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Review Article

Physiological and pharmacological features of the non-saponin components in Korean Red Ginseng

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ABSTRACT

Panax ginseng, a medicinal plant, has been used as a blood-nourishing tonic for thousands of years in Asia, including Korea and China. *P. ginseng* exhibits adaptogen activity that maintains homeostasis by restoring general biological functions and non-specifically enhancing the body's resistance to external stress. Several *P. ginseng* effects have been reported. Korean Red Ginseng, in particular, has been reported in both basic and clinical studies to possess diverse effects such as enhanced immunity, fatigue relief, memory, blood circulation, and anti-oxidation. Moreover, it also protects against menopausal symptoms, cancer, cardiac diseases, and neurological disorders. The active components found in most Korean Red Ginseng varieties are known to include ginsenosides, polysaccharides, peptides, alkaloids, polyacetylene, and phenolic compounds. In this review, the identity and bioactivity of the non-saponin components of Korean Red Ginseng discovered to date are evaluated and the components are classified into polysaccharide and nitrogen compounds (protein, peptide, amino acid, nucleic acid, and alkaloid), as well as fat-soluble components such as polyacetylene, phenols, essential oils, and phytosterols. The distinct bioactivity of Korean Red Ginseng was found to originate from both saponin and non-saponin components rather than from only one or two specific components. Therefore, it is important to consider saponin and non-saponin elements together.

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1. Introduction

Ginseng is a medicinal herb that has long been used as a blood-enriching and tonifying agent in Korea, China, and other parts of East Asia. In 1843, ginseng was first named *Panax ginseng* C.A. Meyer, meaning 'cure-all', by the Russian scientist, C.A. Meyer. Ginseng and similar herbs are also used in the US, China, Japan, and Russia but they differ from *P. ginseng* in terms of their taxonomy, morphology, and constituents. Globally, there are 6–7 known species in the genus *Panax*; however, only three ginseng species are cultivated and commercially distributed globally [1]. These are *P. ginseng* (geographically distributed and cultivated in Far East Asia, including South Korea and China), American ginseng (*P. quinquefolium* L., cultivated in the US and Canada), and Chinese ginseng (*P. notoginseng* (Burk) F.H. Chen, produced in the Yunnan and Guangxi provinces in southern China) [2]. American ginseng and Chinese ginseng are different species from *P. ginseng*; thus, the term 'ginseng' is generally only used for *P. ginseng*.

The pharmacological histories of American ginseng and Chinese ginseng are much shorter than that of *P. ginseng*. Chinese ginseng has been used medicinally since the 16th century whereas American ginseng has only been used since the early 18th century when it was first discovered in Canada and became known to Chinese merchants [3]. At that time, *P. ginseng* was rare and very expensive in China, so Chinese ginseng and American ginseng were used as alternatives. The authentic ginseng, which has a long pharmacological history and is still recognized as one of the most important traditional medicines today, is the *P. ginseng* species [1]. Historically, after Korea became known internationally by its current name, the ginseng cultivated and produced in Korea has been called *P. ginseng*. It is a global product that is promoted on a backdrop of the mountainous scenery of South Korea and is currently considered the 'ultimate' ginseng [4,5]. *P. ginseng* is an intermediate shade-tolerant perennial plant in the family Araliaceae, genus *Panax*.

Depending on the processing method used, ginseng can be broadly categorized into fresh ginseng, white ginseng, and red ginseng. Fresh ginseng is a natural product that takes 4–6 years to mature and is sourced from the earth; the unique ginseng compounds are preserved, and given that the water content is 70–80%, the product can decay and be damaged easily during distribution, so long-term storage is difficult without specialized storage facilities or packaging. White ginseng is produced by sun-drying or hot air-drying of 4–6-year-old fresh ginseng either in its original state or after removing the outer layer; its water content accounts for ≤14% and it is milky-white or pale yellow in color. Red ginseng is produced by steam cooking and then drying the fresh ginseng; its water content accounts for ≤15.5% and it can be pale red or red-brown in color. Depending on its quality, red ginseng is divided into *chonsam*, *jisam*, and *yangsam* [6]. In the process of steaming and drying fresh ginseng to make red ginseng, there are changes in the types and concentrations of unique compounds found in ginseng known as ginsenosides. There are also physical and chemical changes in polysaccharides, the most abundant compounds in Korean Red Ginseng; notably, starch gelatinization enables long-term storage [4,5,7–14]. Korean Red Ginseng contains a high concentration (60–70%) of carbohydrates, including starch, but also includes a number of specific compounds that are not found in other plants, including ginsenosides, proteins that are nitrogen-containing compounds, peptides, alkaloids, polyacetylenes that are liposoluble, and polysaccharides as well as flavonoids and fatty acids (Table 1) [4,7,15].

A Japanese team led by Shibata and Tanaka embarked on intensive research on the chemical structure of ginsenosides in 1962 and clarified the chemical structures of the ginsenoside aglycones, i.e., protopanaxadiol and protopanaxatriol [16–21]. Subsequent research led to the purification of the ginsenosides, i.e., saponins, from *P. ginseng* and the chemical structures of the individual saponins were revealed in the late 1960s [19,22,23]. Since the early 1980s, research has focused on the saponin composition in red and white ginseng, classified according to the processing methods used, and each type of ginseng was found to contain unique saponins [24]. Since the 1960s, when the first studies on the chemical purification of ginsenosides were performed, the chemical structures of least 43 saponins have been isolated from *P. ginseng* [6]. Now that it is possible to purify individual saponins from Korean Red Ginseng, the effects of Korean Red Ginseng have been investigated at the compound level and various effects have been demonstrated for each saponin. Furthermore, several studies that used high-quality analytic devices and techniques have analyzed additional components in Korean Red Ginseng compounds including polysaccharides, polyacetylenes, phenol compounds, essential oils, peptides, alkaloids, and vitamins [6].

The non-saponin fraction has been demonstrated to have various types of pharmacological activity; this has led to multifaceted exploratory research on the pharmacology of the active fraction [25,26]. Although some physiologically active non-saponin contents of Korean Red Ginseng have been identified in other herbs and natural products, some contents are unique to Korean Red Ginseng and are contributing substantially to our understanding of the efficacy of ginsenosides and the diverse effects of Korean Red Ginseng [27]. The first research on the non-saponin compounds in Korean Red Ginseng was performed in Japan in 1914 by Sakai who isolated an aromatic compound from an ether extract of Korean Red Ginseng and named it panacene. Thereafter, chemical analyses of phytosterols [28] and polyacetylenes [29] were pursued, but since most of these compounds are also present in other herbal medicines, they received little attention as active substances in Korean Red Ginseng. At that time, ginsenosides were emphasized as unique compounds in Korean Red Ginseng, resulting in even less research on the effects of non-saponin compounds. However, from the late 1960s onwards, Korean researchers isolated maltol and several phenolic compounds from Korean Red Ginseng and tested their activity [30]. For instance, the alkaloid fraction in Korean Red Ginseng was reported to suppress the proliferation of cancer cells [31], as was a petroleum ether extract [32]. This was the starting point for considerable exploratory research on the active compounds in Korean Red Ginseng, focusing on non-saponin compounds. While there has been much research on the saponin content in Korean Red Ginseng, there has been relatively little research on its non-saponin content. There is a misperception that all the effects of Korean Red Ginseng are mediated by saponins; recently, there has been a surge of marketing claiming that a stronger saponin effect can be achieved by increasing the absorption rate of certain saponins. Korean Red Ginseng contains saponin but facilitates the best effects when ingested with non-saponin components evenly. In this review, various studies on the physiological effects of non-saponin compounds in Korean Red Ginseng are evaluated to demonstrate that these compounds also have a variety of actions.

2. Polysaccharides

Until the 1960s, there was almost no research on the chemistry or physiological effects of Korean Red Ginseng polysaccharides, which are macromolecules. With developments in the life sciences, it was discovered that carbohydrates have important functions as simple structural molecules or energy sources and as signal transmitters for biological functions, leading to renewed recognition of their importance [33]. Polysaccharides are the most abundant compounds in Korean Red Ginseng. Some polysaccharides are formed from chains of many simple sugars, including monosaccharides, such as glucose and fructose, and disaccharides, such as maltose and sucrose. Pectin is a polysaccharide that has been isolated from Korean Red Ginseng and is a major constituent of

Table 1
Saponin and non-saponin components existing in Korean Red Ginseng

Common components		
Saponin	Ginsenosides	Protopanaxadiol (27 types)
		Protopanaxatriol (14 types)
		Oleanane (2 types)
Non-saponin	Saccharides	Monosaccharide, disaccharide, trisaccharide, polysaccharides (including red ginseng polysaccharide, etc.), crude fiber, pectin
	Nitrogen-containing compounds	Protein, peptide, amino acid, nucleic acids, alkaloid
	Fat-soluble components	Lipid, fatty acid, polyacetylenes, phenolic compounds, essential oils, phytosterols, organic acid, terpenoid
	Vitamin	Water-soluble vitamins
	Ash	Minerals

Table 2
Physiological activity of polysaccharides

Components	Physiological activity	Reference
Panaxans A–U	Hypoglycemic activity	[36,41]
	Decrease in glycogen levels in the liver, promoting insulin secretion	[42]
Water-soluble and alkali-soluble fraction	Anti-complementary activity	[43]
Korean Red Ginseng acidic polysaccharide	Immune activity	[45–50,53,55,56]
	Anticancer activity	[49–52]
	Hyperlipidemia inhibition	[54]
	Influenza defense	[58]
Crude polysaccharides	Immune activity	[57]
	Influenza defense	[58]

galacturonic acid, glucose, galactose, and arabinose. Pectin is also a minor constituent of xylose, rhamnose, and galacturonan [33].

