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Ginseng Compounds: An Update on Their Molecular Mechanisms and Medical Applications

Jian-Ming Lü, **Qizhi Yao**, and **Changyi Chen***
Molecular Surgeon Research Center, Division of Vascular Surgery and Endovascular Therapy, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX 77030, USA

Abstract

Ginseng is one of the most widely used herbal medicines and is reported to have a wide range of therapeutic and pharmacological applications. Ginsenosides, the major pharmacologically active ingredients of ginseng, appear to be responsible for most of the activities of ginseng including vasorelaxation, antioxidation, anti-inflammation and anti-cancer. Approximately 40 ginsenoside compounds have been identified. Researchers are now focused on using purified individual ginsenoside to reveal the specific mechanism of functions of ginseng instead of using whole ginseng root extracts. Each ginsenoside may have different effects in pharmacology and mechanisms due to their different chemical structures. Among them the most commonly studied ginsenosides are Rb1, Rg1, Rg3, Re, Rd and Rh1. The molecular mechanisms and medical applications of ginsenosides have attracted much attention and hundreds of papers have been published in the last few years. The general purpose of this update is to provide current information on recently described effects of ginsenosides on antioxidation, vascular system, signal transduction pathways and interaction with receptors. Their therapeutic applications in animal models and humans as well as the pharmacokinetics and toxicity of ginsenosides are also discussed in this review. This review concludes with some thoughts for future directions in the further development of ginseng compounds as effective therapeutic agents.

Keywords

Ginsenoside; antioxidant; structure; eNOS; receptor; signal transduction pathway; therapeutic application; pharmacokinetics; toxicity

I. INTRODUCTION

Ginseng is a perennial herb of the Araliaceae family, species in the genus Panax, and a highly valued medicinal plant in the Far East that has gained popularity in the West during the past decade [1,2]. The name ginseng comes from the Chinese words “Jen Sheng”, meaning “man-herb”, because of the humanoid shape of the root or rhizome of the plant, which is part of the plant most commonly consumed. The name Panax means “all healing,” which describes the traditional belief that ginseng has properties to heal all aspects of the body. The most common ginsengs are Asian ginseng (*Panax ginseng C. A. Meyer*) and American ginseng (*Panax quinquefolium L.*). Panax ginseng cultivated in China, Japan, Korea and Russia has been used as a medicinal plant in China for thousands of years [1].

*To whom correspondence and reprint requests should be addressed: Changyi (Johnny) Chen, MD, PhD, Michael E. DeBakey Department of Surgery (MARB413), Baylor College of Medicine, One Baylor Plaza, Mail Stop: BCM390, Houston, Texas 77030, USA, jchen@bcm.tmc.edu.

Panax quinquefolium L., grown in the United States and Canada and been used by Native Americans for hundreds of years [3], is a more popular herbal and nutritional supplement used throughout the world [2,4]. Ginseng and its constituents, ginsenosides, are thought to possess antineoplastic, antistress and antioxidant effects.

Ginseng is one of the most frequently purchased herbs in the US due to its potential as a chemopreventive agent or adjuvant treatment [5]. In 2002, a national survey of men and women in the US estimated that 4–5% of those aged 45–64 years used ginseng [6]. Two Canadian surveys found that 17–32% of patients with cardiovascular disease reported use of herbs and 6% of those using herbs reported ginseng use [7,8]. Many H–V infected patients on antiretroviral therapy also take herbal medicines or natural health products. One survey found that 67% of HIV-infected patients on antiretroviral therapy were also taking a natural health product [9]. It was reported to be the 10th most used complementary and alternative medicine in HIV infected patients, used by 34% of those studied [10].

Ginseng is reported to have a wide range of therapeutic and pharmacological uses [11–14]. Researchers are now focused on using purified individual ginsenoside to reveal the mechanism of functions of ginseng instead of using whole ginseng root [11–16]. This may avoid discrepancies as previously reviewed [11,12,14]. Each ginsenoside may have different effect in pharmacology and mechanisms due to their different structures. Approximately 40 ginsenoside compounds have been identified, and the separation and analysis methods of ginsenosides are well reviewed [17]. Ginsenosides appear to be responsible for most of the activities of ginseng including vasorelaxation, antioxidation, anti-inflammation and anti-cancer. Among them the most commonly studied ginsenosides are Rb1, Rg1, Rg3, Re, and Rd. A detailed review about effects of ginsenosides Rb1 and Rg1 on anti-amnestic and anti-aging and the mechanism of action was published [16]. Nah *et al.* also reviewed the studies of effects of ginsenosides on the central nervous system and the peripheral nervous system [18]. A few years ago we reviewed the history of ginseng and the molecular mechanisms and cardiovascular clinical applications of ginseng root [15]. The molecular mechanisms and medical applications of ginsenosides have attracted much attention and hundreds of papers have been published in the last few years. Thereby, it is timely to update recent research progresses of ginsenosides as antioxidants, ligands of receptors and of medical effects on the cardiovascular, immune and neurological systems, signal transduction pathways, and clinical applications as well as pharmacokinetics and toxicity issues.

