r), Rb1, Rc, Rb2, Rd, Rg3(s), and Rg3 stimulated the antiviral cytokines IFN-γ and IFN-α in response to H5N1 influenza virus challenge [51]. In addition, this herb has activity against H1N1, H3N2, and H9N2 influenza viruses [52,53]. A clinical study reported that KRG slowed down the depletion of CD4 T-cells and diminished the antigen level of serum soluble CD8 in patients infected with HIV type-1 [54–56].

Other studies have suggested that ginseng can combat coxsackievirus B3, enterovirus 71, human rhinovirus 3, human herpesvirus, hepatitis A virus, hepatitis B virus, and feline calicivirus (Table S4). As a bactericidal agent, ginseng increased resistance to experimental sepsis due to *E. coli* infection by downregulating Toll-like receptor–mediated TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, phospho-JNK1/2, phospho-p38, and NF-κB expression [47]. This herb also has activity against methicillin-resistant bacteria. For example, Sung and Lee [57] reported that ginseng saponins together with kanamycin and cefotaxime successfully disrupted the cell membrane of *Staphylococcus aureus*, thereby decreasing infection. Moreover, extracts of ginseng and its components have activity against various other bacteria including *Bacillus cereus*, *Bacillus subtilis*, *Clostridium perfringens*, *Cryptococcus neoformans*, *Fusobacterium nucleatum*, *Helicobacter pylori*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Porphyromonas gingivalis*, *Salmonella enteritidis*, and *Streptococcus pneumonia*, as highlighted in Table S5.

2.4.4. Anticardiovascular disease activity

Cardiovascular disease comprises a range of conditions involving the heart or blood vessels and is one of the leading causes of death around the globe [58]. Active components of ginseng can stimulate nitric oxide production, inhibit ROS production, increase blood circulation, and help in adjusting lipid profiles [59]. In the cardiovascular system, calcium ions (Ca^{2+}) play a critical role in the regulation of contraction and intracellular signaling, which are vital for heart function (Fig. 6). Different studies have revealed that ginsenosides can inhibit Ca^{2+} entry, and thus improve cardiac functions (Table S6). One in vivo study showed that ginsenoside Rb1 (GRb1) can inhibit cardiac hypertrophy in a rat model [60]. Studies showed that *P. ginseng* can help maintain proper blood circulation and can boost vascular endothelial cell-derived nitric oxide secretion, which decreases blood pressure [5,61]. Other studies have reported that the components of ginseng also function as anticoagulation agents in the circulatory system (Table S6). In vitro and in vivo studies have demonstrated that ginsenosides Rg1, Rg3, and water extract of KRG suppressed platelet aggregation

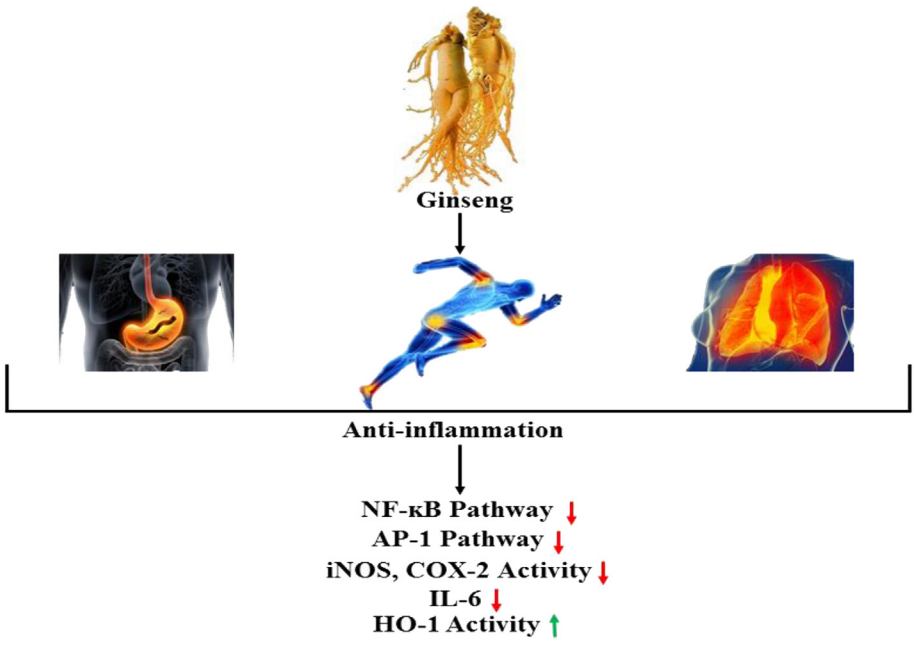

Fig. 4. The antiinflammatory effects of ginseng.

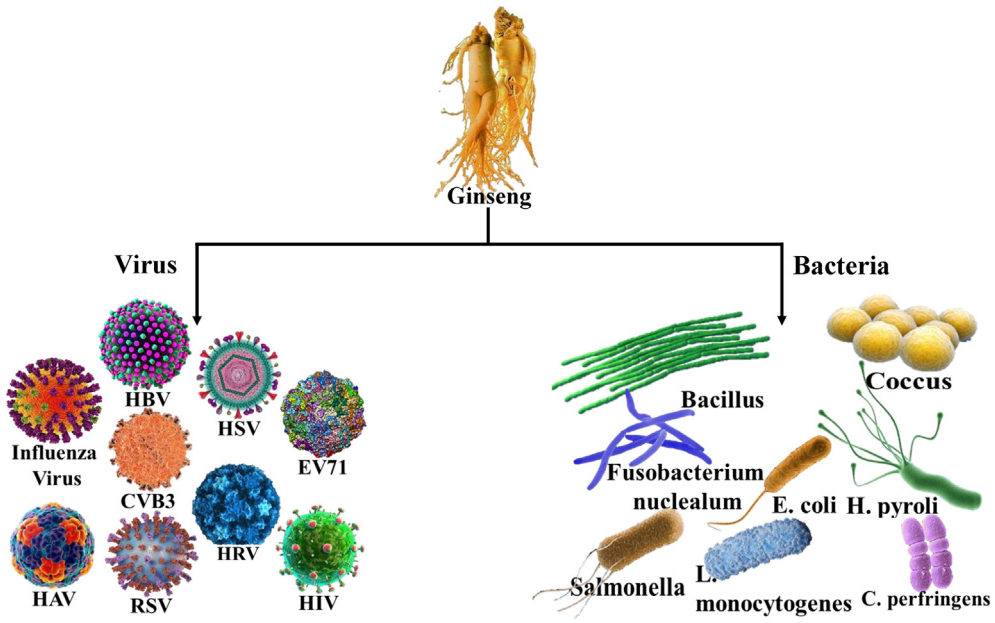

Fig. 5. Viruses and bacteria targeted by ginseng.

by downregulating thrombin-enhanced fibrinogen binding and P-selectin expression via downstream signaling elements, for example., cAMP and ERK2, in addition to the release of 1,2-diacylglycerol [62–64]. The n-butanol extract (NE3) and saponins from *P. notoginseng*, as well as radix notoginseng have been shown to regulate total cholesterol, triglyceride (TG), and low-density lipoprotein-cholesterol (LDL-C) levels based on in vivo experiments [65].

2.4.5. Antiobesity

Obesity is one of the major public health problems in the modern age. Obesity is associated with major noncommunicable diseases such as coronary heart disease, diabetes mellitus, cancer, and sleep breathing disorders [66]. Unfortunately, drugs that are used in the treatment of obesity have major side effects. Alternative medicines for reducing weight are therefore of great interest. Studies, including clinical studies, have reported that ginseng has an antiobesogenic effect (Fig. 7) [67–69], but the antiobesity mechanisms of ginseng have not been clearly elucidated (Table S7). In vitro and in vivo studies have suggested that ginsenosides have the potential to increase energy expenditure by stimulating the adenosine monophosphate–activated kinase pathway and are capable of reducing energy intake in a similar way [70]. Kim and Park [71]reported that serum levels of total cholesterol, triacylglycerol (TAG), and LDL decreased while those of high-density lipoprotein increased after the administration of ginseng extract for 8 weeks. However, the study had several limitations.