Likely due to their structural complexity, research on Korean Red Ginseng polysaccharides and their activity started much later than similar research on saponins. In 1984, a research team led by Hikino and Tomoda first isolated panaxans A, B, C, D, and E from Korean Red Ginseng and subsequently isolated panaxans F to U, giving a total of 21 panaxan types [34–40]. Regarding physiological activity, these polysaccharides showed notable hypoglycemic activity in diabetic mice [36,41]. Yang et al also administered polysaccharides from Korean Red Ginseng to animals and reported that they lowered blood glucose, reduced glycogen levels in the liver, and promoted insulin secretion [42]. The water-soluble and alkali-soluble (0.5M sodium hydroxide) polysaccharide fractions from *P. ginseng* show anti-complementary activity that was strongest for the acidic polysaccharide fraction [43]. Over a period of 10 years, Okuda et al isolated acidic polysaccharides from the water extract of Korean Red Ginseng and found the chemical structure of these compounds to consist of an α-1, 4-polygalacturonan backbone similar to pectin with several acetoxy groups [44]. After this, two new acidic polysaccharides were isolated, ginsenan PA and ginsenan PB; these had molecular weights of 16,000 and 5,500, respectively, and their chemical structure consisted of α-arabino-β-3,6-galactan-type and rhamnogalacturonan-type structural units.

Compared to white ginseng, red ginseng is reported to have far higher levels of pectin [8]. Heating causes an increase in galacturonic acid because esterified galacturonic acid is converted into non-esterified galacturonic acid [8]. Recently, there has been much research on the physiological actions of acidic polysaccharides. The red ginseng polysaccharide fraction inhibits immunotoxicity by increasing hemolytic plaque-forming cells and the white blood cell count; also, spleen weight is decreased by cyclophosphamide treatment [45]. Administering Korean Red Ginseng polysaccharides to sarcoma 180-bearing mice inhibited cancer development, increased the number of hemolytic plaque-forming cells that are involved in the production of antibodies, and increased phagocytic activity in the reticuloendothelial system; these effects were strongest in the acidic polysaccharide fraction found in red ginseng [45,46]. Park et al administered Korean Red Ginseng acidic polysaccharide (RGAP) to mice and reported a significant increase in the peritoneal macrophage count and a significantly increased production of antibodies against sheep red blood cells [47]. In a tumor graft mouse model, RGAP promoted the production of nitric oxide (NO) by macrophages and increased natural killer (NK) cell activation. Furthermore, tumorigenesis was greatly suppressed, and the lifespan of the mice was extended [48].

There have also been studies on suppressing the growth of solid cancers and lung cancer metastasis where RGAP significantly increased the phagocytic index of macrophages, significantly reduced the weight of solid tumors, and suppressed lung cancer metastasis because of a melanoma cell graft [49]. To investigate whether RGAP has a protective effect against the immunotoxicity of anticancer treatment and to explore its role as an adjuvant anticancer treatment, RGAP was administered with or without paclitaxel; the RGAP combination therapy group showed significantly increased NK cell activity in splenocytes and an increase in the cytotoxicity of macrophages from 15% to 45%, indicating a protective effect against immunotoxicity. Moreover, paclitaxel + RGAP combination therapy significantly increased the lifespan and reduced the weight of the solid tumors, demonstrating the potential of RGAP as an adjuvant anticancer therapy [50].

Kwak et al investigated the possibility of using RGAP in combination with cyclophosphamide or 5-fluorouracil as an immune-enhancing agent and to alleviate the adverse effects of immunotoxicity [51]. They reported an extended lifespan and significantly reduced tumor weight and size in mice grafted with sarcoma 180 or Lewis lung/2 lung carcinoma. RGAP inhibited the phagocytic activity of *Brucella abortus* by suppressing the levels of mitogen-activated protein kinase (MAPK) signaling proteins, extracellular signal-regulated kinase, Jun N-terminal kinase, and p38 and inhibited the intracellular replication of *B. abortus* by enhancing phagolysosome fusion. This indicates that RGAP could be used effectively for the control or treatment of *Brucella* spp. [52].

Byeon et al investigated the mechanisms of immune enhancement of Korean Red Ginseng via RGAP. Regular consumption of Korean Red Ginseng activated macrophages, promoting immune protein migration into the nucleus and inducing active secretion of factors (e.g., NO, reactive oxygen species, and tumor necrosis factors) that destroy cancer cells, various viruses, and bacteria [53]. In animals with acute hyperlipidemia, RGAP significantly suppressed levels of non-esterified fatty acids and triglycerides in the serum and liver and induced a significant dose-dependent increase, of up to 80%, in the activity of lipoprotein lipase, a major lipoprotein hydrolase. This demonstrates that RGAP is effective against hyperlipidemia [54].

When RGAP and pidotimod were administered in combination to immune-deficient mice to test the synergistic immune-enhancing effect, there were significant increases in concanavalin A-induced T-cell proliferation in the spleen and in lipopolysaccharide (LPS)-stimulated B-cell proliferation. Furthermore, NO production increased from peritoneal macrophages, NK cell activity increased, and interleukin (IL)-12 and interferon gamma (IFN-γ levels) increased, demonstrating heightened immune activity [55]. In another study, tumor cell death increased when murine B16 melanoma cells were exposed to a combination of RGAP + recombinant IFN-γ; moreover, IL-1, IL-6, tumor necrosis factor alpha (TNF-α), and NO productions were stimulated, showing a synergistic effect on macrophage activity [56]. Crude polysaccharides obtained after dividing water extract from red ginseng into α-amylase and amyloglucosidase significantly increased the intestinal immune system modulating activity and macrophage stimulating activity [57]. When whole red ginseng
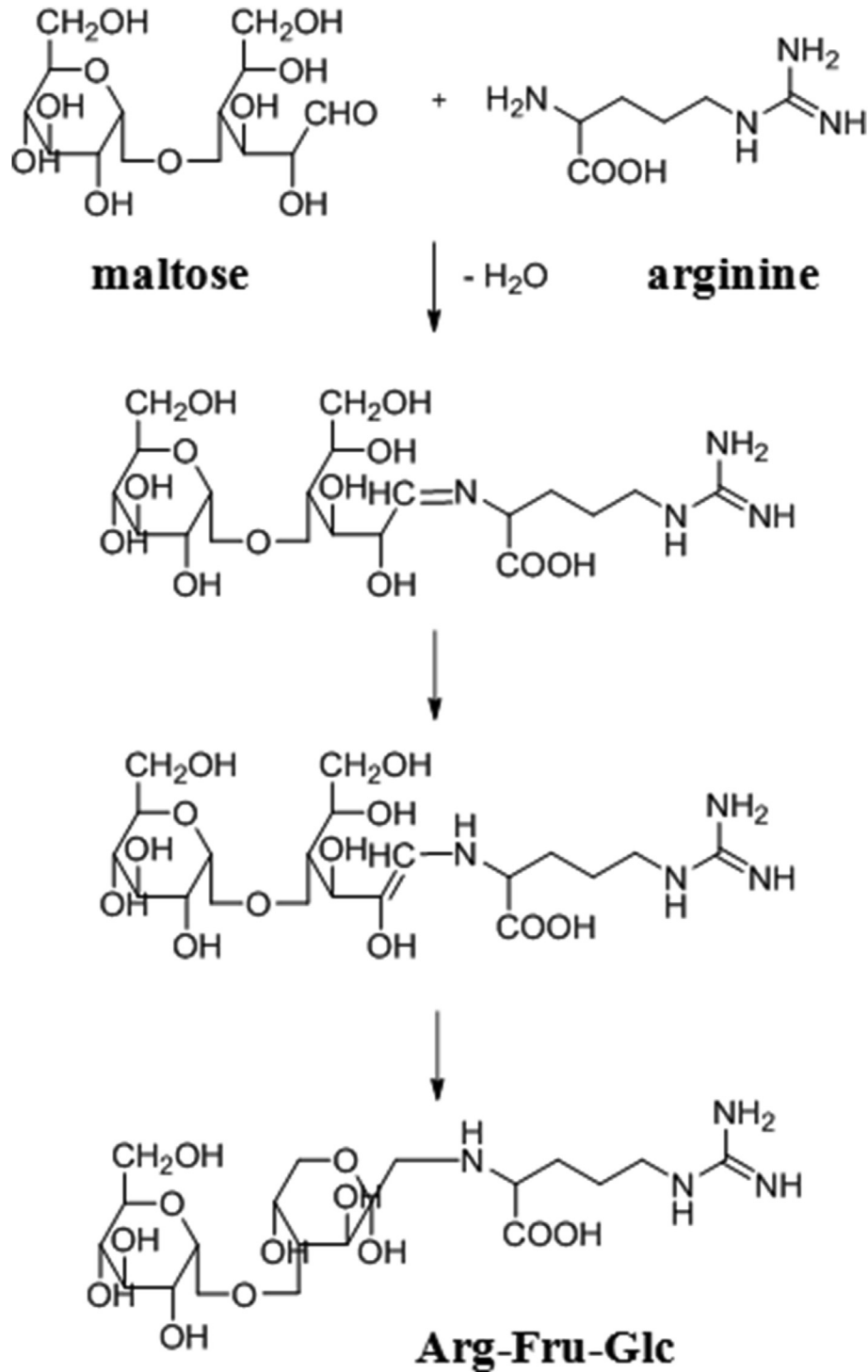
Fig. 1. The process by which AFG is produced in the red ginseng manufacturing process. AFG, arginine-fructose-glucose; Arg, arginine; Fru, fructose; Glc, glucose; H, hydrogen, N, nitrogen, OH, hydroxide; CH_2OH, hydroxymethyl; O, oxygen; CHO, aldehyde; H_2N, amidogen-d2; COOH, carboxylic acid; H_2O, water.

extract and Korean Red Ginseng polysaccharide and saponin fractions were administered orally for 14 days in mice infected with influenza A and uninfected controls, the survival rate in the group infected with influenza was 78% higher if they received the polysaccharide fraction, 67% if they received the water extract, and 56% if they received the saponin fraction, indicating that the polysaccharide fraction has the greatest survival benefits. Notably, the polysaccharide fraction was also the most effective at reducing the accumulation of TNF-α/inducible nitric oxide synthase (iNOS)-producing dendritic cells in the mouse lung [58]. Accordingly, the polysaccharide component is attracting attention as the main active ingredient of ginseng; more analyses and efficacy studies for physiologically active polysaccharide components are needed in

the future. Table 2 summarizes the physiological activity of polysaccharides.