II. CHEMICAL STRUCTURES AND CLASSIFICATIONS

Accumulating evidence suggests that ginsenosides, also called ginseng saponins, are the major pharmacologically active ingredients of ginseng. The ginseng root contains 2–3% ginsenosides of which Rg1, Rc, Rd, Re, Rb1, Rb2, and Rb0 are quantitatively the most important. American ginseng has a higher content of ginsenosides than other ginseng species such as Asian ginseng (Panax ginseng) [19]. Ginsenosides have a 4-ring, steroid-like structure with sugar moieties attached, and, thus far, more than 40 different ginsenosides have been identified and isolated from the root of P. ginseng [16,20]. Each ginsenoside has at least 2 (carbon-3 and -20) or 3 (carbon-3, -6 and -20) hydroxyl groups, which are free or bound to monomeric, dimeric, or trimeric sugars. Ginsenosides also exist as stereoisomers depending on the position of hydroxyl group on carbon-20. Based on their chemical structures, ginsenosides are generally divided into 2 groups: protopanaxadiols (PD) and protopanaxatriols (PT). The sugar moities in the PD group attach to 3-position of dammarane-type triterpine including Rb1, Rb2, Rc, Rd, Rg3, Rh2, and Rh3 (Fig. 1A), whereas the sugar moities in the PT group attach to 6-position of dammarane-type triterpine including Re, Rf, Rg1, Rg2, and Rh1 (Fig. 1B) [21]. The pseudoginsenoside F11 belongs to PT group although the carbon chain at 20-position is replaced by a tetrahydrofuran ring (Fig.

1C). Several new ginsenosides such as 25-OH-PPD and 25-OH–PPT were recently isolated from ginseng fruit and 25-OH-PPD shows a strong preventive effect to cancer cells (Fig. 1D) [22–24]. Four malonyl derivatives of ginsenosides Rb1, Rb2, Rc and Rd have also been reported (Fig 1C) [25]. The malonyl derivatives and ginsenosides Ro are also called “acidic” ginsenosides while the others are named “neutral” ginsenosides [17].

III. GINSENOSIDES AND ANTIOXIDATION

Reactive oxygen species (ROS) have been shown to play a key role in atherosclerotic plaque formation and to be involved in various vascular injuries. Extensive studies have been conducted on the protective effects of ginseng against free radical damage on the vascular endothelium. American ginseng has also been reported to have antioxidant activity *in vitro* [26]. American ginseng administration increased the activity of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPX) in rats [27]. Zhong *et al*. examined cellular structures of free radical damage on myocardial cells induced by xanthine [28]. They measured free radicals with an electron spin resonance technique and discovered certain ginsenosides (Rb1, Rb2, Rb3, Rc, Re, Rg1, Rg2, and Rh1) counteracting the action of free radicals induced by xanthine. In an animal model, Chen *et al.* [29] showed that ginsenosides protected against myocardial reperfusion injury with a concomitant increase in 6-keto-Prostaglandin F1a and a decrease in lipid peroxidation, and also protected the rabbit pulmonary and aortic endothelium against electrolysis-induced free radical damage. Additionally, Gillis showed the protective effects of ginsenosides on an injured rabbit pulmonary endothelium induced by a variant of ROS [12]. Ginseng prevented manifestations of ROS injury by promoting the release of nitric oxide (NO). We demonstrate that the endothelial dysfunction induced by homocysteine and HIV protease inhibitors was effectively blocked by Rb1 and other ginsenosides [30,31] and these results proved that Rb1 and other ginsenosides fully blocked ROS production. Ginsenoside Re has shown antioxidant effects in cardiomyocytes [32], and neuroprotective effects on amyloid and serum free medium induced cellular damage [33]. Ginsenoside Rd can enhance astrocyte differentiation from neural stem cells [34]. Ginsenosides have proved to exert protective effects that are attributed to their antioxidant ability through increasing internal antioxidant enzymes and acting as a free-radical scavenger [32,35–37].