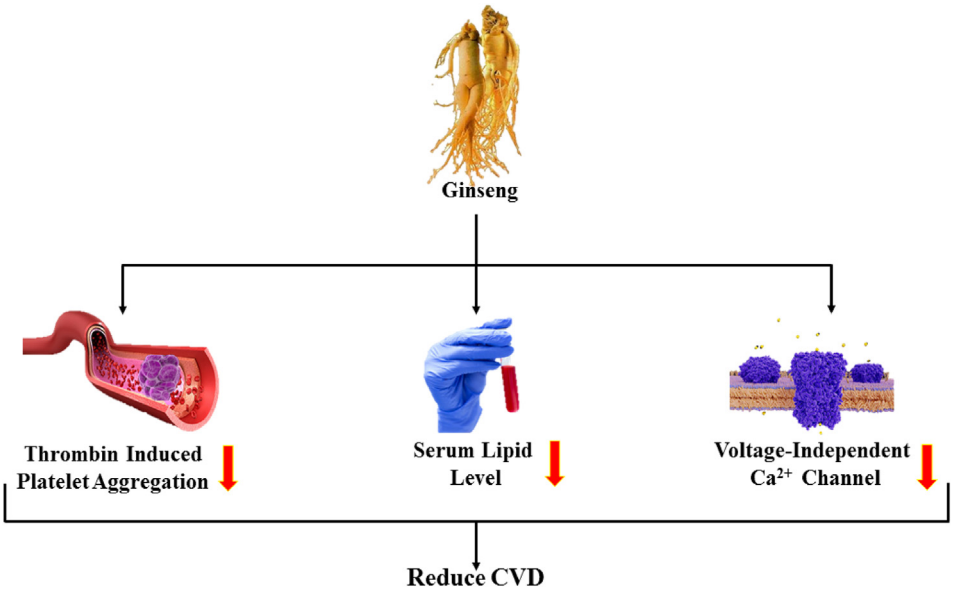

Fig. 6. Cardioprotective activity of ginseng.

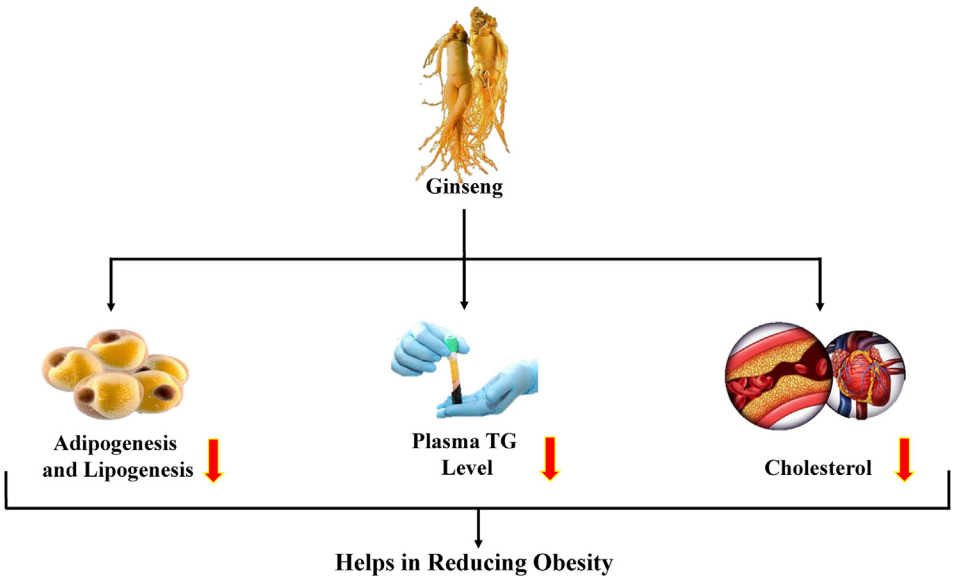

Fig. 7. Effects of ginseng in reducing obesity.

2.4.6. Antidiabetes effect

Diabetes mellitus (DM) is a metabolic condition that impairs the ability of the body to process blood glucose due to defects in insulin secretion, insulin action, or both. There are two major categories of DM: type 1 diabetes mellitus, commonly known as insulin-dependent DM, and type 2 diabetes mellitus, commonly known as noninsulin-dependent DM [72]. Ginseng is used as a traditional medicine for treating DM in China, Korea, and Japan (Table S8) [73,74]. Yun et al [75] investigated the antidiabetic effects of wild ginseng ethanol extract on high-fat diet-induced Institute of Cancer Research (ICR) mice for 8 weeks. Wild ginseng ethanol extract significantly reduced fasting blood glucose in a dose-dependent manner [75]. Different in vitro and in vivo studies have shown that compound K, an active metabolite of ginsenosides, can stimulate insulin secretion by primary cultured islets (Fig. 8). Compound K enhanced insulin secretion in a concentration-dependent manner through K-channel–dependent pathways. Vuksan et al [76] examined the clinical efficacy of KRG in 19 participants with well-controlled type 2 diabetes, and after 12 weeks of supplementation, found that it improved glucose and insulin regulation.

2.4.7. Anticentral nervous system disorder effect

Different studies have revealed that the components of *Panax ginseng*, especially the ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, and Rg3, have significant therapeutic effects (Fig. 9) in various neurological disorders [7,15,77–79], such as memory, anxiety, depression, epilepsy, stroke, amyotrophic lateral sclerosis, AD, PD, and Huntington disease (Table S9). Ginsenoside Rb1 protects against depression by upregulating 5-HT2A receptors [80]. Another *in vivo* study reported that compound K increased noradrenaline (NA) levels in the brain regions of rats, thereby functioning as an antidepressant agent; furthermore, Rg3, Rh2, and 20(S)-protopanaxadiol had similar effects [81]. AD is a progressive neurodegenerative disorder and the most common type of dementia. Amyloid plaques and neurofibrillary tangles are the two core pathological hallmarks of AD. The amyloid cascade hypothesis states that amyloid β deposition triggers neuronal dysfunction and death in the brain. According to the tau hypothesis, tau protein abnormalities initiate the disease cascade [82]. Various in vivo and in vitro studies have shown that ginsenosides Re, Rg1, Rg3, Rb1, Rb2, and notoginsenoside R1 can reduce the amyloid β peptide concentration, which in turn protects against AD [83]. PD is the second most common neurodegenerative disorder and affects central nervous system motor function. The exact cause of PD is not clear, but different studies have suggested that both genetic and nongenetic factors such as environmental factors play a pivotal role in disease progression. Oxidative stress, mitochondrial dysfunction, and protein mishandling are all thought to be involved in PD pathogenesis. Owing to cell death in the substantia nigra, dopamine expression decreases, resulting in classical motor symptoms in an affected person. Lewy bodies and loss of dopaminergic neurons in the substantia nigra are common attributes of PD [84]. Recent studies reported that ROS, high reactive iron levels, and an impaired antioxidant defense system can cause neural degeneration [85]. A number of studies have showed that the ginsenosides Rb1, Rg1, and Rd can exert neuroprotective effects by inhibiting oxidative stress and neuroinflammation. These ginsenosides also decrease toxin-induced apoptosis. An in vivo study reported that Rg1 protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced apoptosis in substantia nigra neurons by decreasing levels of cleaved caspase-3, Bax, and inducible nitric oxide synthase (iNOS) and increasing levels of Bcl-2 and Bcl-xl [86]. However, total ginsenosides were found to exert an antiepileptic effect by inhibiting kainic acid (KA)-induced synaptosomal oxidative stress related to hippocampal degeneration via activation of adenosine A2A receptors [87]. In vivo experiments revealed that ginsenoside Rd can play a protective role in cerebral ischemia by upregulating ERK1/2 and PI3K/Akt signaling pathways [88]. Another ginsenoside, Rg3, improved learning and memory impairments in lipopolysaccharide-induced cognitively impaired mice. A clinical study was conducted among patients with AD in the Department of Neurology at the Clinical Research Institute in South Korea, and the results suggested that taking ginseng root daily for 12 weeks improved mental performance significantly [89].