3. Protein and peptide

The main nitrogen-containing compounds in Korean Red Ginseng are soluble proteins, peptides, and free amino acids; glycoproteins, amines, alkaloids, free nucleosides, and nucleic acid bases are also present in small quantities. In terms of research on the nitrogen-containing compounds in Korean Red Ginseng, although most of their chemical structures have been identified, there has been little research on their physiological activity. One reason for this is that most of the nitrogen-containing compounds in Korean Red Ginseng, such as amino acids, are primary metabolites that are commonly detected in other plants as well. Unlike saponins, which are secondary metabolites, the nitrogen-containing compounds are not unique to Korean Red Ginseng. Nevertheless, a correlation study on the traditional indicators of the quality of Korean Red Ginseng and on its chemical constituents has highlighted the importance of nitrogen-containing compounds in Korean Red Ginseng [59].

Around 60–90% of the nitrogen content in Korean Red Ginseng root (2–3% of the total content) is soluble nitrogen. Twenty percent of this is soluble protein that dissipates when the ginseng is boiled in water. Korean Red Ginseng protects against radiation, such as X-rays, and the active substance responsible for this is a non-saponin protein; specifically, it is reported to be a thermostable protein that is not denatured by heat, even when boiled in water [60]. Korean Red Ginseng proteins have been shown to provide strong protection against DNA injury caused by gamma-ray or ultraviolet irradiation [61–64]. The initial research on Korean Red Ginseng peptides began in the 1960s when Gstirner et al obtained five peptide fractions from soluble Korean Red Ginseng extract and showed that these fractions had diverse amino acid compositions representing at least 20 different amino acids; however, these peptides were not purified and their physiological activity was not studied [65]. In the late 1980s, there was more focus on the soluble components of Korean Red Ginseng and more research was conducted to evaluate the chemistry and pharmacological activity of the peptides in Korean Red Ginseng. Okuda et al found that Korean Red Ginseng contains adenosine and an acidic substance that inhibits epinephrine-induced lipolysis in adipose cells and stimulates insulin-mediated lipogenesis [66]. This acidic substance was identified as pyroglutamic acid [67]. Adenosine and pyroglutamic acid were demonstrated to act as selective modulators that suppress lipolysis but promote lipid synthesis from glucose. Furthermore, a novel amino acid derivative was discovered to be a physiologically active substance in Korean Red Ginseng. The chemical structure of this substance with a molecular weight of 498 ($C_{18}H_{34}N_4O_{12}$) is arginine-fructose-glucose (AFG), in which an arginine molecule is linked to a fructose molecule that in turn binds to a glucose molecule. In manufacturing red ginseng, the Amadori rearrangement occurs between arginine and maltose or in glucose production including the amino sugars AFG and AF (Fig. 1) during the heating process. As the final product of the Maillard reaction, maltol is produced from these amino sugars [12,14,68].

The decrease in free sugar and amino acid content in Korean Red Ginseng is due to the production of amino sugars followed by the formation of caramel coloring as a product of thermolysis [14]. In terms of physiological activity, these substances have been shown to exert anti-obesity effects via inhibiting the enzymatic activity of sucrase and maltase in the gastric mucosa, consequently suppressing the absorption of starch in the gastrointestinal tract [69]. These physiologically active substances constitute about 5% of

Table 3
The major amino acids found in Korean Red Ginseng

Amino acids	
Aspartic acid	Methionine
Threonine	Isoleucine
Serine	Leucine
Glutamic acid	Tyrosine
Glycine	Lysine
Alanine	Histidine
Valine	Arginine
Cystine	Proline

Korean Red Ginseng, which is a higher concentration than that of white ginseng; this is because of the heating process used to create red ginseng and the fact that the concentration of these substances is higher in thicker roots as they have more starch content than thinner roots [69].

Hyun et al reported that AFG-enriched extracts significantly increased the LPS content, concanavalin A-induced splenocyte proliferation, and both the immune cell count and antibody activity in cyclophosphamide-induced immune-deficient animals [70]. Shao et al also found that AFG had strong immune activity in cyclophosphamide-induced immune-deficient animals, promoting splenic lymphocyte transformation and increasing IL-2 production [71]. Moreover, it has been reported that AF and AFG may have anti-diabetic effects by inhibiting carbohydrate absorption in the stomach, thereby restricting the postprandial elevation of blood glucose [72]. After long-term AF administration to diabetic mice, Lee et al observed inhibited glucose absorption and a reduced hemoglobin A1c level, indicating improved postprandial hyperglycemia [73]. In a double-blind, placebo-controlled study of 60 Koreans with prediabetes or type 2 diabetes, blood glucose was measured after consuming an AF dose of 1500 mg/day for 6 weeks; there was a significant decrease in postprandial blood glucose [74]. When the antioxidant activity of AF and AFG was measured, both showed antioxidant effects by increasing the permeability of cell membranes and boosting the scavenging ability of peroxyl and hydroxyl radicals [12,75]. AFG has also been reported to be effective in the treatment of renal dysfunction [76]. Following the oral administration of 40 mg/kg or 80 mg/kg of AFG in animals, there was a decrease in serum creatinine and blood urea nitrogen levels and a considerable improvement of cisplatin-induced renal dysfunction. Interestingly, after pretreatment with AFG, all oxidative stress indices showed sustained improvement for 10 days reflecting that AFG attenuates the cascade initiation steps for nuclear factor kappa B signals and modulates the participation of the phosphatidylinositol 3-kinase/protein kinase B signal pathway, thereby reducing cisplatin-induced inflammation and apoptosis.

4. Amino acids

There are 24 amino acids in *P. ginseng*, and the composition of amino acids in Korean Red Ginseng varies slightly from report to report, but a characteristically high arginine content is a ubiquitous finding. The major amino acids found in Korean Red Ginseng are shown in Table 3.

The free amino acid content in Korean Red Ginseng is around 2% with arginine accounting for over 50% of the total amino acid content [77]. Arginine has been reported to have immune-enhancing effects. When arginine becomes a precursor of NO or iNO, it can promote the secretion of Th1 or Th2 cytokines [78,79]. Arginine plays an important role in the synthesis of proline (involved in wound healing and collagen synthesis) and polyamine, both of which are important for cell growth and proliferation.

Arginine is an essential amino acid for angiogenesis, hemodynamic maintenance, spermatogenesis, embryo survival, and fetal and neonatal growth. Moreover, dietary supplementation or intravenous administration of arginine enhances genital, cardiovascular, pulmonary, renal, gastric, hepatic, and immune function while also promoting wound healing and improving insulin sensitivity [80]. Pyroglutamic acid selectively modulated opposing metabolic pathways in rat adipocytes, inhibiting lipolysis and stimulating lipogenesis [67]. Given that Korean Red Ginseng contains a high concentration of arginine, which plays an important role in the body, and glutamic acid, which acts as a selective modulator, we anticipate more research on the physiological activity of amino acid derivatives from Korean Red Ginseng.

5. Nucleic acids

Korean Red Ginseng contains nucleic acids such as uracil, guanine, adenine, uridine, adenosine, cytidine, cytosine, thymine, and orotic acid [81]. Ando et al demonstrated the presence of adenosine in Korean Red Ginseng powder, which inhibits epinephrine-induced lipolysis and stimulates insulin-mediated lipogenesis from glucose [66]. Takaku et al found that adenosine inhibited lipolysis in rat adipocytes but stimulated lipogenesis [67]. In view of these results, adenosine was described as a "selective modulator". Table 4 summarizes the major physiological activity of red ginseng proteins, peptides, amino acids, and nucleic acids.

6. Alkaloids

Given that alkaloids tend to show physiological activity, even in small quantities, researchers have long been interested in knowing the presence of alkaloids in Korean Red Ginseng. In 1963, to identify anti-hypertensive agents in Korean Red Ginseng, choline was first isolated and identified from Korean Red Ginseng alcohol extract [82]. The alkaloids in Korean Red Ginseng are shown in Table 5.