The relationship between the structure of ginsenoside and its antioxidative or prooxidative activity has been studied in free radical-induced hemolysis of human erythrocytes by Liu *et al.* [38–41]. It was found that the individual ginsenoside (20(S)-protopanaxadiol or 20(S)-protopanaxatriol) behaves as an antioxidant if a glucose is attached to the 20-position of the triterpene dammarane, such as Re, Rd, and R1, but as a prooxidant if there are no sugar moieties attached to the 20-position of the ginsenoside such as Rg3, Rh2 and Rg2. If a glucose attached to the 6-position instead of 20-position sugar moieties, however, the ginsenoside still act as an antioxidant, that is Rh1. Liu *et al.* demonstrated that the positions of sugar moieties make the protective activities complicated. On the other hand, the electron paramagnetic resonance (EPR) study of hydroxyl radical-scavenging of ginsenosides found that several ginsenosides showed strong hydroxyl radical scavenging activity and among them 20(S)-Rg3 showed the strongest activity [42–44]. It is not in line to the hemolysis study where the 20(S)-Rg3 act as a prooxidant which means Rg3 did not protect the radical-induced hemolysis or scavenge the radical. Therefore, there are still many unknown factors to be further investigated.

IV. EFFECTS ON THE eNOS SYSTEM

Recently, we have demonstrated that highly active antiretroviral therapy (HAART) drugs may cause vasomotor dysfunction, endothelial nitric oxide synthase (eNOS) downregulation

and oxidative stress of the porcine arteries and human endothelial cells, while ginsenosides Rb1, Rc and Re can effectively block these detrimental effects of HAART in vitro [30,45]. Recent studies from us and others indicated that the eNOS system and ROS may play a crucial role in HAART-associated side effects. Ginseng compounds have a potential to be developed for this purpose because of their history of therapeutic applications and recent discoveries of the molecular actions [30,45]. For example, ginsenoside Rb1 can effectively block homocysteine-induced endothelial dysfunction and superoxide anion production as well as eNOS downregulation in porcine coronary arteries [30]. Ginsenoside Rb1 also has protective effects on oxidized low-density lipoprotein (oxLDL)-injuring human vascular endothelial cells [46].

Ginsenosides have been shown to stimulate NO production in several systems. Yu *et al.* examined the purified ginsenoside Rb1 inducing NO production in human aortic endothelial cells [47]. Leung *et al.* found that Rg1 increased the phosphorylation of glucocorticoid receptor (GR), phosphatidylinositol-3 kinase (PI3K), Akt/PKB and eNOS leading to increase NO production in human umbilical vein endothelial cells (HUVECs) [48]. Kang *et al.* investigated the relaxation mechanism of ginsenoside Rg_3 using isolated canine corpus cavernosum [49]. These results indicate that the mechanism responsible for the relaxation by ginsenoside Rg_3 is not by stimulating eNOS for the canine corporal smooth muscle relaxation, but by increasing cyclic nucleotide levels through phosphodiesterases (PDE) inhibition [49]. Furukawa *et al.* provided compelling evidence that ginsenoside Re activates eNOS to release NO, resulting in activation of the slowly activating delayed rectifier K^+ current [50]. Ginsenoside Rg1 enhances NO production and the expression of eNOS mRNA in TNF-α-stimulated HUVECs. Ginsenoside Rg1 regulates the expression of many genes in endothelial cells and protected endothelial cells from TNF-α-induced activation. Microarray analysis has provided with valuable insights into the atheroprotective mechanism by gingsenoside Rg1 [51]. Further studies on the functional roles of these genes in TNF-α-induced activation are warranted.

V. SIGNAL TRANSDUCTION PATHWAYS

Although ginsenosides have been widely used as pharmacological agents for a long time, only a few reports have demonstrated their effects on signal transduction pathways in recent years [52,53]. Ginsenosides are responsible for their effects on the central nervous system and the peripheral nervous system through the regulation of various types of ion channels, such as voltage-dependent and ligand-gated ion channels, in neuronal and heterologously expressed cells. For example, Xue *et al.* observed that ginsenosides Rg1 and Rb1 played a major role on the modulation of neurotransmission, where Rb1 promotes neurotransmitter release by increasing the phosphorylation of synapsins via the PKA pathway, while the Rg1 has no relation with the phosphorylation of synapsins [53]. Nah *et al.* reviewed studies of effects of ginsenosides on the central nervous system [18].

Ginsenosides also play a major inhibitory effect on signal transduction pathways. Ginsenoside Rg1 can block C-Jun N-terminal kinase (JNK) signaling cascade through the protective effect of Rg1 against the phosphorylation of JNK [54]. Ginsenoside Rh2 and compound K showed a significant inhibitory effect on TNF-α-induced expression of intercellular adhesion molecule-1 in human astroglial cells by suppressing TNF-α-induced phosphorylation of IκBα kinase and the subsequent phosphorylation and degradation of IκBα [55]. Additionally, the same treatment inhibited TNF-α-induced phosphorylation of MKK4 and the subsequent activation of the JNK-AP-1 pathway.