2.4.8. Enhancing energy and sexuality

Ginseng gained popularity as an herbal dietary supplement because it was marketed as being able to enhance sexual endurance, strength, and energy (Fig. 10). The saponin constituents of this herbal plant are the prime sources of pharmacologically active

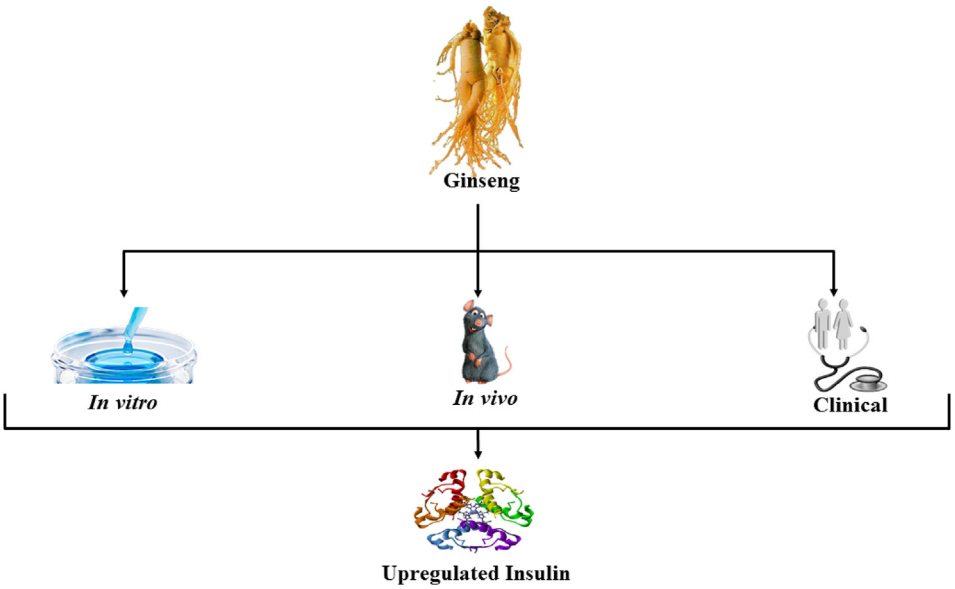

Fig. 8. Effects of ginseng in diabetes mellitus.

compounds (Table S10). Ginsenosides have a dammarane skeleton with a variety of sugar moieties such as glucose, xylose, rhamnose, and arabinose. However, the levels of ginsenosides may differ depending on the species, harvesting season, age of the plant, and other factors [90]. Tan et al assessed the pharmacological actions of GRb1 against in a rat model of fatigue syndrome and reported that GRb1 had a potent antifatigue effect [91]. This effect was attained by suppression of skeletal muscle oxidative stress and improvement in energy metabolism [91]. Ginseng can also downregulate the peroxidation of hydroxyl radical and lipids and facilitate mitochondrial activity during physical exercise [92]. Ginseng has also been used for sexual management, for example., erectile dysfunction in China since 3,500-2,600 BCE. This herb can stimulate the human sex drive in terms of increasing male and female sexual arousal (Table S10) [93]. One in vivo study revealed that ginseng can improve sperm kinematic values compared with an immobilization control group. It can attenuate altered expression levels of spermatogenesis-related proteins such as nectin-2, cAMP responsive element binding protein-1, inhibin-α, and sex hormone receptors in the testes [94–96]. A clinical study of 45 men who had moderate to severe erectile dysfunction found that three daily doses of 900 mg Korean ginseng for 8 weeks resulted in a significant improvement in erectile performance and sexual satisfaction scores [97].

2.4.9. Anticancer activity

Cancer is one of the leading causes of death around the globe [98]. Medicinal plants and their derivative phytocompounds are being increasingly recognized as useful complementary treatments for cancer (Fig. 11). Ginsenosides isolated from ginseng

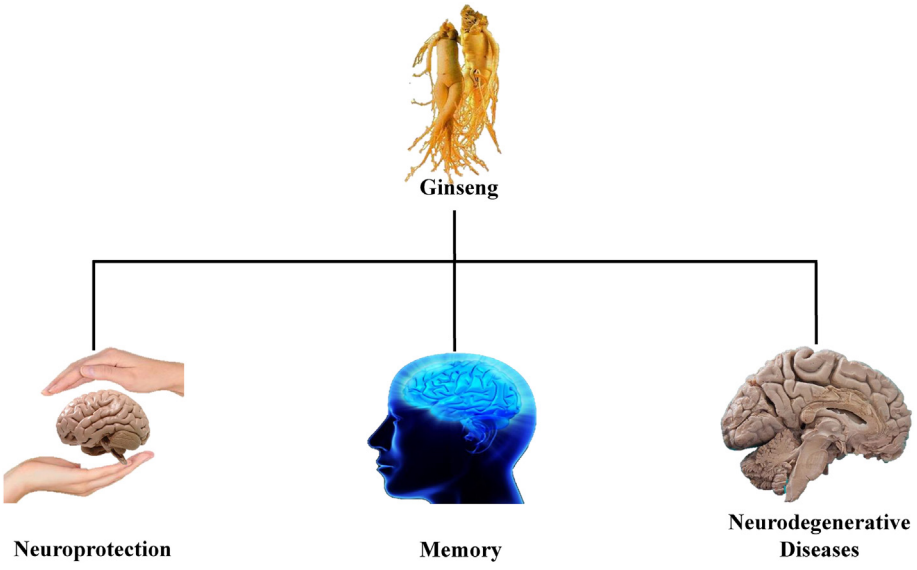

Fig. 9. Effects of ginseng on neuroprotective and memory function.

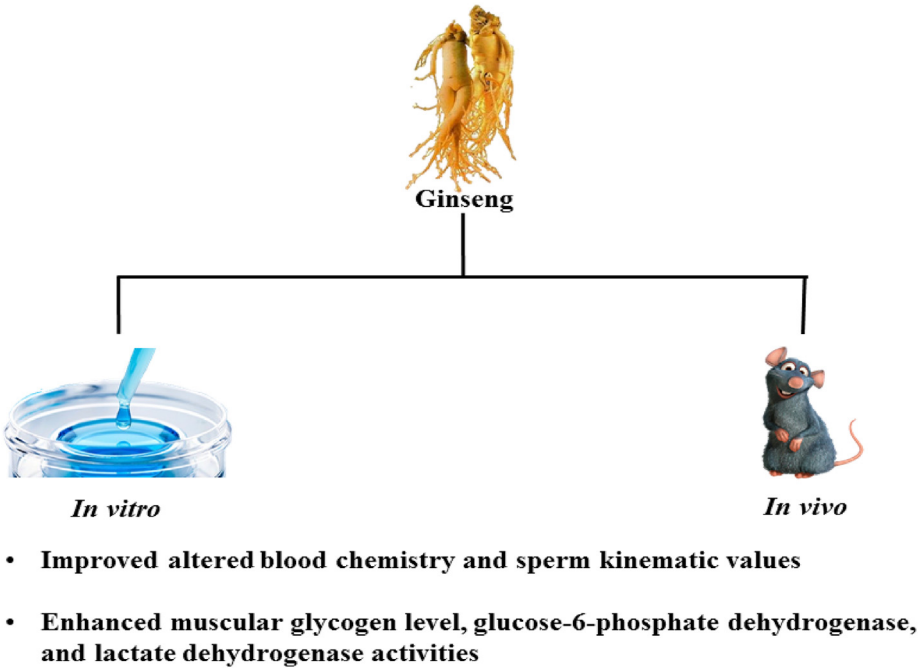

Fig. 10. Effects of ginseng on energy and sexuality.

belong to the family of steroids with a four trans-ring steroid skeleton. Heat-processed Korean ginseng (steamed at 98 to 100°C for 2 to 3 h), sun ginseng (steamed at 120°C for 2 to 3 h), and black ginseng (repeatedly steamed and dried 9 times) were shown to have a decreased content of common ginsenosides (Rb1, Rc, Rd, Re, and Rg1) but an array of other ginsenosides including Rg5, Rk1, Rk2, Rk3, Rs4, Rs5, Rs6, and Rs7 [99]. Such changes in the composition of ginsenosides give heat-processed ginseng its unique anticancer properties (Table S11) [100–104]. Ginseng and its extracts such as compound K, ginsenoside Rh1, F2, Rg3, and Rp1 have been shown to have anticancer properties [102,104,105]. As far back as 1980, it was reported that red ginseng extract inhibited the induction of lung tumors in mice exposed to urethane, 9,10-dimethyl-l1,2-benzanthracene, and aflatoxin B1 [100,106]. Ginsenoside Rb1 inhibited the viability and invasiveness of lung cancer by targeting c-Fos, c-Jun, vascular endothelial growth factor (VEGF), and caspases [99]. Ginsenoside Rd can downregulate the expression of iNOS, COX-2, and NF-κB and can suppress the phosphorylation of extracellular signal-regulated kinase. In liver cancer, ginsenosides Rd and Rh2 have been shown to inhibit tumor migration and metastasis [107]. Nakata et al [108] revealed that cis-diaminedi-chloroplatinum (II) (CDDP) combined with ginsenoside Rh2 given intraperitoneally or orally to nude mice with tumors formed through the inoculation of human ovarian cancer cells significantly inhibited tumor growth. The incidence of skin carcinogenesis has increased rapidly in recent decades due to depletion of the ozone layer. KRG has been demonstrated to have significant inhibitory effects on skin, prostate, and colon cancers,