Choline is a precursor of the cell membrane component lecithin and shows physiological activity in terms of suppressing fat accumulation, lowering blood pressure, and improving memory [83]. In 1986, as part of research on the non-saponins in Korean Red Ginseng, Han et al became interested in trace alkaloids in Korean Red Ginseng. They obtained a crude alkaloid fraction from the ether-soluble fraction, identified positive Dragendorff spots on thin-layer chromatograms, and, using column chromatography, purified 3 β-carboline alkaloids for the first time [32]. When alkaloids were added to cell culture medium, they inhibited DNA and total protein synthesis, thereby limiting cancer cell proliferation [84]. The alkaloid fraction showed protective effects against radiation by suppressing radiation-induced chromosome damage and promoting the repair and regeneration of injured cells [85,86]. The alkaloid fraction also mitigated the chronic mutagenic effects of

Table 5
The alkaloids found in Korean Red Ginseng

Components	
N-Formyl-1-methyl-β-carboline	Harman
1-Carbobutoxy-β-carboline	4-Methyl-5-thiazoleethanol
1-Carboethoxy-β-carboline	Spinacine
1-Carbomethoxy-β-carboline	Choline
1-(5-Hydroxymethyl-2-furyl)-β-carboline	α-Pyrrolidone
Norharman	

radiation by reducing the rate of double-stranded breaks in DNA, preventing cellular injury, and delaying the repair time of the slow component [87]. Table 6 summarizes the major physiological activity of Korean Red Ginseng alkaloids.

7. Polyacetylenes

The first study on the polyacetylene content in Korean Red Ginseng was performed in 1964 in Japan by Takahashi et al who obtained a fraction with a high boiling point (120–152°C) from Korean Red Ginseng ether extract and isolated the yellow oil panaxynol [29]. In 1980, Poplawski et al manufactured an alcohol extract of Korean Red Ginseng in Poland and identified panaxynol in the petroleum ether-soluble fraction of the extract [88], while Dabrowski et al (1980) isolated heptadeca-1-ene-4,6-diyn-3,9-diol [89]. Kitagawa et al subsequently isolated panaxyol, panaxynol, and panaxytriol from the ether-soluble fractions of white ginseng and Korean Red Ginseng in Japan and identified panaxytriol as a unique constituent of Korean Red Ginseng (Fig. 2) [90]. So far, more than 20 polyacetylene components have been reported from Korean Red Ginseng (Table 7).

Panaxydol, panaxynol, and panaxytriol are the best-known polyacetylenes; panaxydol and panaxynol account for over 90% of the total polyacetylene content. There have been several studies on their physiological activity, including research on inhibiting cancer cell proliferation and the mechanisms involved [31,91–95] as well as on inhibiting lipid peroxidation [96]. Panaxydol shows the strongest cytotoxicity against cancer cells [97]. Polyacetylenes have been shown to inhibit NO production in Raw 264.7 cells by blocking LPS-induced iNOS expression [98]. Panaxydol was reported to inhibit hypercholesterolemia in rats and mice fed a high-cholesterol diet [99], whereas panaxynol was shown to improve memory in a scopolamine-induced animal model of memory impairment [100]. Choi et al reported that polyacetylene (9R,10S)-epoxyheptadecan-4,6-diyn-3-one had an analgesic effect by inhibiting the sodium current in primary sensory neurons [101]. In another study, panaxydol was administered to mice to investigate whether it suppressed the formation of benzo(a)pyrene metabolite–DNA adducts in the liver; a clear decrease was noted in benzo(a)pyrene binding. This indicates that panaxynol and

Table 4
Physiological activity of proteins, peptides, amino acids, and nucleic acids

| Components	Physiological activity	Reference
Protein fraction	Protection against DNA injury	[61–64]
Peptide fraction	Lipolysis inhibition	[66,67]
Arginine-fructose-glucose	Anti-obesity effects	[69]
	Immune activity	[70,71]
	Anti-diabetic effects	[12,72–75]
	Kidney injury protection	[76]
Arginine	Immune activity	[78,79]
	Genital, cardiovascular, pulmonary, renal, gastric, hepatic, wound healing, and insulin sensitivity enhancement	[80]
Adenosine	Lipolysis inhibition and lipogenesis stimulation	[66,67,81]

Table 6
Physiological activity of alkaloids

Components	Physiological activity	Reference
Choline	Anti-hypertensive effect	[82]
	Suppression of fat accumulation, lowering blood pressure, and improving memory	[83]
Alkaloid fraction	Cancer cell proliferation inhibition	[84]
	Inhibition of DNA damage by radiation	[85–87]

panaxydol are effective in suppressing genetic mutations and oncogenesis [102].

These polyacetylenes show inhibitory effects on the proliferation of cancer cells at low concentrations but show cytotoxicity in healthy cells at much higher concentrations, indicating that they have cancer-specific cytotoxicity [102]. Panaxytriol, which is unique to Korean Red Ginseng, has been reported to inhibit cancer cell proliferation and to have antitumor effects in animal studies [103–105]. Lee et al observed that polyacetylenes were involved in the selective expression of enzymes that take part in benzo(a)pyrene (a chemical carcinogen) metabolism in the body [106]. Park et al administered polyacetylene compounds (20–40 μM/kg body weight) intraperitoneally to healthy mice for 3 days, consecutively, to assess toxicity; compared with a control group, the group that received the highest dose (40 μM/kg) showed a 17% decrease in body weight but no major changes in organ mass or liver tissue, whereas the group that received the lowest dose (20 μM/kg) showed a 10% decrease in body weight with an increase in the weight loss rate in the order of panaxydol < panaxynol < panaxytriol [107]. Choi et al found that the polyacetylene compounds in Korean Red Ginseng had an inhibitory effect on the micronucleus formation induced by various carcinogens [108]. Table 8 summarizes the major physiological activity of Korean Red Ginseng polyacetylenes.

8. Phenolic compounds

Han et al revealed that the phenolic compounds, in the non-saponin fraction, such as maltol, vanillic acid, salicylic acid, ferulic acid, and caffeic acid have strong antioxidant and anti-fatigue effects [109,110]. Furthermore, although these phenolic substances show strong antioxidant activity, purified ginsenosides show no
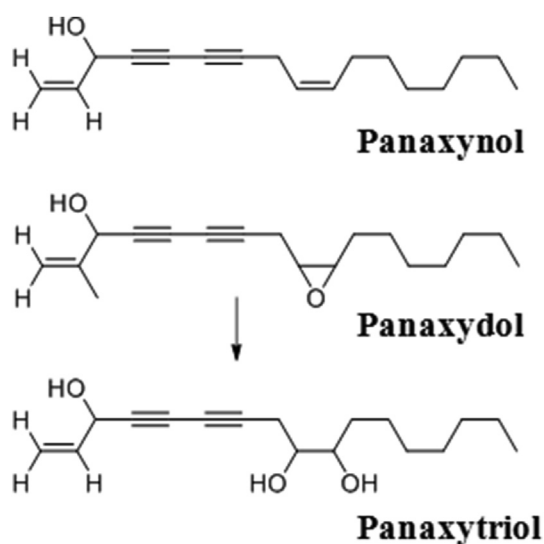
Fig. 2. The process by which panaxytriol is produced in the red ginseng manufacturing process. H, hydrogen, HO, hydroxide; O, oxygen.

such activity. Maltol is not detected in fresh ginseng; it is unique to Korean Red Ginseng, from which it is produced by heat during the steaming process [111]. During steaming, maltose reacts with amino acids to produce unstable 4-0-α-D-glucosyl-deoxy-2,3-diketosaccharide, with further cyclization of a 2-ketone group, and a C-6-hydroxyl group produces glycoside B; this substance undergoes further rearrangement and deglycosylation to produce the aglycone compound maltol [112]. This reaction is known to follow the Maillard reaction.

Maltol has neuroprotective effects in hypoxia-induced neuro-retinal cells; this effect is activated by nuclear factor kappa B and MAPK signaling pathways [113]. In a mouse model of carbon tetrachloride-induced liver injury, maltol showed a hepatoprotective effect by suppressing inflammation, reducing serum alanine transaminase and aspartate transaminase levels, and inhibiting cell apoptosis [114]. Similarly, in an animal model of alcohol-induced liver oxidative injury, maltol showed a hepatoprotective effect by increasing the activity of antioxidant enzymes [115]. Maltol has also been reported to have a protective effect against diabetic kidney injuries [116,117] as well as antioxidant effects [118–122]. Maltol ameliorated liver fibrosis by inhibiting the activation of hepatic stellate cells and inducing the apoptosis of activated hepatic stellate cells via the transforming growth factor-β1-mediated phosphoinositide 3-kinase/Akt signaling pathway [123].

In addition, p-coumaric acid, another phenolic compound in Korean Red Ginseng, inhibits platelet aggregation and suppresses the production of prostaglandins by modulating the metabolism of arachidonic acid [59]. p-Coumaric acid shows strong activity in terms of scavenging NO, hydroxide, and peroxynitrite [120–122]. It also increases cellular reactive oxygen species generation, superoxide dismutase activity, and glutathione levels [124]. Moreover, p-coumaric acid significantly lowers melanin levels, inhibits cellular tyrosinase activity, and reduces tyrosinase protein expression, thereby suppressing production of melanin [124]. Phenolic substances other than this component are not unique to red ginseng; thus, they cannot be considered distinct active ingredients that can represent the physiological activity of red ginseng. However, phenol is a meaningful component of the physiological activities of red ginseng. Table 9 summarizes the major phenolic compounds found in Korean Red Ginseng and Table 10 summarizes the major physiological activity of Korean Red Ginseng phenolic compounds.