Ginsenosides are involved in ion channel regulation. Ginsenoside 20(*S*)- but not 20(*R*)-Rg3 and carbohydrate portion of Rg3 play important roles in rat brain NaV1.2 channel

regulations, which inhibits voltage-dependent brain Na^+ channel activity expressed in *Xenopus laevis* oocytes [56]. A recent study by the same group found that reduction of double bond in aliphatic side of Rg3 cause an enhancement or loss of brain Na^+ channel current inhibitions. These results provide evidence that the aliphatic side chain of Rg3 is involved in Na^+ channel regulation and that the enhancement or loss on Na^+ channel current inhibitions by Rg3 depends on chemical structures of the aliphatic side chain of Rg3 [57]. Jiang *et al.* [58,59] examined the antihypertrophic effect of ginsenoside Rb_1-induced by prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) *in vitro* and investigated the possible mechanisms involved in the calcineurin (CaN) signal transduction pathway. Their data imply that Rb_1 attenuates cardiac hypertrophy, and the underlying mechanism may be involved in the inhibition of the Ca^{2+}-CaN signal transduction pathway [58,59].

VI. INTERACTION WITH POTENTIAL RECEPTORS

Most natural products can act as full agonist to activate the receptor and result in a maximal biological response. Ligand-induced changes in receptors result in physiological changes which constitute the biological activity of the ligands. Ginsenosides were demonstrated to exert beneficial effects on the cardiovascular system, in which ginsenoside-Re was reported to stimulate vasodilation and angiogenesis in vivo [60,61]. Angiogenesis is a fundamental process in both physiological and pathological conditions. Therapeutic angiogenesis is now drawing more attention as a treatment of chronic wound or gastric ulcer as well as ischemic tissues [62,63].

Ginsenosides have been used as ligands for receptors, and their activities and mechanisms were investigated. Ginsenosides Re, Rg1 and Rb1 were demonstrated being functional ligands of glucocorticoid receptor (GR) [48,64–66], and androgen receptor [47]. They acted as agonists and induced rapid ion influx and NO production in endothelial cells as mentioned in the eNOS section above [48,50,64,65]. For example, Rg1 can indeed serve as an agonist ligand for GR and the activated GR then induces a rapid NO production from eNOS via the non-transcriptional PI3K/Akt pathway [48]. Re acts as a specific agonist for the nongenomic pathway of sex steroid receptors, and NO released from activated eNOS underlies cardiac K^+ channel activation and protection against ischemia-reperfusion injury [50]. Ginsenoside Re releases NO via a membrane sex steroid receptors, resulting in K(Ca) channel activation in vascular smooth muscle cells, promoting vasodilation and preventing severe arterial contraction [66].

Rhule *et al.* investigated the potential for notoginseng extracts to modulate Toll-like receptor (TLR) ligand-induced activation of cultured dendritic cells (DC2.4) and found that ginsenoside Rg1 and Rb1 effectively inhibited lipopolysaccharide-stimulated cytokine production [67]. Dendritic cells (DC2.4) play a central role in the regulation of both inflammation and adaptive immunity. Lee *et al.* demonstrated that ginsenoside Rg3 inhibited non-competitively 5-hydroxytryptamine 3A subunit receptor ($5\text{-}HT_{3A}$) channel activity on extracellular side of the cell through interactions with residues V291, F292, and I295 in the channel gating region of TM2 [68–70].

Panax ginseng may inhibit tumor growth by affecting both cancer cells and their blood supply. Researchers have found so far that 3 purified ginsenosides are capable of affecting neovascularization and angiogenesis-related properties of endothelial cells. For example, ginsenoside Rb1 can potently inhibit angiogenesis in vivo and in vitro which is a crucial step in tumor growth and metastasis [71]. Its mechanism was that Rb1 suppressed the formation of endothelial tube-like structures through modulation of pigment epithelium-derived factor via estrogen receptor-β (ERβ) [71,72]. Rg1 was found to be a phytoestrogen that exerted estrogen-like activity even without direct interaction with oestrogen receptor (ER) in human

breast cancer (MCF-7) cells via phosphorylation of AF-1 domain in the absence of receptor binding [73]. These actions of ginsenosides may have potential value in anti-cancer and anti-angiogenesis therapy although some discrepancy still remained in these studies [72].