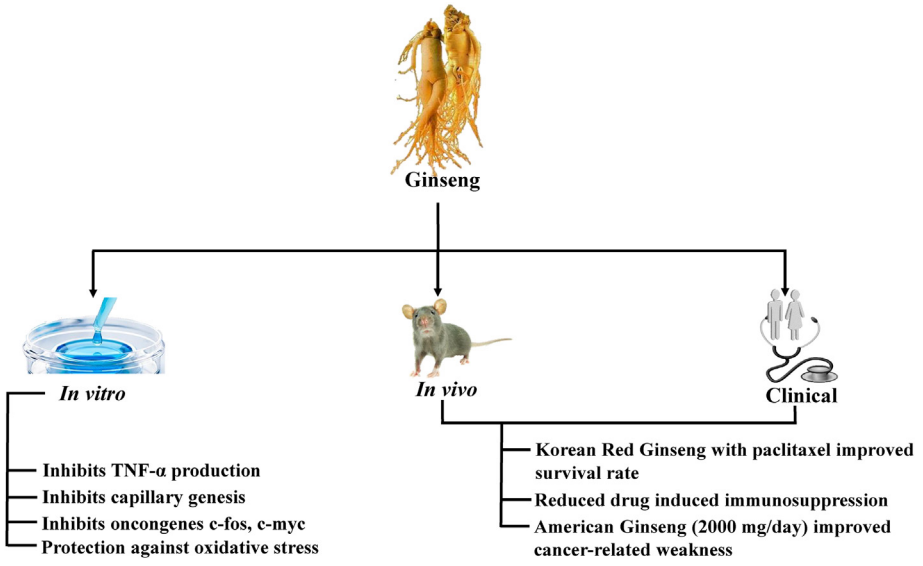

Fig. 11. Anticancer effects of ginseng.

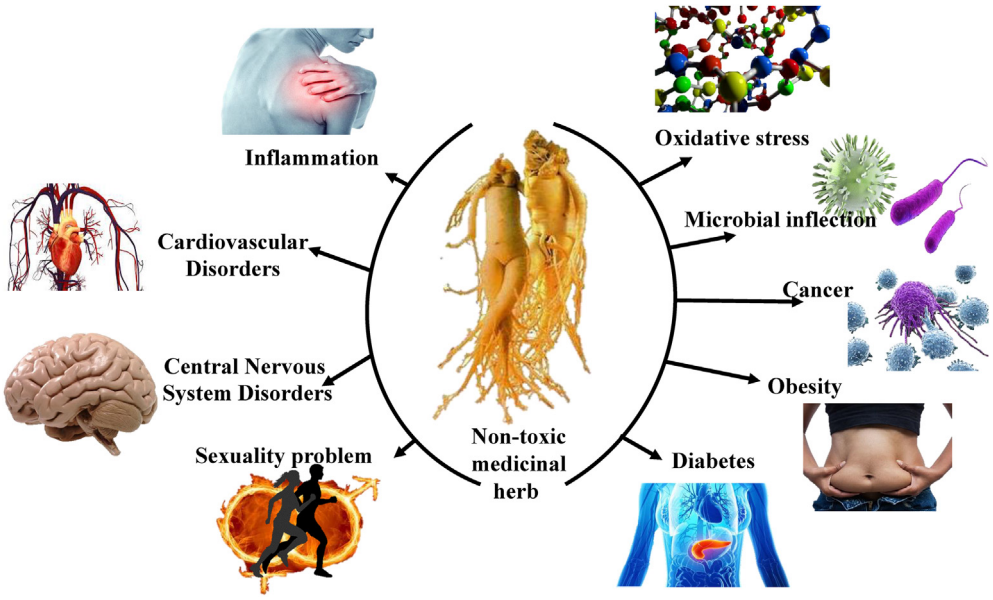

Fig. 12. Summary of ginseng-derived pharmacological activities.

as well as leukemia [102,109–111]. Compound K induced apoptosis of breast cancer cells by generating ROS and suppressing cell growth [101,102,112]. Weakness is one of the most common symptoms in patients with cancer. A comprehensive study presented during the 2012 Annual Meeting of the American Society of Clinical Oncology revealed that a high dose (2000 mg/day) of American ginseng was useful at treating cancer-related weakness [113].

2.5. Commercial ginseng products

South Korea, China, Canada, and the US are the main producers of ginseng, and the total production of fresh ginseng is about 79,769 tons. The world ginseng market, including ginseng root and processed products, is estimated to be worth $2,084 million (USD). Ginseng is distributed in 35 countries around the globe and among them, 19 countries including South Korea and China are both importers and exporters [21]. People use different types of commercial ginseng products (Table S12). Great technical progress has been made in the extraction of Rg1, Re, Rh2, and Rg3 with yields up to several kilograms. However, this is not enough to meet the demand, and newer synthesis methods need to be developed to meet industrial production requirements.

2.6. Ginseng toxicity

As an herbal medication as well as a dietary supplement, ginseng and ginseng products have been well studied. The Web of Science had a total of 3,974 records for *P. ginseng* research from 1959 to 2016 published by authors from 64 countries [114]. Nevertheless, to the best of our knowledge, there are a limited number of studies regarding ginseng toxicity; most of these studies have focused on ginseng abuse or misuse. Some case studies reported that ginseng exerted a toxic effect on humans regardless of gender and age. Examples of toxic or adverse effects caused by ginseng abuse or misuse include maniac episodes, uterine bleeding, gynecomastia, long QT syndrome, atrial fibrillation with bradycardia, hypertensive crisis, and acute lobular hepatitis [115,116]. Ethanol-extracted ginseng can cause cerebral arteritis, and ginseng is one of the causes of Stevens-Johnson syndrome [117]. A recent study also claimed the occurrence of cutaneous adverse effects in a 60-year-old woman, that is, inflammatory papules due to consumption of ginseng [118]. A more recent study reported that standardized *P. ginseng* extract, depending on dose and usage duration, can affect cardiac function by causing heart failure, decreasing blood pressure, and causing diastolic dysfunction [119]. Furthermore, a few studies raised the concern that interactions between ginseng and other drugs might be hazardous for health, especially in patients taking warfarin to prevent fatal strokes and thromboembolism [120–122]. Ginseng consumption during the first trimester of pregnancy and lactation may also have a toxic effect, and this herb should be taken with caution by pregnant women [123]. A substantial amount of research is required to determine the safety profile of ginseng and its active ingredients.

2.7. Recent developments: nanoginseng

The past decade has seen the development of ginseng based nanoparticles and nanocomposite technologies [15,124]. A study in 2019 reported delivery of GRb1 from *P. notoginseng* using chitosan/alginate nanocomposite film; the rate of GRb1 liberation from that composite film was 'proportional to the increase in pH solution and inversely proportional to the content of loaded GRb1' [125]. Another study in 2018 claimed that direct conjugation of superparamagnetic iron oxide nanoparticles, compound K, and ginsenoside Rg3 in lipopolysaccharide-induced RAW 264.7 cells diminished nitric oxide and iNOS activity depending on the doses administered [126].