9. Essential oils

Korean Red Ginseng contains several volatile compounds with low or high boiling points. The compounds with a low boiling point (71–110°C) include panacene, contributing to the distinctive aroma of Korean Red Ginseng, and β-elemene, a type of β-sesquiterpenoid [29]. To date, there have been almost no studies on the physiological activity of the compounds that produce the distinctive aroma of Korean Red Ginseng; however, they are an important element in terms of sensory quality [125]. These compounds can be broadly divided into earthy, woody, hay-like, toast-like, and sweet; moreover, there are differences between fresh, white, and red

Table 7
The major polyacetylenes found in Korean Red Ginseng

Components	
Panaxydol	Heptadeca-1,8-t-diene-4,6-diyn-3,10-diol heptadeca-1-ene-
Panaxynol	4,6-diyn-3,9-diol
Panaxytriol	10-Acetylpanaxytriol
Panaxyne	Panaxydol chlorohydrin
Panaxyne epoxide	Ginsenoyne A ~ K
Acetylpanaxydol	

ginseng depending on the processing methods used. The aroma of fresh ginseng is attributable to panacene, discovered in the initial studies of aroma compounds, as well as a complex mixture of several aroma-related compounds including methoxypyrazine and panasino A and B, which are sesquiterpene alcohols, and ginsenol [126]. Sensory evaluation of the Korean Red Ginseng aroma from different regions in the overseas Korean Red Ginseng market found that Korean Red Ginseng had a stronger aroma than Chinese red ginseng. Son et al investigated these differences by performing a pattern analysis of the major aroma-related compounds and a sensory evaluation of the fractions within these compounds using gas chromatography of the major headspace components in Korean and Chinese ginseng (both red and white) [127]. Specifically regarding characteristic patterns, among the aroma-related compounds identified, the mean β-patchoulene/ϒ- muurolene ratio was much higher in Korean Red Ginseng (≥1.0) than in Chinese ginseng (around 0.5) and Korean Red Ginseng had a stronger ginseng-like, toast-like, or sweet aroma. Park et al identified approximately 70 aroma-related compounds in fried red ginseng residue in distilled water and reported that the fragrant aromas, toasted rice, and refreshing aromas became stronger after frying whereas any unpleasant aroma was very weak [128].

10. Phytosterols

The main phytosterols in Korean Red Ginseng are stigmasterol [129] and β-sitosterol; these are mostly found in the unsaponifiable fraction [28]. There has been very little oil development from red ginseng because the compounds are present in such small quantities. However, Korean Red Ginseng oil (RGO) has recently been extracted and research is ongoing. Unlike typical plant oils, RGO has a very high linoleic acid concentration in fatty acids (18:2). The phytosterols in RGO include β-sitosterol, stigmasterol, and

campesterol; approximately 87.0% of the phytosterol content is β-sitosterol, differentiating RGO from other plant oils.

RGO promotes the production of peroxyl radicals, improves the scavenging ability of free radicals, and inhibits oxidative stress in HepG2 cells [130]. Bak et al administered RGO to HepG2 cells under hydrogen peroxide-mediated oxidative stress and in an animal model of carbon tetrachloride-induced liver injury; the restoration of activity and the expression of antioxidant enzymes such as peroxide dismutase, catalase, and glutathione peroxidase were observed [131]. RGO suppresses lipid peroxidation by directly eliminating reactive oxygen species and simultaneously inducing cellular antioxidant enzyme activity and expression via the inhibition of MAPK, thereby protecting cells and tissues from oxidative injury [131]. RGO was found to induce nuclear factor erythroid 2-related factor 2/antioxidant response element-mediated phase II enzymes via the apoptosis signal-regulating kinase 1-MAPK 4/7–Jun N-terminal kinase and p38 MAPK signaling pathways, suggesting that RGO has potential as a natural chemopreventive and cellular defensive agent [132].

RGO has also been demonstrated to have anti-inflammatory effects [133]. In a study on the protective effects of RGO against Aβ$_{25-35}$-induced oxidative stress and neuroinflammation, RGO protected against Aβ-induced cellular injury in an *in vitro* model of Alzheimer's disease [134]. RGO protects against *B. abortus* infection *in vitro* and *in vivo* and was found to be effective in the prevention and treatment of brucellosis [135]. RGO has shown a strong beneficial effect in terms of hair growth, so it demonstrates potential as an effective treatment for androgenetic alopecia [136]. Table 11 summarizes the major physiological activity of Korean Red Ginseng phytosterols.

11. Other trace compounds

The vitamins in Korean Red Ginseng include B-complex vitamins (thiamine [B1], riboflavin [B2], cobalamin [B12], niacin, biotin, pantothenic acid, and folic acid. Minerals in Korean Red Ginseng include manganese, copper, vanadium, cobalt, arsenic, germanium, phosphorus, aluminum, and nickel. Germanium has been shown to have anti-cancer activity and to promote a shift from aged cells to new cells [137]. Furthermore, the lignans gomisin-A and gomisin-N have been isolated from red ginseng [138]. Gomisin-A and gomisin-

Table 8
Physiological activity of polyacetylenes

Components	Physiological activity	Reference
Panaxydol	Cancer cell proliferation inhibition	[31,91,93–95,97]
	Lipid peroxidation inhibition	[96]
	NO production inhibition	[98]
	Hypercholesterolemia inhibition	[99]
	Analgesic effect	[101]
	Suppressing genetic mutation and oncogenesis	[102]
	Toxicity relief	[106–108]
Panaxytriol	Cancer cell proliferation inhibition	[31,92–95,103–105]
	Lipid peroxidation inhibition	[96]
	NO production inhibition	[98]
	Toxicity relief	[106–108]
Panaxynol	Memory improvement	[100]
	Suppressing genetic mutation and oncogenesis	[102]
	Toxicity relief	[106–108]

Table 9
The major phenolic compounds found in Korean Red Ginseng

Components	
Maltol	Gentisic acid
Salicylic acid	Cinnamic acid
Vanillic acid	Protocatechuic acid
p-Coumaric acid	m-Coumaric acid
Ferulic acid	Polyphenol
p-Hydroxybenzoic acid	Salicyl alcohol
Caffeic acid	p-Hydroxybenzyl alcohol

Table 10
Physiological activity of phenolic compounds

Components	Physiological activity	Reference
Maltol	Antioxidant activity	[111,118−122]
	Neuroprotective effects	[113]
	Hepatoprotective effect	[114,115,123]
	Kidney injury protection	[116,117]
p-Coumaric acid	Platelet aggregation inhibition	[59]
	Antioxidant activity	[120−122,124]

Table 11
Physiological activity of phytosterols

Components	Physiological activity	Reference
Korean Red Ginseng oil	Antioxidant activity	[130−132]
(including β-sitosterol,	Hepatoprotective effect	[131]
stigmasterol, and campesterol)	Anti-inflammatory effects	[133,134]
	Brucellosis infection prevention	[135]
	Hair growth	[136]

N are the substances responsible for the adaptogenic and anti-hepatotoxic effects of *Schisandra chinensis*.

12. Conclusion

The current knowledge on the effects of non-saponins in Korean Red Ginseng has been discussed and evaluated. The distinct bioactivity of Korean Red Ginseng was found not to originate from only one or two specific components but from both saponin and non-saponin components, suggesting that both components should be studied collectively. Since Korean Red Ginseng contains various ingredients, it shows various effects. Therefore, if a variety of efficacy is desired via ingesting Korean Red Ginseng, it is important to eat all of its various ingredients. So far, research on non-saponin components is very poor compared to that of saponins. Until now, the importance of non-saponins in Korean Red Ginseng was overlooked due to its structural complexity, the separation into single components, and purification difficulties. In the future, it will be necessary to standardize the analysis method for the non-saponin components discussed above; also, it will be essential to upgrade the bioactivity verification by methods incorporating the latest science and technology. There are many non-saponin components other than the non-saponins discussed above. The search for new non-saponin components is also considered indispensable.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