VII. THERAPEUTIC APPLICATIONS IN ANIMAL MODELS

In animal models, ginseng is able to decrease platelet aggregation [15,74,75]. This inhibitory action may be mediated by raising platelet cAMP levels, decreasing production and release of thromboxane A2, and inhibiting prostacyclin (PGI2) production. The retardation of aortic atherosclerotic plaque formation was observed in the rabbit model after eight weeks of feeding ginseng orally [76]. Ginsenosides Rd and Rb were able to attenuate oxidative damage [77,78], while Re to possess significant anti-hyperglycemic actions and to normalize effectively the impaired oxidative stress in the kidney and eye of the diabetic rats [79]. The preventive effect of ginsenosides on angioplasty-induced neointimal formation was seen in a rat model [80]. Animal studies suggested that ginsenoside Rb1 increased glucose uptake into sheep erythrocytes in a dose dependent manner, while another ginsenoside Rb2 increased the activity of the rate-limiting glycolytic enzymes that affect insulin secretion and modulate glucose disposal [81,82].

Ginsenosides Rg1 and Rb1 enhance glutamate release in rat cerebrocortical nerve terminals [83]. They have also been shown to have beneficial effects on the central nervous system, especially cognitive function like learning and memory [14,84]. It has been demonstrated, for example, that ginsenoside Rg1 or Rb1 administration is able to increase the performance in different animal models of learning/memory, such as passive avoidance and Morris water maze tasks [85–87].

In animal model studies, ginsenosides have shown protective or inhibitory effects on some diseases or reactions [77,78,83,88–96]. Ginsenoside Rb1 can prevent the ischemic brain damage or ischemic injury to spiral ganglion cells [78,90,91,93], possibly by acting as a neurotropic factor-like agent and by scavenging free radicals, which are overproduced in situ during and after brain ischemia [78]. The results suggest that gisenosides may be useful for the treatment of neurodegenerative diseases such as Parkinson disease and Alzheimer disease [93]. Rg1 has a protective effect on glutamate-induced lung injury in mice, indicating its clinical application in some lung diseases associated with glutamate toxicity [97]. Orally administered Rd has an immunological adjuvant activity and elicits a Th1 and Th2 immune response by regulating production and gene expression of Th1 cytokines and Th2 cytokines [96]. Ginsenosides potently inhibited the passive cutaneous anaphylaxis (PCA) reaction induced by IgE [95]. These ginsenosides also significantly reduced mRNA expression levels of cyclooxygenase (COX)-2, interleukin (IL)-1β, TNF-α and interferon-γ induced by oxazolone applied to mouse ears [95]. In a rat model with vascular dementia, ginsenoside Rg2 protects memory impairment via anti-apoptosis [89]. The capacity for ginsenoside Rg2 to modulate the expression of apoptotic related proteins suggests that ginsenoside Rg2 may represent a potential treatment strategy for vascular dementia or other ischemic insults [89].

VIII. CLINICAL APPLICATIONS

Natural products and/or their synthetically developed active components have been used in medicine to prevent and treat a variety of disorders. Ginseng is one of the most commonly used natural products with a number of pharmacological effects including immunomodulatory, anti-inflammatory and anti-tumor activities. For example, clinical studies on the effects of ginseng supplements showed that ginseng, added to conventional treatment of diabetes, significantly improved glycemic control by lowering postprandial glycemia without precipitating preprandial hypoglycemia in type II diabetics [98]; treating

impotent men with erectile dysfunction (ED) with Korean Red Ginseng (KRG) can effectively improve male ED [99]. Clinically, ginseng has been frequently used in combination with chemotherapy to reduce the side effects of anti-cancer drugs [100]. Furthermore, clinical trials have demonstrated certain therapeutic benefits of ginseng in treating hypertension, attenuating atherosclerotic processes, and improving cardiac function [14,101–104]. Detail information about clinical studies of ginseng root can be obtained from several reviews [12,13,83,98,105].

Individual ginsenoside, however, due to incomplete pharmacokinetic parameters and unknown toxicities [106–109], has not been reported for the clinical study so far. There are only few pharmacokinetic studies about ginseng or ginsenosides in humans [110,111]. Many studies about purified ginsenosides have been devoted to the investigation of their beneficial effects on the pharmacological activities by using animal models and cultured cells. In animal studies, ginsenosides had many protective activities as discussed above, which can be potentially used to treat human diseases. Ginsenosides Rg3 and Rh2 have been reported to have a cell-growth suppressive effect on various cancer cells [112,113]. Ginsenoside 25-OH-PPD had significant, dose-dependent effects on apoptosis, proliferation, and cell cycle progression [114] and showed preventive effect to cancer cells [22,23]. Ginsinosides Rh2 and Rb1 have also shown activity in reducing ischemic brain injury in rats after oral administration [78,90,91,93,115].