In addition to nanocomposites, several studies have promoted ginseng nanoparticles as novel drug delivery systems for cancer, inflammation, and neurological disorders. A 2016 study reported that 100-nm-diameter GRb1 nanoparticles with a drug loading capacity of approximately 35 wt% betulinic acid, 32 wt% dihydroartemisinin, and 21 wt% hydroxycamptothecine exerted an antitumor effect in a xenograft mouse model [127]. Another study found that 110-nm-diameter GRb1 nanoparticles with 96.8% drug loading efficiency and 27.9 wt% capacity had both in vitro and in vivo anticancer activity [127]. Along with inhibitory actions, ginseng-based nanotechnology can also be used to image cancer cells. Re-based carbon dots were applied for bioimaging, and

nanohybrid-conjugated ginsenosides were used to enhance magnetic resonance imaging (MRI) imaging of hepatocellular carcinomas in a nude mice model [128,129]. Ginsenoside Rg1 nanoparticles tagged with poly-γ-glutamic acid, poly-γ-glutamic acid, and OX26 antibody passed through the blood–brain barrier and decreased cerebral infarction, as well as neuronal recovery in diabetic rats [130]. A 2018 in vitro study reported that the poly(lactic-co-glycolic acid)-ginsenoside Rg3 nanoparticles crossed the blood–brain barrier and decreased αβ plaques, as well as inhibited gene expression of β-amyloid A4 precursor protein in AD [131]. These recent advancements in ginseng research may lead to a novel nanotheranostics for the treatment of various diseases.

3. Conclusions

There is great interest in pharmacological agents from natural sources that have predictable health benefits against inflammation, oxidative stress, microbial infection, cancer, diabetes, sexuality problem, central nervous system disorders, and cardiovascular disorders with no toxicity property as summarized in Fig. 12. However, the job of discovering new ginseng constituents is still underway. Ginseng is distributed in 35 countries around the globe, and the ginseng market is estimated to be worth $2,084 million. The pharmaceutical industry is a rapidly growing industry; in 2014, global pharmaceutical revenues had surpassed one trillion dollar benchmark. Traditional herbs are a great source of therapeutic agents, for example, artemisinin from *Artemisia annua*. Several studies have revealed that ginsenosides and their derivatives have great pharmaceutical potential to prevent and treat different diseases. We strongly believe that traditional herbs will open up new horizons for the pharmaceutical industry in the future. Governments, healthcare agencies, and Research and Development (R&D) groups of different pharmaceutical industries could benefit from focusing on ginseng research.

Author contributions

Z.A.R., J.L., and J.Y.C. wrote and edited this manuscript. Z.A.R., M.F.H., Y.H.H., J.O.L., J.L., and J.Y.C. designed this manuscript and collected all information and publications.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgments

This work was supported by the BK21 plus program and the Basic Science Research Program (2017R1A6A1A03015642) of the National Research Foundation of Korea (NRF), funded by the Ministry of Education, and by a grant in 2018 to J.Y.C. from the Korean Society of Ginseng, Republic of Korea.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2020.02.004.

References

[1] Yu T, Yang Y, Kwak Y-S, Song GG, Kim M-Y, Rhee MH, Cho JY. Ginsenoside Rc from Panax ginseng exerts anti-inflammatory activity by targeting TANK-binding kinase 1/interferon regulatory factor-3 and p38/ATF-2. J Ginseng Res 2017;41:127–33.
[2] Im D-s, Nah S-y. Yin and Yang of ginseng pharmacology: ginsenosides vs gintonin. Acta Pharmacol Sin 2013;34:1367.
[3] Lee BH, Choi SH, Kim HJ, Park SD, Rhim H, Kim HC, Hwang SH, Nah SY. Gintonin absorption in intestinal model systems. J Ginseng Res 2018;42:35–41.
[4] Cho HJ, Choi SH, Kim HJ, Lee BH, Rhim H, Kim HC, Hwang SH, Nah SY. Bioactive lipids in gintonin-enriched fraction from ginseng. J Ginseng Res 2019;43:209–17.
[5] Kim J-H. Pharmacological and medical applications of Panax ginseng and ginsenosides: a review for use in cardiovascular diseases. J Ginseng Res 2018;42:264–9.
[6] Kim KH, Lee D, Lee HL, Kim CE, Jung K, Kang KS. Beneficial effects of Panax ginseng for the treatment and prevention of neurodegenerative diseases: past findings and future directions. J Ginseng Res 2018;42:239–47.
[7] Kim HJ, Jung SW, Kim SY, Cho IH, Kim HC, Rhim H, Kim M, Nah SY. Panax ginseng as an adjuvant treatment for Alzheimer's disease. J Ginseng Res 2018;42:401–11.
[8] Kim JH, Yi YS, Kim MY, Cho JY. Role of ginsenosides, the main active components of Panax ginseng, in inflammatory responses and diseases. J Ginseng Res 2017;41:435–43.
[9] Mohanan P, Subramaniyam S, Mathiyalagan R, Yang D-C. Molecular signaling of ginsenosides Rb1, Rg1, and Rg3 and their mode of actions. J Ginseng Res 2018;42:123–32.
[10] Han SY, Kim J, Kim E, Kim SH, Seo DB, Kim JH, Shin SS, Cho JY. AKT-targeted anti-inflammatory activity of Panax ginseng calyx ethanolic extract. J Ginseng Res 2018;42:496–503.
[11] Wahid F, Khan T, Subhan F, Khan M, Kim Y. Ginseng pharmacology: multiple molecular targets and recent clinical trials. Drugs Future 2010;35:399–407.
[12] Lee D, Lee DS, Jung K, Hwang GS, Lee HL, Yamabe N, Lee HJ, Eom DW, Kim KH, Kang KS. Protective effect of ginsenoside Rb1 against tacrolimus-induced apoptosis in renal proximal tubular LLC-PK1 cells. J Ginseng Res 2018;42:75–80.
[13] Kim MK, Kang H, Baek CW, Jung YH, Woo YC, Choi GJ, Shin HY, Kim KS. Antinociceptive and anti-inflammatory effects of ginsenoside Rf in a rat model of incisional pain. J Ginseng Res 2018;42:183–91.
[14] Choi SY, Kim KJ, Song JH, Lee BY. Ginsenoside Rg5 prevents apoptosis by modulating heme-oxygenase-1/nuclear factor E2-related factor 2 signaling and alters the expression of cognitive impairment-associated genes in thermal stress-exposed HT22 cells. J Ginseng Res 2018;42:225–8.
[15] Shim JS, Song MY, Yim SV, Lee SE, Park KS. Global analysis of ginsenoside Rg1 protective effects in beta-amyloid-treated neuronal cells. J Ginseng Res 2017;41:566–71.
[16] Thomford N, Senthebane D, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K. Natural products for drug discovery in the 21st century: innovations for novel drug discovery. Int J Mol Sci 2018;19:1578.
[17] He Y, Yang J, Lv Y, Chen J, Yin F, Huang J, Zheng Q. A review of ginseng clinical trials registered in the WHO international clinical trials registry platform. BioMed Res Int 2018;2018.
[18] Lu J-M, Yao Q, Chen C. Ginseng compounds: an update on their molecular mechanisms and medical applications. Curr Vasc Pharmacol 2009;7:293–302.
[19] Yun TK. Brief introduction of panax ginseng CA meyer. J Korean Med Sci 2001;16:S3.
[20] Cho IH, Lee HJ, Kim Y-S. Differences in the volatile compositions of ginseng species (Panax sp.). J Agric Food Chem 2012;60:7616–22.
[21] Baeg I-H, So S-H. The world ginseng market and the ginseng (Korea). J Ginseng Res 2013;37:1.
[22] Qi L-W, Wang C-Z, Yuan C-S. Isolation and analysis of ginseng: advances and challenges. Nat Prod Rep 2011;28:467–95.
[23] Yang W-z, Hu Y, Wu W-y, Ye M, Guo D-a. Saponins in the genus Panax L.(Araliaceae): a systematic review of their chemical diversity. Phytochemistry 2014;106:7–24.
[24] Qi L-W, Wang C-Z, Du G-J, Zhang Z-Y, Calway T, Yuan C-S. Metabolism of ginseng and its interactions with drugs. Curr Drug Metabol 2011;12:818–22.
[25] Kim SJ, Choi S, Kim M, Park C, Kim GL, Lee SO, Kang W, Rhee DK. Effect of Korean Red Ginseng extracts on drug-drug interactions. J Ginseng Res 2018;42:370–8.
[26] Chen J, Li M, Chen L, Wang Y, Li S, Zhang Y, Zhang L, Song M, Liu C, Hua M, et al. Effects of processing method on the pharmacokinetics and tissue distribution of orally administered ginseng. J Ginseng Res 2018;42:27–34.
[27] Kim DH. Gut microbiota-mediated pharmacokinetics of ginseng saponins. J Ginseng Res 2018;42:255–63.
[28] Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem 2015;30:11–26.
[29] Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci: IJBS 2008;4:89.
[30] Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn Rev 2010;4:118.
[31] Lee JW, Mo EJ, Choi JE, Jo YH, Jang H, Jeong JY, Jin Q, Chung HN, Hwang BY, Lee MK. Effect of Korean Red Ginseng extraction conditions on antioxidant activity, extraction yield, and ginsenoside Rg1 and phenolic content: optimization using response surface methodology. J Ginseng Res 2016;40:229–36.
[32] Zhou Y, Yang Z, Gao L, Liu W, Liu R, Zhao J, You J. Changes in element accumulation, phenolic metabolism, and antioxidative enzyme activities in the red-skin roots of Panax ginseng. J Ginseng Res 2017;41:307–15.