[1] Hu SY. The genus Panax (Ginseng) in Chinese medicine. Econ Bot 1976;30:11−28.
[2] Hu SY. The ecology, phytogeography and ethnobotany of ginseng. In: Proceedings of the 2nd international ginseng symposium. Seoul, Korea: Korea Ginseng Research Institute; 1978. p. 149−57.
[3] Presons WS. American ginseng, Green gold. Asheville, NC: Bright Mountain Book, Inc.; 1994. p. 16−30.
[4] Shin BK, Kwon SW, Park JH. Chemical diversity of ginseng saponins from Panax ginseng. J Ginseng Res 2015;39:287−98.
[5] Wang Y, Choi HK, Brinckmann JA, Jiang X, Huang L. Chemical analysis of Panax quinquefolius (North American ginseng): a review. J Chromatogr A 2015;1426:1−15.
[6] So SH, Lee JW, Kim YS, Hyun SH, Han CK. Red ginseng monograph. J Ginseng Res 2018;42:549−61.
[7] Christensen LP. Ginsenosides: chemistry, biosynthesis, analysis, and potential health effects. Adv Food Nutr Res 2009;55:1−99.
[8] Jiaoa L, Zhanga X, Wanga M, Li B, Liua Z, Liu S. Chemical and anti-hyperglycemic activity changes of ginseng pectin induced by heat processing. Carbohydr Polym 2014;114:567−73.
[9] Zhang YC, Li G, Jiang C, Yang B, Yang HJ, Xu HY, Huang LQ. Tissue-specific distribution of ginsenosides in different aged ginseng and antioxidant activity of ginseng leaf. Molecules 2014;19:1781−99.
[10] Blumenthal M, Goldberg A, Brinkmann J. Herbal medicine: expanded commission E monographs. Austin, TX: Integrative Medicine Communications; 2000. p. 170−7.
[11] Shan SM, Luo JG, Huang F, Kong LY. Chemical characteristics combined with bioactivity for comprehensive evaluation of Panax ginseng C.A. Meyer in different ages and seasons based on HPLC-DAD and chemometric methods. J Pharm Biomed Anal 2014;89:76−82.
[12] Kim GN, Lee JS, Song JH, Oh Ch, Kwon YI, Jang HD. Heat processing decreases Amadori products and increases total phenolic content and antioxidant activity of Korean Red ginseng. J Med Food 2010;13:1478−84.
[13] Matsuura Y, Zheng Y, Takaku T, Kameda K, Okuda H. Isolation and physiological activities of new amino acid derivatives from Korean Red ginseng. J Ginseng Res 1994;18:204−11.
[14] Matsuura Y, Hirao Y, Yoshida S, Kunihiro K, Fuwa T, Kasai R, Tanaka O. Study on Red ginseng: new ginsenosides and a note on the occurrence of maltol. Chem Pharm Bull (Tokyo) 1984;32:4674−7.
[15] Lee SM, Bae BS, Park HW, Ahn NG, Cho BG, Cho YL, Kwark YS. Characterization of Korean Red ginseng (Panax ginseng Meyer): history, preparation method, and chemical composition. J Ginseng Res 2015;39:382−91.
[16] Shibata S, Fujita M, Itowa H, Tanaka O, Ishii T. The structure of panaxadiol, a sapogenin of ginseng. Tetrahedron Lett 1962;10:419−22.
[17] Shibata S, Fujita M, Itokawa H, Tanaka O, Ishii T. Panaxadiol, a sapogenin of ginseng roots (1). Chem Pharm Bull (Tokyo) 1963;11:759−76.
[18] Shibata S, Tanaka O, Nagai M, Ishii T. Studies of the constituents of Japanese and Chinese crude drugs, XII. a sapogenin of ginseng root (2). Chem Pharm Bull (Tokyo) 1963;11:762−5.
[19] Shibata S, Tanaka O, Soma K, Iita Y, Ando T, Nakamura H. Studies on saponins and sapogenins of ginseng. The structure of panaxatriol. Tetrahedron Lett 1965;3:207−13.
[20] Shibata S, Tanaka T, Ando T, Sado M, Tsushima S, Ohsawa T. Chemical studies on oriental plant drugs (XIV). Protopanaxadiol, a genuine sapogenin of ginseng saponins. Chem Pharm Bull (Tokyo) 1966;14:595−600.
[21] Tanaka O, Nagai M, Ohsawa T, Tanaka N, Shibata S. Stereochemistry of protopanaxadiol. Tetrahedron Lett 1967;5:391−6.
[22] Nagai Y, Tanaka O, Shibata S. Structure of ginsenosede Rg1, a neutral saponin of ginseng root. Tetrahedron 1971;27:881−92.
[23] Sanada S, Konso N, Shoji J, Tanaka O, Shibata S. Studies on the saponins of ginseng I. Structures of ginsenosides Ro, Rb1, Rb2 Rc and Rd. Chem Pharm Bull (Tokyo) 1974;22:421−8.
[24] Kitagawa I. Chemical investigation of naturally occurring drug materials. Elucidation of scientific basis for traditional medicines and exploitation of new naturally occurring drugs. Yakugaku Zasshi 1992;112:1−4.
[25] Yuo CR, Yong JJ, Popovich DG. Isolation and characterization of bioactive polyacetylenes Panax ginseng Meyer roots. J Pharmaceut Biomed Anal 2017;139:148−55.
[26] Kitagawa I, Yoshikawa M, Yoshihara M, Hayashi T, Taniyama T. Chemical studies on crude drug precession. I. On the constituents of ginseng radix rubra (1). Yakugaku Zasshi 1983;103:612.
[27] Hiromichi O, Lee SD, Yukinaga M, Yinan Z, Takeshi T, Kenji K, Kumi H, Kazuhiro O, Osamu T, Toshiie S. Biological activities of non-saponin compounds isolated from Korean Red ginseng. J Ginseng Res 1990;14:157−61.
[28] Horhammer L, Wagner H, Lay B. Contents of Panax ginseng root, preliminary report. Pharm Ztg 1961;106:1307−12.
[29] Takahashi M, Yoshikura M. [Studies on the components of Panax ginseng C.A. Meyer. V. On the structure of a new acetylene derivative "Panaxynol" (3). Synthesis of 1,9-(cis)-heptadecadiene-4,6-diyn-3-ol]. Yakugaku Zasshi 1966;86:1053−6. Article in Japanese.
[30] Woo LK, Suh CS, Chang JJ, Shin KH. Presence of α-pyrrolidone in ginseng extracts. Yakhak Hoeji 1969;13:121.
[31] Shim SC, Koh HY, Han BH. Polyacetylene compounds from panax ginseng CA Meyer. Bull Korean Chem Soc 1983;4:183−8.
[32] Han BH, Park MH, Han YN, Woo LK. Alkaloidal components of Panax ginseng. Arch Pharm Res 1986;9:21.
[33] Ovodov YS, Solov'eva TF. Polysaccharides of panax ginseng. Chem Nat Compd 1966;2:243−5.
[34] Tomoda M, Shimada K, Konno C, Sugiyama K, Hikino H. Partial structure of panaxan A, a hypoglycaemic glycan of Panax ginseng roots. Planta Med 1984;50:436−8.
[35] Tomoda M, Shimada K, Konno C, Hikono H. Structure of panaxan B, A, hypoglycemic glycan of Panax ginseng roots. Phytochemistry 1985;24. 2431−23.
[36] Konno C, Sugiyama K, Kano M, Takahashi M, Hikino H. Isolation and hypoglycaemic activity of panaxans A, B, C, D and E, glycans of Panax ginseng roots. Planta Med 1984;50:434−6.
[37] Konno C, Murakami M, Oshima Y, Hikino H. Isolation and hypoglycemic activity of panaxans Q, R, S, T and U, glycans of Panax ginseng roots. J Ethnopharmacol 1985;14:69−74.
[38] Konno C, Hikino H. Isolation and hypoglycemic activity of panaxans M, N, O and P, glycans of Panax ginseng roots. Int J Crude Drug Res 1987;25:53−6.

[39] Hikino H, Oshima Y, Suzuki Y, Konno C. Isolation and hypoglycemic activity of panaxans F, G and H, glycans of Panax ginseng roots. Jpn J Pharmacogn 1985;39:331—3.

[40] Oshima Y, Konno C, Hikino H. Isolation and hypoglycemic activity of pan-axans I, J, K and L, glycans of Panax ginseng roots. J Ethnopharmacol 1985;14:255—9.

[41] Ng TB, Yeung HW. Hypoglycemic constituents of Panax ginseng. Gen Phar-macol 1985;16:549—52.

[42] Yang M, Wang BX, Jin YL, Wang Y, Cui ZY. Effects of ginseng polysaccharides on reducing blood glucose and liver glycogen. Zhongguo Yao Li Xue Bao 1990;11. 520—4. Chinese.

[43] Gao QP, Kiyohara H, Cyong JC, Yamada H. Chemical properties and anti-complementary activities of polysaccharide fractions from roots and leaves of Panax ginseng. Planta Med 1989;55:9—12.

[44] Lee DK, Kameda K, Takaku T, Keizo S, Kumi HH, Kazuhiro O, Osamu T, Hiromichi O. Effect of acidic polysaccharide of red ginseng on lipolytic action of toxohormone-L, from cancerous ascites fluid. Korean J Ginseng Sci 1990;14:1—5.

[45] Kim YS, Kang KS, Kim SI. Study on antitumor and immunomodulating ac-tivities of polysaccharide fractions from Panax ginseng: comparison of effects of neutral and acidic polysaccharide fraction. Arch Pharm Res 1990;13:330—7.

[46] Kim YS, Kang KS, Kim SI. Effects of Ginseng components on immunotoxicity of cyclophosphamide. J Ginseng Res 1991;15:13—20.

[47] Park KM, Kim YS, Jeong TC, Joe CO, Shin HJ, Lee YH, Nam KY, Park JD. Nitric oxide is involved in the immunomodulating activities of acidic poly-saccharide from Panax ginseng. Planta Medica 2001;67:122—6.

[48] Kim YS, Park KM, Shin HJ, Song KS, Nam KY, Park JD. Anticancer activities of red ginseng acidic polysaccharide by activation of macrophages and natural killer cells. Yakhak Hoeji 2002;46:113—9.

[49] Shin HJ, Kim YS, Kwak YS, Song YB, Kyung JS, Wee JJ, Park JD. A further study on the inhibition of tumor growth and metastasis by Red ginseng acidic polysaccharide (RGAP). Natural Product Sciences 2004;10:284—8.

[50] Shin HJ, Kim YS, Kwak YS, Song YB, Kim YS, Park JD. Enhancement of anti-tumor effects of paclitaxel (Taxol) in combination with Red ginseng acidic polysaccharide (RGAP). Planta Med 2004;70:1—6.

[51] Kwak YS, Kim SK, Shin HJ, Song YB, Park JD. Anticancer activities by com-bines treatment of red ginseng acidic polysaccharide (RGAP) and anticancer agents. J Ginseng Res 2003;27:47—51.

[52] Reyes AW, Simborio HL, Hop HT, Arayan LT, Min WG, Lee HJ, Rhee MH, Chang HH, Kim S. Inhibitory effect of red ginseng acidic polysaccharide from Korean Red ginseng on phagocytic activity and intracellular replication of Brucella abortus in RAW 264.7 cells. J Vet Sci 2016;17:315—21.

[53] Byeon SE, Lee J, Kim JH, Yang WS, Kwak YS, Kim SY, Choung ES, Rhee MH, Cho JY. Molecular mechanism of macrophage activation by red ginseng acidic polysaccharide from Korean Red ginseng. Mediators Inflamm 2012;2012:732860.

[54] Kwak YS, Kyung JS, Kim JS, Cho JY, Rhee MH. Anti-hyperlipidemic effects of red ginseng acidic polysaccharide from Korean Red ginseng. Biol Pharm Bull 2010;33:468—72.