Researchers have studied safe dosage of ginsenosides used on animals. For example, a low dose (10 μM or 11.09 μg/ml) of Rb1 has significant preventive effect on HUVEC proliferation and superoxide anion production in vitro and found that Rb1 completely blocked the effect of homocysteine on endothelial cells [30,46,116]. Orally administered ginsenoside Re, Rg1, or Rg3 of only 25 mg/kg of the compounds in the Tg2576 mouse model results in a significant reduction the amount of Alzheimer's Aβ peptide detected in the brains of these animals at 18 h post-drug administration [117]. Although results from animal teratogenicity study may not reflect the circumstances in humans, we should be careful with using ginsenosides [108]

IX. PHARMACOKINETICS AND TOXICITY ISSUES

The investigations of the pharmacokinetics and bioavailability of ginsenosides can link data from pharmacological assays to clinical effects and also help in designing rational dosage regimens. The analytical methods for determining ginsenosides have been achieved using thin layer chromatography (TLC), enzyme immunoassay (EIA), high performance liquid chromatography with ultraviolet detection (HPLC–UV), high performance liquid chromatography with fluorescence detection (HPLC–FLD), liquid chromatography–evaporative light-scattering detection (LC–ELSD), and LC MS and liquid chromatography-tandem mass spectrometry (LC–MS/MS) [17,118]. Among these methods, HPLC–MS and MS/MS techniques provide excellent methods for the simultaneous quantification of multiple ginsenosides in animal plasma and are successfully applied to the pharmacokinetic study of a multiple-constituent natural medicine even at a low dose There are a few reports on LC/MS analysis of ginsenosides extracted from biological samples [114,118–124].

The only pharmacokinetics studies of ginsenosides in human are reported by Cui *et al.* [110,111], which showed that ginsenosides are present in urine after oral ingestion. About 1.2% of the dose was recovered in 5 days. Further investigations are necessary to evaluate the pharmacokinetics and placental transfer of ginsenosides in humans.

Generally, ginsenosides are very poorly absorbed following oral administration in vivo [114,121]. Li *et al.* studied the pharmacokinetic of the oral administration of ginseng powder in rats and found that the absorption of ginsenosides was quick, but the maximum

concentration of R1, Rg1, Rd, Re and Rb1 in rat plasma was from 1.5 to 6.4 μg/ml [122,123]. The absolute bioavailability of Panax notoginsenoside R1, ginsenside Rg1, Rd, Re and Rb1 were of 9.29%, 6.06%, 2.36%, 7.06% and 1.18%, respectively. Wang *et al.* reported the absolute bioavailability of Rd in dogs was 0.26% [121]. It was reported the absolute bioavailability of ginsenoside Rg3 in rats was 2.63% [125] or undetectable in oral dosing samples [126]. Xu *et al.* reported the oral bioavailability of Rg1 was 18.4% in rats [127] and Li *et al.* reported the absolute bioavailability was 15.62% for Rg1, 0.28% for Rb1 and 0.34% for Rd [128]. Paek *et al.* reported the absolute bioavailability was 35.0% for a ginseng saponin metabolite compound K at the 20 mg/kg dose [129].

Several newly identified ginsenosides, such as 25-OH-PPD, 20(S)-25-methoxyl-dammarane-3β, 12β, 20-triol (25-OCH_3-PPD) [22–24], had significant, dose-dependent effects on apoptosis, proliferation, and cell cycle progression. 25-OH-PPD, its IC_{50} values for most cell lines were in the range of 10–60 μM, demonstrating a 5–15 fold greater growth inhibition than Rg3 [114]. The absolute bioavailability of 25-OH-PPD is 64.8±14.3% (range 44.1–75.9%) which is the highest among the reports in ginseng compounds, and it is very beneficial to the drug with anti-tumor activity in clinical applications in the future. Pharmacokinetic studies of selected ginsenosides in rats, dogs or human plasmas are provided in Table 1.

The reasons of the poor bioavailability of ginsenosides include that these compounds may be destroyed in the gastrointestinal tract, metabolized by intestinal microflora and excreted from bile or urine [130]. On the other hand, low membrane permeability may be a more important factor in determining the extent of absorption [130]. The higher absolute bioavailability is found in the rats and it could be hypothesized that 25-OH-PPD possesses deglycosylated mother aglycone structure, lower molecular weight, higher hydrophobility than those of ginsenoside Rg3. Thus, 25-OH-PPD is well absorbed by the digestive tract [114].