[33] Hossen MJ, Hong YD, Baek KS, Yoo S, Hong YH, Kim JH, Lee JO, Kim D, Park J, Cho JY. In vitro antioxidative and anti-inflammatory effects of the compound K-rich fraction BIOGF1K, prepared from Panax ginseng. J Ginseng Res 2017;41:43–51.
[34] Sohn S-H, Kim S-K, Kim Y-O, Kim H-D, Shin Y-S, Yang S-O, Kim S-Y, Lee S-W. A comparison of antioxidant activity of Korean White and Red Ginsengs on H2O2-induced oxidative stress in HepG2 hepatoma cells. J Ginseng Res 2013;37:442.
[35] Yang Y, Ren C, Zhang Y, Wu X. Ginseng: an nonnegligible natural remedy for healthy aging. Aging Dis 2017;8:708.
[36] Yang WS, Ratan ZA, Kim G, Lee Y, Kim M-Y, Kim J-H, Cho JY. 4-Isopropyl-2, 6-bis (1-phenylethyl) aniline 1, an analogue of KTH-13 isolated from Cordyceps bassiana, inhibits the NF-κB-mediated inflammatory response. Med Inflamm 2015;2015.
[37] Lee DC, Yang CL, Chik SC, Li JC, Rong J-h, Chan GC, Lau AS. Bioactivity-guided identification and cell signaling technology to delineate the immunomodulatory effects of Panax ginseng on human promonocytic U937 cells. J Transl Med 2009;7:34.
[38] Jung JH, Kang IG, Kim DY, Hwang YJ, Kim ST. The effect of Korean red ginseng on allergic inflammation in a murine model of allergic rhinitis. J Ginseng Res 2013;37:167.
[39] Lee JH, Min DS, Lee CW, Song KH, Kim YS, Kim HP. Ginsenosides from Korean Red Ginseng ameliorate lung inflammatory responses: inhibition of the MAPKs/NF-kappaB/c-Fos pathways. J Ginseng Res 2018;42:476–84.
[40] Lee MJ, Chang BJ, Oh S, Nah SY, Cho IH. Korean Red Ginseng mitigates spinal demyelination in a model of acute multiple sclerosis by downregulating p38 mitogen-activated protein kinase and nuclear factor-kappaB signaling pathways. J Ginseng Res 2018;42:436–46.
[41] Choi JH, Jang M, Nah SY, Oh S, Cho IH. Multitarget effects of Korean Red Ginseng in animal model of Parkinson's disease: antiapoptosis, antioxidant, antiinflammation, and maintenance of blood-brain barrier integrity. J Ginseng Res 2018;42:379–88.
[42] Kang S, Park SJ, Lee AY, Huang J, Chung HY, Im DS. Ginsenoside Rg3 promotes inflammation resolution through M2 macrophage polarization. J Ginseng Res 2018;42:68–74.
[43] Lee I-A, Hyam SR, Jang S-E, Han MJ, Kim D-H. Ginsenoside Re ameliorates inflammation by inhibiting the binding of lipopolysaccharide to TLR4 on macrophages. J Agric Food Chem 2012;60:9595–602.
[44] Rhule A, Navarro S, Smith JR, Shepherd DM. Panax notoginseng attenuates LPS-induced pro-inflammatory mediators in RAW264. 7 cells. J Ethnopharmacol 2006;106:121–8.
[45] Kee JY, Jeon YD, Kim DS, Han YH, Park J, Youn DH, Kim SJ, Ahn KS, Um JY, Hong SH. Korean Red Ginseng improves atopic dermatitis-like skin lesions by suppressing expression of proinflammatory cytokines and chemokines in vivo and in vitro. J Ginseng Res 2017;41:134–43.
[46] Han BC, Ahn H, Lee J, Jeon E, Seo S, Jang KH, Lee SH, Kim CH, Lee GS. Non-saponin fractions of Korean Red Ginseng extracts prime activation of NLRP3 inflammasome. J Ginseng Res 2017;41:513–23.
[47] Ahn JY, Choi IS, Shim JY, Yun EK, Yun YS, Jeong G, Song JY. The immunomodulator ginsan induces resistance to experimental sepsis by inhibiting Toll-like receptor-mediated inflammatory signals. Eur J Immunol 2006;36: 37–45.
[48] Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, Cohen J, Findlay D, Gyssens I, Heure O. The global threat of antimicrobial resistance: science for intervention. New Microbes New Infect 2015;6:22–9.
[49] Lee J, Lee Y-N, Lee Y-T, Hwang H, Kim K-H, Ko E-J, Kim M-C, Kang S-M. Ginseng protects against respiratory syncytial virus by modulating multiple immune cells and inhibiting viral replication. Nutrients 2015;7:1021–36.
[50] Lee JS, Ko E-J, Hwang HS, Lee Y-N, Kwon Y-M, Kim M-C, Kang S-M. Antiviral activity of ginseng extract against respiratory syncytial virus infection. Int J Mol Med 2014;34:183–90.
[51] Park EH, Yum J, Ku KB, Kim HM, Kang YM, Kim JC, Kim JA, Kang YK, Seo SH. Red Ginseng-containing diet helps to protect mice and ferrets from the lethal infection by highly pathogenic H5N1 influenza virus. J Ginseng Res 2014;38: 40–6.
[52] Yoo D-G, Kim M-C, Park M-K, Song J-M, Quan F-S, Park K-M, Cho Y-K, Kang S-M. Protective effect of Korean red ginseng extract on the infections by H1N1 and H3N2 influenza viruses in mice. J Med Food 2012;15:855–62.
[53] Chan LY, Kwok HH, Chan RWY, Peiris MJS, Mak NK, Wong RNS, Chan MCW, Yue PYK. Dual functions of ginsenosides in protecting human endothelial cells against influenza H9N2-induced inflammation and apoptosis. J Ethnopharmacol 2011;137:1542–6.
[54] Sung H, Kang S-M, Lee M-S, Kim TG, Cho Y-K. Korean red ginseng slows depletion of CD4 T cells in human immunodeficiency virus type 1-infected patients. Clin Diagn Lab Immunol 2005;12:497–501.
[55] Cho YK, Kim JE. Effect of Korean Red Ginseng intake on the survival duration of human immunodeficiency virus type 1 patients. J Ginseng Res 2017;41: 222–6.
[56] Cho YK, Kim JE, Woo JH. Genetic defects in the nef gene are associated with Korean Red Ginseng intake: monitoring of nef sequence polymorphisms over 20 years. J Ginseng Res 2017;41:144–50.