[55] Du XF, Jiang CZ, Wu CF, Won EK, Choung SY. Synergistic immunostimulating activity of pidotimod and red ginseng acidic polysaccharide against cyclophosphamide-induced immunosuppression. Arch Pharm Res 2008;31: 1153—9.

[56] Choi HS, Kim KH, Sohn E, Park JD, Kim BO, Moon EY, Rhee DK, Pyo S. Red ginseng acidic polysaccharide (RGAP) in combination with IFN-gamma re-sults in enhanced macrophage function through activation of the NF-kappaB pathway. Biosci Biotechnol Biochem 2008;72:1817—25.

[57] Kim H, Kim HW, Yu KW, Suh HJ. Polysaccharides fractionated from enzyme digests of Korean Red ginseng water extracts enhance the immunostimu-latory activity. Int J Biol Macromol 2019;121. 913—20. Arch Pharm Res 2008;31:1153—1159.

[58] Yin SY, Kim HJ, Kim HJ. A comparative study of the effects of whole red ginseng extract and polysaccharide and saponin fractions on influenza A (H1N1) virus infection. Biol Pharm Bull 2013;36:1002—7.

[59] Park H, Cho BG, Lee MK. Nitrogen compounds of Korea ginseng and their physiological significance. J Ginseng Res 1990;14:317—31.

[60] Yonezawa M, Katoh N, Takeda A. Restoration of radiation injury by ginseng. II. Some properties of the radioprotective substances. J Radiat Res 1981;22: 336—43.

[61] Kim CM, Han GS. Radioprotective effects of ginseng proteins. Yakhak Hoeji 1985;29:246—52.

[62] Kim CM, Choi JE. Effects of radioprotective ginseng protein on UV induced sister chromatid exchanges. Arch Pharm Res 1988;11:93—8.

[63] Kim CM, Choi MK. DNA repair enhancement by radioprotective ginseng protein fraction. Yakhak Hoeji 1992;36:449—54.

[64] Kim CM. Mechanisms of the radioprotective activity of ginseng protein fraction. J Ginseng Res 1990;14:279—83.

[65] Gstirner F, Vogt HJ. On peptides in White Korean ginseng. Arch Pharm Ber Dtsch Pharm Ges 1966;299:936—44.

[66] Ando T, Muraoka T, Yamasaki N, Okuda H. Preparation of anti-lipolytic substance from Panax ginseng. Planta Med 1980;38:18—23.

[67] Takaku T, Kameda K, Matsuura Y, Sekiya K, Okuda H. Studies on insulin-like substances in Korean Red ginseng. Planta Med 1990;56:27—30.

[68] Matsuura Y, Zheng Y, Takaku T, Kameda K, Okuda H. Isolation and physio-logical activities of new amino acid derivatives from Korean Red ginseng. Korean J Ginseng Sci 1994;18:204—11.

[69] Matsuura Y, Zheng Y, Takaku T, Kameda K, Okuda H. Isolation and physio-logical activities of a new amino acid derivative from Korean Red ginseng. J Trad Med 1994;11:256—63.

[70] Hyun SH, Kim YS, Lee JW, Han CK, Park MS, So SH. Immunomodulatory ef-fects of arginine-fructose-glucose enriched extracts of Red ginseng. Korean Soc J Food Nutr 2018;47:1—6.

[71] Shao Y, Sun RH, Wang D, Li W, Zheng YN, Zhang J. The protective effect of arginyl-fructosyl-glucose against cyclophosphamide-induced immunosup-pression in mice. Acta Nutr Sin 2015;3. 022.

[72] Ha KS, Jo SH, Kang BH, Apostolidis E, Lee MS, Jang HD, Kwon YI. In vitro and in vivo antihyperglycemic effect of 2 Amadori rearrangement compounds, arginyl-fructose and arginyl-fructosyl-glucose. J Food Sci 2011;76:H188—93.

[73] Lee KH, Ha KS, Jo SH, Lee CM, Kim YC, Chung KH, Kwon YI. Effect of long-term dietary arginyl-fructose (AF) on hyperglycemia and HbA1c in diabetic db/db mice. Int J Mol Sci 2014;12(15):8352—9.

[74] Park SE, Kim OH, Kwak JH, Lee KH, Kwon YI, Chung KH, Lee JH. Anti-hyperglycemic effect of short-term arginyl-fructose supplementation in subjects with prediabetes and newly diagnosed type 2 diabetes: randomized, double-blinded, placebo-controlled trial. Trials 2015;16:521.

[75] Lee JS, Kim GN, Lee SH, Kim ES, Ha KS, Kwon YI, Jeong HS, Jang HD. In vitro and cellular antioxidant activity of arginyl-fructose and arginyl-fructosyl-glucose. Food Sci Biotechnol 2009;18:1505—10.

[76] Li RY, Zhang WZ, Yan XT, Hou JG, Wang Z, Ding CB, Liu WC, Zheng YN, Chen C. Arginyl-fructosyl-glucose, a major Maillard reaction product of Red ginseng, attenuates cisplatin-induced acute kidney injury by regulating nu-clear factor κB and phosphatidylinositol 3-kinase/protein kinase B signaling pathways. J Agric Food Chem 2019;67:5754—63.

[77] Cho EJ, Piao XL, Jang MH, Baek SH, Kim HY, Kang KS, Kwon SW, Park JH. The effect of steaming on the free amino acid contents and antioxidant activity of Panax ginseng. Food Chem 2008;107:876—82.

[78] Popovic PJ, Zeh 3rd HJ, Ochoa JB. Arginine and immunity. J Nutr 2007;137. 1681S—6S.

[79] Bronte V, Zanovello P. Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol 2005;5:641—54.

[80] Wu G, Bazer FW, Davis TA, Kim SW, Li P, Rhoads JM, Satterfield MC, Smith SB, Spencer TE, Yin Y. Arginine metabolism and nutrition in growth, health and disease. Amino Acids 2009;37:153—60.

[81] Hiyama C, Miyai S, Yoshida H, Yamasaki K, Tanaka O. Application of high-speed liquid chromatography and dual wave-length thin-layer chromatograph-densitometry to analysis of crude drugs: nucleosides and free bases of nucleic acids in Ginseng roots. Yakugaku Zasshi 1978;98:1132—7.

[82] Takatori K, Kato T, Ozaki M, Nakashima T. Choline in panax ginseng C. A. Meyer. Chem Pharm Bull (Tokyo) 1963;11:1342—3.

[83] Hou JP. The chemical constituents of Ginseng plants. Comp Med East West 1977;5:123—45.

[84] Woo LK, Nakamura Y, Donati L. Effect of Korean ginseng on the growth rate of cells. Arch Ital Patol Clin Tumori 1965;8:53—61.

[85] Cho CK, Kim TH, Yoo SY, Koh KH, Kim MS, Kim JH, Kim SH, Yoon HK, Ji YH. The effects of alkaloid fraction of Korean ginseng on the radiation-induced DNA strand breaks. J Korean Soc Ther Radiol 1995;13:113—20.

[86] Kim SH, Cho CK, Yoo SY, Koh KH, Yun HG, Kim TH. In vivo radioprotective activity of Panax ginseng and diethyldithiocarbamate. Vivo 1993;7:467—70.

[87] Yoo SY, Cho CK, Kim MS, Yoo HJ, Kim SH, Kim TH. An experimental study of radioprotective effect of ginseng alkaloid fraction on cellular damage. J Radiat Protection Res 1997;22:195.

[88] Poplawski Z, Wrobel JT, Glinka T. Panaxydol, a new polyacetyleneic epoxide from Panax ginseng roots. Phytochemistry 1980;19:1539.

[89] Dabrowski Z, Wrobel JT, Wojtasiewicz K. Structure of an acetylenic com-pound from Panax ginseng. Phytochemistry 1980;19:2464.

[90] Kitagawa I, Taniyama T, Shibuya H, Noda T, Yoshikawa M. Chemical studies on crude drug processing. V. On the constituents of ginseng radix rubra (2): comparison of the constituents of white ginseng and red ginseng prepared from the same Panax ginseng root. Yakugaku Zasshi 1987;107:495—505.

[91] Ahn BZ, Kim SI. Relationship between structure and cytotoxic activity of panaxydol analogs against L1210 cells. Arch Pharm (Weinheim) 1988;321: 61—3. Article in Germany.

[92] Kim SI, Lee YH, Kang KS. 10-Acetyl panaxytriol, a new cytotoxic poly-acetylene from Panax ginseng. Yakhak Hoeji 1989;33:118—23.

[93] Kim YS, Shin II, Hahn DR. Effect of polyacetylene compounds from Panax ginseng on macromolecule synthesis of lymphoid leukemia L1210. Yakhak Hoeji 1989;32:137—40.

[94] Kim YS, Jin SH, Kim SI, Hahn DR. Studies on the mechanism of cytotoxicities of polyacetylenes against L1210 cell. Arch Pharm Res 1989;12:207.

[95] Kim DC, Lee JY, In MJ, Chae HJ, Hwang YK, Hwang WI. Effects of poly-acetylenes in ginseng on activity of enzymes related to post-translational modification of ras protein and effects of petroleum ether extract of ginseng on progression of cell cycle. J Ginseng Res 2001;25:156—61.

[96] Kim HY, Lee YH, Kim SI. Effects of polyacetylene compounds from Panax ginseng CA Meyer on CCl_4-induced lipid peroxidation in mouse liver. Toxicol Res 1988;4:13—22.