These ginsenosides 25-OH-PPD, 20(S)-25-methoxyl-dammarane-3β, 12β, 20-triol (25-OCH3-PPD) also have low toxicity to non-cancer cells and no observable host toxicity in animals either alone or in combination with conventional therapies [22–24]. These compounds may have potential as novel prostate cancer therapeutic agents [22–24]. Furthermore, ginsenoside Rg3 in mouse model studies has a preventive effect on DNA damage and cell death induced by cyclophosphamide [131] and has an inhibitory effect on genotoxicity, chemical and histological changes induced by ethylenediaminetetraacetic acid (EDTA), which is widely used in food [132]. The dosage used in these studies was 20 mg/kg and it was found that ginsenoside Rg3 alone did not induce any genotoxicity in mouse peripheral lymphocyte cells and bone marrow cells [131].

However, ginseng is commonly used by pregnant women and the most common reason for consumption is ‘good for pregnancy and fetus. Data concerning the potential beneficial and adverse effects of ginseng during pregnancy is sparse. As discussed in the clinical applications, individual ginsenoside has not been used on the patients due to its unknown toxicity. Researchers have investigated the toxicity of ginsenosides Rb1, Re, Rc, and Rh2 recently using a whole mouse embryo culture model and in intestinal Caco-2 cells [106–109]. Chan *et al.* reported that ginsenosides Rb1 and Re were embryotoxic. Rb1 or Re induced a strong embryotoxic effect at a concentration of 50 μg/ml. However, Rc did not demonstrate any adverse effect towards developing rat embryos at the same concentration as of Re. It seems that Re induced a severe developmental delay with significant reduction in morphological scores of all systems assessed, rather than a teratogenic effect on a particular organ system. Using the same model, Liu *et al.* found that ginsenoside Rb1 at 50 mg/ml affected allantois, flexion, branchial arch, and limb buds [108]. At this concentration, the

embryonic crown-rump length, head length, and somite number were also reduced significantly compared to the control group [108]. Although results from animal tests may not reflect the true complexion in humans and the potential mechanism of developmental toxicity of ginsenosides remains unclear, these results suggest that ginseng compounds should be used with caution by pregnant women until more human data are available [107,108].

X. SUMMARY AND FUTURE DIRECTIONS

Ginseng is believed to be the most traditional medical herb contains many active constituent ginsenosides. It has extensive pharmacological effects and specific mechanisms of action in Chinese herb medicine. Ginsenosides can inhibit ROS production, stimulate NO production, increase immune function, enhance central nervous system function, and prevent cardiovascular or other diseases. Animal studies indicate that ginsenosides have different activities in both physiological and pathologic conditions. How these effects relate to the ginsenoside structures are not yet fully elucidated. Future research involving each ginsenoside should include the mechanisms of action, specificity, structure and function relationship, detailed pharmacokinetics and toxicity studies, and therapeutic studies in both animal models and human trials.

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LIST OF ABBREVIATIONS

COX	cyclooxygenase
CaN	calcineurin
DC2.4	dendritic cells
eNOS	endothelial nitric oxide synthase
EPR	electron paramagnetic resonance
GPX	glutathione peroxidase
GR	glucocorticoid receptor
HAART	highly active antiretroviral therapy
Hcy	homocysteine
HPLC	high performance liquid chromatography
HUVEC	human umbilical vein endothelial cell
IC_{50}	half maximal (50%) inhibitory concentration (IC) of a substance
JNK	C-Jun N-terminal kinase
LC–MS/MS	liquid chromatography-tadem mass spectrometry
NO	nitric oxide
oxLDL	oxidized low density lipoprotein
PD	protopanaxadiols

PDE	phosphodiesterases
$PGF_{2\alpha}$	prostaglandin $F_{2\alpha}$
PI3K	phosphatidylinositol-3 kinase
PKB	protein kinase B
PT	protopanaxatriols
ROS	reactive oxygen species
SOD	superoxide dismutase
TLR	toll-like receptor
TNF-α	tumor necrosis factor-alpha