[57] Sung WS, Lee DG. The combination effect of Korean red ginseng saponins with kanamycin and cefotaxime against methicillin-resistant Staphylococcus aureus. Biol Pharm Bulletin 2008;31:1614–7.
[58] Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. Circulation 2013;127:749–56.
[59] So SH, Lee JW, Kim YS, Hyun SH, Han CK. Red ginseng monograph. J Ginseng Res 2018;42:549–61.
[60] Kim J-H. Cardiovascular diseases and Panax ginseng: a review on molecular mechanisms and medical applications. J Ginseng Res 2012;36:16.
[61] Qin N, Gong Q-h, Wei L-w, Wu Q, Huang X-n. Total ginsenosides inhibit the right ventricular hypertrophy induced by monocrotaline in rats. Biol Pharm Bulletin 2008;31:1530–5.
[62] Zhou Q, Jiang L, Xu C, Luo D, Zeng C, Liu P, Yue M, Liu Y, Hu X, Hu H. Ginsenoside Rg1 inhibits platelet activation and arterial thrombosis. Thromb Res 2014;133:57–65.
[63] Lee WM, Kim SD, Park MH, Cho JY, Park HJ, Seo GS, Rhee MH. Inhibitory mechanisms of dihydroginsenoside Rg3 in platelet aggregation: critical roles of ERK2 and cAMP. J Pharm Pharmacol 2008;60:1531–6.
[64] Hwang SY, Son DJ, Kim IW, Kim DM, Sohn SH, Lee JJ, Kim SK. Korean red ginseng attenuates hypercholesterolemia-enhanced platelet aggregation through suppression of diacylglycerol liberation in high-cholesterol-diet-fed rabbits. Phytother Res: An Int J Dev Pharmacol Toxicol Evalu Nat Prod Deriv 2008;22:778–83.
[65] Ji W, Gong B. Hypolipidemic effects and mechanisms of Panax notoginseng on lipid profile in hyperlipidemic rats. J Ethnopharmacol 2007;113:318–24.
[66] Kopelman PG. Obesity as a medical problem. Nature 2000;404:635–43.
[67] Sharmila J, Aravinthan A, Shin DG, Seo JH, Kim B, Kim NS, Kang CW, Kim JH. GBCK25, fermented ginseng, attenuates cardiac dysfunction in high fat diet-induced obese mice. J Ginseng Res 2018;42:356–60.
[68] Li Z, Kim HJ, Park MS, Ji GE. Effects of fermented ginseng root and ginseng berry on obesity and lipid metabolism in mice fed a high-fat diet. J Ginseng Res 2018;42:312–9.
[69] Koh EJ, Kim KJ, Choi J, Jeon HJ, Seo MJ, Lee BY. Ginsenoside Rg1 suppresses early stage of adipocyte development via activation of C/EBP homologous protein-10 in 3T3-L1 and attenuates fat accumulation in high fat diet-induced obese zebrafish. J Ginseng Res 2017;41:23–30.
[70] Karachaliou N, Gonzalez-Cao M, Crespo G, Drozdowskyj A, Aldeguer E, Gimenez-Capitan A, Teixido C, Molina-Vila MA, Viteri S, De Los Llanos Gil M, et al. Interferon gamma, an important marker of response to immune checkpoint blockade in non-small cell lung cancer and melanoma patients. Ther Adv Med Oncol 2018;10. 1758834017749748.
[71] Kim S-H, Park K-S. Effects of Panax ginseng extract on lipid metabolism in humans. Pharmacol Res 2003;48:511–3.
[72] American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36(Suppl 1):S67–74.
[73] Choi MR, Kwak SM, Bang SH, Jeong JE, Kim DJ. Chronic saponin treatment attenuates damage to the pancreas in chronic alcohol-treated diabetic rats. J Ginseng Res 2017;41:503–12.
[74] Oh MJ, Kim HJ, Park EY, Ha NH, Song MG, Choi SH, Chun BG, Kim DH. The effect of Korean Red Ginseng extract on rosiglitazone-induced improvement of glucose regulation in diet-induced obese mice. J Ginseng Res 2017;41:52–9.
[75] Yun SN, Moon SJ, Ko SK, Im BO, Chung SH. Wild ginseng prevents the onset of high-fat diet induced hyperglycemia and obesity in ICR mice. Arch Pharm Res 2004;27:790–6.
[76] Vuksan V, Sung M-K, Sievenpiper JL, Stavro PM, Jenkins AL, Di Buono M, Lee K-S, Leiter LA, Nam KY, Arnason JT, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutr Metabol Cardiovasc Dis 2008;18:46–56.
[77] Cho SK, Kim D, Yoo D, Jang EJ, Jun JB, Sung YK. Korean Red Ginseng exhibits no significant adverse effect on disease activity in patients with rheumatoid arthritis: a randomized, double-blind, crossover study. J Ginseng Res 2018;42:144–8.
[78] Choi JH, Lee MJ, Jang M, Kim HJ, Lee S, Lee SW, Kim YO, Cho IH. Panax ginseng exerts antidepressant-like effects by suppressing neuroinflammatory response and upregulating nuclear factor erythroid 2 related factor 2 signaling in the amygdala. J Ginseng Res 2018;42:107–15.
[79] Park SY, Park JH, Kim HS, Lee CY, Lee HJ, Kang KS, Kim CE. Systems-level mechanisms of action of Panax ginseng: a network pharmacological approach. J Ginseng Res 2018;42:98–106.
[80] Yamada N, Araki H, Yoshimura H. Identification of antidepressant-like ingredients in ginseng root (Panax ginseng C.A. Meyer) using a menopausal depressive-like state in female mice: participation of 5-HT2A receptors. Psychopharmacology (Berl) 2011;216:589–99.
[81] Zhang H, Li Z, Zhou Z, Yang H, Zhong Z, Lou C. Antidepressant-like effects of ginsenosides: a comparison of ginsenoside Rb3 and its four deglycosylated derivatives, Rg3, Rh2, compound K, and 20(S)-protopanaxadiol in mice models of despair. Pharmacol Biochem Behav 2016;140:17–26.
[82] Iqbal K, del C, Alonso A, Chen S, Chohan MO, El-Akkad E, Gong C-X, Khatoon S, Li B, Liu F, et al. Tau pathology in Alzheimer disease and other tauopathies. Biochimica et Biophysica Acta (BBA) - Mol Basis Dis 2005;1739: 198–210.
[83] Chen F, Eckman EA, Eckman CB. Reductions in levels of the Alzheimer's amyloid beta peptide after oral administration of ginsenosides. Faseb J 2006;20:1269–71.