[97] Ahn BZ, Kim SI. [Relationship between structure and cytotoxic activity of panaxydol analogs against L1210 cells]. Arch Pharm (Weinheim) 1988;321: 61–3. Article in German.

[98] Ryu JH, Jang SR, Lee SY, Lee HJ, Han YN. Inhibitors of nitric oxide synthesis from ginseng in activated macrophages. J Ginseng Res 1998;22:181–7.

[99] Hyun HC, Park JK, Nam KY, Park KH. Hypocholesterolemic effect of panaxydol in high cholesterol diet fed rats and mice. J Ginseng Res 2001;25:162–6.

[100] Yamazaki M, Hirakura K, Miyaichi Y, Imakura K, Kita M, Chiba K, Mohri T. Effect of polyacetylenes on the neurite outgrowth of neuronal culture cells and scopolamine-induced memory impairment in mice. Biol Pharm Bull 2001;24:1434–6.

[101] Choi SJ, Kim TH, Shin YK, Lee CS, Park M, Lee HS, Song JH. Effects of a polyacetylene from Panax ginseng on Na+ currents in rat dorsal root ganglion neurons. Brain Res 2008;1191:75–83.

[102] Park JK, Kim SI. Inhibition of the formation of adducts between metabolites of benzo(a)pyrene and DNA by Panaxydol in vivo and in vitro. J Ginseng Res 1989;13:42–8.

[103] Matsunaga H, Katano M, Yamamoto H, Mori M, Takata K. Studies on the panaxytriol of Panax ginseng C. A. Meyer. Isolation, determination and antitumor activity. Chem Pharm Bull (Tokyo) 1989;37:1279–81.

[104] Matsunaga H, Katano M, Yamamoto H, Fujito H, Mori M, Takata K. Cytotoxic activity of polyacetylene compounds in Panax ginseng C. A. Meyer. Chem Pharm Bull (Tokyo) 1990;38:3480–2.

[105] Matsunaga H, Katano M, Saita T, Yamamoto H, Mori M. Potentiation of cytotoxicity of mitomycin C by a polyacetylenic alcohol, panaxytriol. Cancer Chemother Pharmacol 1994;33:291–7.

[106] Lee FC, Park JK, Ko JH, Lee JS, Kim KY, Kim CK. Effects of panax ginseng extract on the benzo(a)pyrene metabolizing enzyme system. Drug Chem Toxicol 1987;10:227.

[107] Park JK, Jin SH. The toxicological parameter assessment in experimental animals for various dosages of polyacetylene compounds. J Ginseng Res 1989;13:49–55.

[108] Choi SG, Heo MY. Anticlastogenic effect of petroleum ether extract of Panax ginseng against carcinogen-induced micromuclei in mice. Yakhak Hoeji 1992;36:334–40.

[109] Han BH, Park MH, Han YN. Studies on the antioxidant components of Korean ginseng (III). Arch Pharm Res 1981;4:53–8.

[110] Han BH, Park MH, Han YN. Chemical and biochemical studies on non-saponin constituents of Korean ginseng. J Ginseng Res 1992;16:228–34.

[111] Matsuura H, Hirao Y, Yoshida S, Kunihiro K, Fuwa T, Kasai R, Tanaka O. Study of red ginseng: new glucosides and a note on the occurrence of maltol. Chem Pharm Bull (Tokyo) 1984;32:4674–7.

[112] Li XG. Studies on the transforming mechanism of amino acid components in the course of ginseng processing. Korean J Ginseng Sci 1992;16:64–7.

[113] Song Y, Hong S, Iizuka Y, Kim CY, Seong GJ. The neuroprotective effect of maltol against oxidative stress on rat retinal neuronal cells. Korean J Ophthalmol 2015;29:58–65.

[114] Liu W, Wang Z, Hou JG, Zhou YD, He YF, Jiang S, Wang YP, Ren S, Li W. The liver protection effects of maltol, a flavoring agent, on carbon tetrachloride-induced acute liver injury in mice via inhibiting apoptosis and inflammatory response. Molecules 2018;23(9).

[115] Han Y, Xu Q, Hu JN, Han XY, Li W, Zhao LC. Maltol, a food flavoring agent, attenuates acute alcohol-induced oxidative damage in mice. Nutrients 2015;7:682–96.

[116] Kang KS, Ham J, Kim YJ, Park JH, Cho EJ, Yamabe N. Heat-processed Panax ginseng and diabetic renal damage: active components and action mechanism. J Ginseng Res 2013;37:379–88.

[117] Kang KS, Yamabe N, Kim HY, Yokozawa T. Role of maltol in advanced glycation end products and free radicals: in-vitro and in-vivo studies. J Pharm Pharmacol 2008;60:445–52.

[118] Yokozawa T, Kang KS, Yamabe N, Kim HY. Therapeutic potential of heat-processed Panax ginseng with respect to oxidative tissue damage. Drug Discov Ther 2007;1:30–44.

[119] Kang KS, Kim HY, Baek SH, Yoo HH, Park JH, Yokozawa T. Study on the hydroxyl radical scavenging activity changes of ginseng and ginsenoside-Rb2 by heat processing. Biol Pharm Bull 2007;30:724–8.

[120] Kang KS, Yokozawa T, Kim HY, Park JH. Study on the nitric oxide scavenging effects of ginseng and its compounds. J Agric Food Chem 2006;54:2558–62.

[121] Kang KS, Kim HY, Pyo JS, Yokozawa T. Increase in the free radical scavenging activity of ginseng by heat-processing. Biol Pharm Bull 2006;29:750–4.

[122] Kang KS, Tanaka T, Cho EJ, Yokozawa T. Evaluation of the peroxynitrite scavenging activity of heat-processed ginseng. J Med Food 2009;12:124–30.

[123] Mi XJ, Hou JG, Jiang Liu Z, Tang S, Liu XX, Wang YP, Chen C, Wang Z, Li W. Maltol mitigates thioacetamide-induced liver fibrosis through TGF-β1-mediated activation of PI3K/Akt signaling pathway. J Agric Food Chem 2019;67:1392–401.

[124] Jiang R, Xu XH, Wang K, Yang XZ, Bi YF, Yan Y, Liu JZ, Chen XN, Wang ZZ, Guo Xl. Ethyl acetate extract from Panax ginseng C.A. Meyer and its main constituents inhibit α-melanocyte-stimulating hormone-induced melanogenesis by suppressing oxidative stress in B16 mouse melanoma cells. J Ethnopharmacol 2017;208:149–56.

[125] Kim MW, Park JD. Studies on the volatile flavor components of fresh ginseng. J Ginseng Res 1984;8:22–31.

[126] Yoshihara K, Hirose Y. The sesquiterpenes of ginseng. Bull Chem Soc Jpn 1975;48:2078.

[127] Sohn HJ, Heo JN, Nho KB, Kim MW. A comparison of the composition of the major headspace volatiles between the Korean ginseng and the Chinese ginseng. J Ginseng Res 1997;21:196–200.

[128] Park MH, Sohn HJ, Jeon BS, Kim NM, Park CK, Kim AK, Kim KC. Studies on flavor components and organoleptic properties in roasted red Ginseng Marc. J Ginseng Res 1999;23:211–6.

[129] Chung BS. Studies on the oil soluble constituents of Korean ginseng -Part 1. On the composition of ginseng sterols. Korean J Pharmacog 1974;5:173–7.

[130] Shon MS, Kim JS, Song JH, Jang HD, Kim GN. Anti-oxidant activity of oil extracted from Korean Red ginseng and its moisturizing function. Kor J Aesthet Cosmetol 2013;11:489–94.

[131] Bak MJ, Jun MR, Jeong WS. Antioxidant and hepatoprotective effects of the Red ginseng essential oil in H2O2-treated HepG2 cells and CCl4-treated mice. Int J Mol Sci 2012;13:2314–30.

[132] Bak MJ, Truong VL, Ko SY, Nguyen XN, Jun M, Hong SG, Lee JW, Jeong WS. Induction of Nrf2/ARE-mediated cytoprotective genes by red ginseng oil through ASK1-MKK4/7-JNK and p38 MAPK signaling pathways in HepG2 cells. J Ginseng Res 2016;40:423–30.

[133] Bak MJ, Hong SG, Lee JW, Jeong WS. Red ginseng marc oil inhibits iNOS and COX-2 via NFκB and p38 pathways in LPS-stimulated RAW 264.7 macrophages. Molecules 2012;17:13769–86.

[134] Lee S, Youn K, Jeong WS, Ho CT, Jun M. Protective effects of Red ginseng oil against Aβ25-35-induced neuronal apoptosis and inflammation in PC12 cells. Int J Mol Sci 2017;18(10):2218.

[135] Reyes AWB, Hop HT, Arayan LT, Huy TXN, Park SJ, Kim KD, Min W, Lee HJ, Rhee MH, Kwak YS. The host immune enhancing agent Korean Red ginseng oil successfully attenuates Brucella abortus infection in a murine model. J Ethnopharmacol 2017;198:5–14.

[136] Truong VL, Bak MJ, Lee C, Jun M, Jeong WS. Hair regenerative mechanisms of Red ginseng oil and its major components in the testosterone-induced delay of anagen entry in C57BL/6 mice. Molecules 2017;8(9):E1505. 22.

[137] Lee MS, Lee JH, Kwon TO, Namkoong SB. Increment of germanium contents in Angelica keiskei Koidz. and Panax Ginseng G.A. Meyer by in vitro propagation. Korean J Medical Crop Sci 1995;3:251–8.

[138] Han BH, Huh BH, Lee IR. Lignan components from Panax ginseng C. A. Meyer. J Ginseng Res 1990;14:217–20.