Review Article

Pharmacological potential of ginseng and its major component ginsenosides

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A B S T R A C T

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, propanoaxadiols, and propanoxatriols, 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.

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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
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 ootillo, 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).](image-url)
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.

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

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**Fig. 3.** Free radical scavenging activity of ginseng as an antioxidant.
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 down-regulating 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.

2.4.3. 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(γ), 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].

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 (Ca2+) 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 Ca2+ 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.
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.
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 non-insulin-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.

2.4.6. Antidiabetes 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].

2.4.7. 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
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
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-1,2-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,
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 manic 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

Fig. 12. Summary of ginseng-derived pharmacological activities.
nanohybrid-conjugated ginsenosides were used to enhance magnetic resonance imaging (MRI) imaging of hepatocellular carcinomas in a nude mouse 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 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.

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Appendix A. Supplementary data

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

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