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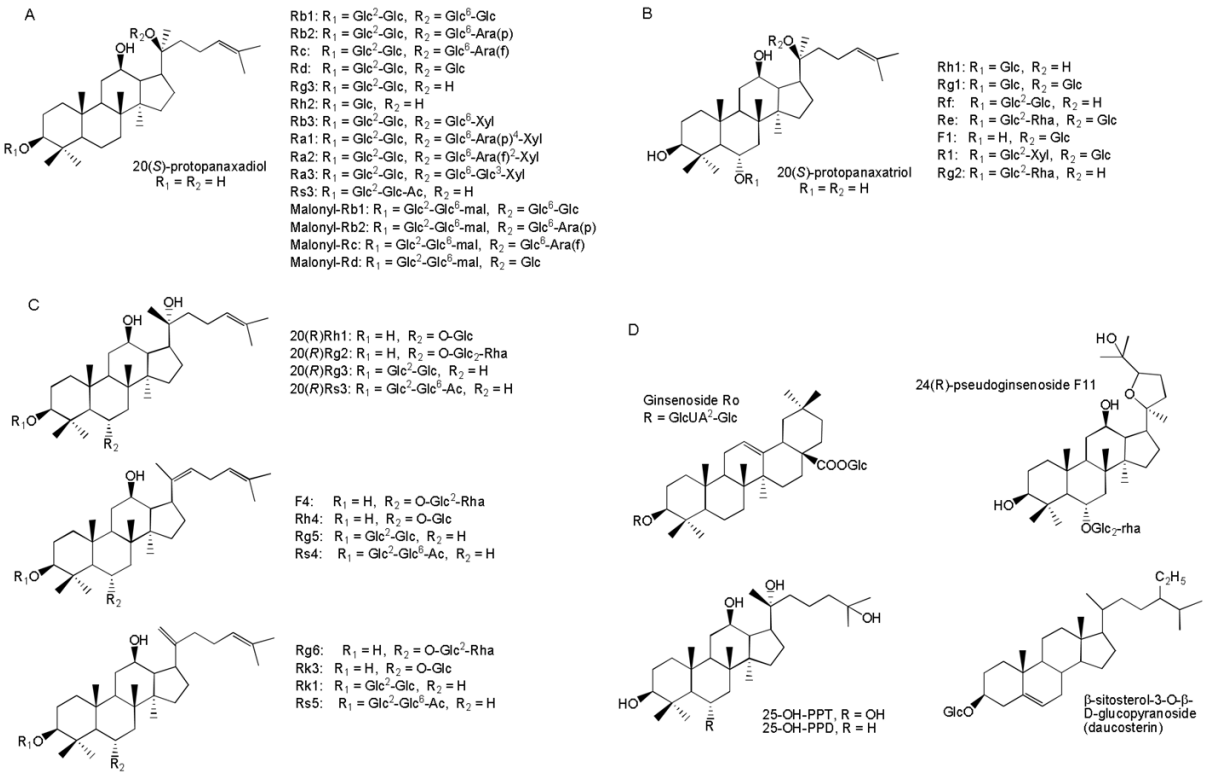

Fig. 1.

Structure of selected ginsenosides. **A.** protopanaxadiols (PD). **B.** protopanaxatriols (PT). **C.** derivatives of PD and PT. **D.** new ginsenosides. Glc, β-D-glucose; Rha, α-L-rhamnose; Ara(p), αL-arabinose(pyranose); Ara(f), α-L-arabinose(furanose); Xyl, β-D-xylose; GlcUA, β-D-glucuronic acid; mal, malonyl; Ac, acetyl.

Table 1

Pharmacokinetic studies of selected ginsenosides in rats, dogs or human plasmas

Ginsinosides	Animal model	Method	Dosage	Absolute bioavailability	Ref.
25-OH-PPD	rat plasma, oral	HPLC/MS	10 mg/kg	64.8%	[114]
Rh2	Rat, oral, in vivo	LC/MS, ESI/MS	100 mg/kg	0.25%	[119]
Rh1, Rg1	Rat plasma, i.v., or i.g.	LC/MS	100 mg/kg	1.33% Rg1	[118]
20(R)-, 20(S)-Rg2	Rat plasma, i.v.,	HPLC	25 mg/kg	-	[120]
Rd	Human plasma, in vivo	LC/ESI/MS	10 mg/kg	-	[124]
R1, Rg1, Rd, Re,	Rat plasma	HPLC/ESI/MS	10 mg/kg Rb1	9.29%, 6.06%, 2.36%, 7.06% and 1.18%	[122,123]
Rd	Dog plasma, i.v., oral	LC/MS	2 mg/kg (oral) 0.2 mg/kg (i.v)	0.26%	[121]
Rg1	Rat, oral, in vivo, in vitro	HPLC	50 mg/kg	1.52–6.60%	[130]
Rg3	Rat plasma	LC/ESI/MS	50 mg/kg	2.63%	[125,126]
multiple	Rat plasma	LC/ESI/MS	300 mg/kg	-	[123]
Rg1, Rb1	Rat plasma	HPLC	50 mg/kg	18.4% (Rg1) 4.35% (Rb1)	[127]
compound K	Rat	LC/MS	20 mg/kg	35.0%	[129]

i.v.: intravenous administration; i.g.: intragastric gavage.