[84] Sulzer D. Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. Trends Neurosci 2007;30:244–50.
[85] Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol 2003;53(Suppl 3):S26–36. discussion S36-28.
[86] Chen XC, Chen Y, Zhu YG, Fang F, Chen LM. Protective effect of ginsenoside Rg1 against MPTP-induced apoptosis in mouse substantia nigra neurons. Acta Pharmacol Sin 2002;23:829–34.
[87] Shin E-J, Koh YH, Kim AY, Nah S-Y, Jeong JH, Chae J-S, Kim SC, Yen TPH, Yoon H-J, Kim W-K, et al. Ginsenosides attenuate kainic acid-induced synaptosomal oxidative stress via stimulation of adenosine A2A receptors in rat hippocampus. Behav Brain Res 2009;197:239–45.
[88] Liu X-y, Zhou X-y, Hou J-c, Zhu H, Wang Z, Liu J-x, Zheng Y-q. Ginsenoside Rd promotes neurogenesis in rat brain after transient focal cerebral ischemia via activation of PI3K/Akt pathway. Acta Pharmacol Sin 2015;36:421–8.
[89] Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord 2008;22:222–6.
[90] Smith RG, Caswell D, Carriere A, Zielke B. Variation in the ginsenoside content of American ginseng, Panax quinquefolius L., roots. Canadian J Botany 1996;74:1616–20.
[91] Tan S, Zhou F, Li N, Dong Q, Zhang X, Ye X, Guo J, Chen B, Yu Z. Anti-fatigue effect of ginsenoside Rb1 on postoperative fatigue syndrome induced by major small intestinal resection in rat. Biol Pharm Bull 2013;36:1634–9.
[92] Zhong G, Jiang Y. Calcium channel blockage and anti-free-radical actions of ginsenosides. Chin Med J (Engl) 1997;110:28–9.
[93] Bella AJ, Shamloul R. Traditional plant aphrodisiacs and male sexual dysfunction. Phytother Res 2014;28:831–5.
[94] Lee S-H, Choi K-H, Cha K-M, Hwang S-Y, Park U-K, Jeong M-S, Hong J-Y, Han C-K, In G, Kopalli SR, et al. Protective effects of Korean Red Ginseng against sub-acute immobilization stress-induced testicular damage in experimental rats. J Ginseng Res 2019;43:125–34.
[95] Kopalli SR, Cha KM, Lee SH, Ryu JH, Hwang SY, Jeong MS, Sung JH, Kim SK. Pectinase-treated Panax ginseng protects against chronic intermittent heat stress-induced testicular damage by modulating hormonal and spermatogenesis-related molecular expression in rats. J Ginseng Res 2017;41:578–88.
[96] Park J, Song H, Kim SK, Lee MS, Rhee DK, Lee Y. Effects of ginseng on two main sex steroid hormone receptors: estrogen and androgen receptors. J Ginseng Res 2017;41:215–21.
[97] Hong B, Ji YH, Hong JH, Nam KIY, Ahn TY. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urol 2002;168:2070–3.
[98] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Canc J Clin 2018;68:394–424.
[99] Ahuja A, Kim JH, Kim J-H, Yi Y-S, Cho JY. Functional role of ginseng-derived compounds in cancer. J Ginseng Res 2018;42:248–54.
[100] Yu JS, Roh HS, Baek KH, Lee S, Kim S, So HM, Moon E, Pang C, Jang TS, Kim KH. Bioactivity-guided isolation of ginsenosides from Korean Red Ginseng with cytotoxic activity against human lung adenocarcinoma cells. J Ginseng Res 2018;42:562–70.
[101] Lee H, Lee S, Jeong D, Kim SJ. Ginsenoside Rh2 epigenetically regulates cell-mediated immune pathway to inhibit proliferation of MCF-7 breast cancer cells. J Ginseng Res 2018;42:455–62.
[102] Kim EJ, Kwon KA, Lee YE, Kim JH, Kim SH. Korean Red Ginseng extract reduces hypoxia-induced epithelial-mesenchymal transition by repressing NF-kappaB and ERK1/2 pathways in colon cancer. J Ginseng Res 2018;42:288–97.
[103] Shin DH, Leem DG, Shin JS, Kim JI, Kim KT, Choi SY, Lee MH, Choi JH, Lee KT. Compound K induced apoptosis via endoplasmic reticulum Ca(2+) release through ryanodine receptor in human lung cancer cells. J Ginseng Res 2018;42:165–74.
[104] Yao CJ, Chow JM, Chuang SE, Chang CL, Yan MD, Lee HL, Lai IC, Lin PC, Lai GM. Induction of Forkhead Class box O3a and apoptosis by a standardized ginsenoside formulation, KG-135, is potentiated by autophagy blockade in A549 human lung cancer cells. J Ginseng Res 2017;41:247–56.
[105] Kim HS, Lim JM, Kim JY, Kim Y, Park S, Sohn J. Panaxydol, a component of P anax ginseng, induces apoptosis in cancer cells through EGFR activation and ER stress and inhibits tumor growth in mouse models. Int J Canc 2016;138:1432–41.
[106] Shin HR, Kim JY, Yun TK, Morgan G, Vainio H. The cancer-preventive potential of Panax ginseng: a review of human and experimental evidence. Canc Causes Control 2000;11:565–76.
[107] Lu J-M, Weakley M, S, Yang Z, Hu M, Yao Q, Chen C. Ginsenoside Rb1 directly scavenges hydroxyl radical and hypochlorous acid. Curr Pharm Des 2012;18:6339–47.
[108] Nakata H, Kikuchi Y, Tode T, Hirata J, Kita T, Ishii K, Kudoh K, Nagata I, Shinomiya N. Inhibitory effects of ginsenoside Rh2 on tumor growth in nude mice bearing human ovarian cancer cells. Jpn J Canc Res 1998;89:733–40.
[109] Xiaoguang C, Hongyan L, Xiaohong L, Zhaodi F, Yan L, Lihua T, Rui H. Cancer chemopreventive and therapeutic activities of red ginseng. J Ethnopharmacol 1998;60:71–8.
[110] Baek KS, Yi YS, Son YJ, Jeong D, Sung NY, Aravinthan A, Kim JH, Cho JY. Comparison of anticancer activities of Korean Red Ginseng-derived fractions. J Ginseng Res 2017;41:386–91.
[111] Wang X, Su GY, Zhao C, Qu FZ, Wang P, Zhao YQ. Anticancer activity and potential mechanisms of 1C, a ginseng saponin derivative, on prostate cancer cells. J Ginseng Res 2018;42:133–43.
[112] Kim AD, Kang KA, Zhang R, Lim CM, Kim HS, Kim DH, Jeon YJ, Lee CH, Park J, Chang WY. Ginseng saponin metabolite induces apoptosis in MCF-7 breast cancer cells through the modulation of AMP-activated protein kinase. Environ Toxicol Pharmacol 2010;30:134–40.
[113] Barton DL, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, McGinn TW, Stella PJ, Seeger GR, Sood A. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. J Nat Canc Ins 2013;105:1230–8.
[114] Xu W, Choi H-K, Huang L. State of Panax ginseng research: a global analysis. Molecules 2017;22:1518.
[115] Paik DJ, Lee CH. Review of cases of patient risk associated with ginseng abuse and misuse. J Ginseng Res 2015;39:89–93.
[116] Seo HW, Suh JH, So SH, Kyung JS, Kim YS, Han CK. Subacute oral toxicity and bacterial mutagenicity study of Korean Red Ginseng oil. J Ginseng Res 2017;41:595–601.
[117] Ryu S-J, Chien Y-Y. Ginseng-associated cerebral arteritis. Neurology 1995;45:829–30.
[118] Chen SX, Cohen PR. The ginseng pimple: an inflammatory papule following ginseng consumption. Dermatology Online Journal 2018;24.
[119] Parlakpinar H, Ozhan O, Ermis N, Vardi N, Cigremis Y, Tanriverdi LH, Colak C, Acet A. Acute and subacute effects of low versus high doses of standardized panax ginseng extract on the heart: an experimental study. Cardiovasc Toxicol 2019:1–15.
[120] Bressler R. Herb-drug interactions: interactions between ginseng and prescription medications. Geriatrics (Basel, Switzerland) 2005;60:16–7.
[121] Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health-Sys Pharm 1997;54:692–3.
[122] Dong H, Ma J, Li T, Xiao Y, Zheng N, Liu J, Gao Y, Shao J, Jia L. Global deregulation of ginseng products may be a safety hazard to warfarin takers: solid evidence of ginseng-warfarin interaction. Sci Rep 2017;7:5813.
[123] Seely D, Dugoua J-J, Perri D, Mills EM, Koren G. Safety and efficacy of panax ginseng during pregnancy and lactation. J Population Therap Clin Pharmacol 2008;15.
[124] Kim H, Lee JH, Kim JE, Kim YS, Ryu CH, Lee HJ, Kim HM, Jeon H, Won HJ, Lee JY, et al. Micro-/nano-sized delivery systems of ginsenosides for improved systemic bioavailability. J Ginseng Res 2018;42:361–9.
[125] Hoang T, Ramadass K, Loc TT, Mai TT, Giang LD, Thang VV, Tuan TM, Chinh NT. Novel drug delivery system based on ginsenoside Rb1 loaded to chitosan/alginate nanocomposite films. J Nanosci Nanotechnol 2019;19:3293–300.
[126] Singh H, Du J, Singh P, Mavlonov GT, Yi TH. Development of superparamagnetic iron oxide nanoparticles via direct conjugation with ginsenosides and its in-vitro study. J Photochem Photobiol B: Biol 2018;185:100–10.
[127] Dai L, Liu K, Si C, Wang L, Liu J, He J, Lei J. Ginsenoside nanoparticle: a new green drug delivery system. J Mater Chem B 2016;4:529–38.
[128] Yao H, Li J, Song Y, Zhao H, Wei Z, Li X, Jin Y, Yang B, Jiang J. Synthesis of ginsenoside Re-based carbon dots applied for bioimaging and effective inhibition of cancer cells. Int J Nanomed 2018;13:6249.
[129] Zhao X, Wang J, Song Y, Chen X. Synthesis of nanomedicines by nanohybrids conjugating ginsenosides with auto-targeting and enhanced MRI contrast for liver cancer therapy. Drug Dev Ind Pharm 2018;44:1307–16.
[130] Shen J, Zhao Z, Shang W, Liu C, Zhang B, Zhao L, Cai H. Ginsenoside Rg1 nanoparticle penetrating the blood–brain barrier to improve the cerebral function of diabetic rats complicated with cerebral infarction. Int J Nanomed 2017;12:6477.
[131] Aalinkeel R, Kutscher HL, Singh A, Cwiklinski K, Khechen N, Schwartz SA, Prasad PN, Mahajan SD. Neuroprotective effects of a biodegradable poly (lactic-co-glycolic acid)-ginsenoside Rg3 nanoformulation: a potential nanotherapy for Alzheimer's disease? J Drug Targ 2018;26:182–93.