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Mini-review article

Implications of red *Panax ginseng* in oxidative stress associated chronic diseases

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ABSTRACT

The steaming process of *Panax ginseng* has been reported to increase its major known bioactive components, ginsenosides, and, therefore, its biological properties as compared to regular *Panax ginseng*. Biological functions of red *Panax ginseng* attenuating pro-oxidant environments associated with chronic diseases are of particular interest, since oxidative stress can be a key contributor to the pathogenesis of chronic diseases. Additionally, proper utilization of various biomarkers for evaluating antioxidant activities in natural products, such as ginseng, can also be important to providing validity to their activities. Thus, studies on the effects of red ginseng against various diseases as determined in cell lines, animal models, and humans were reviewed, along with applied biomarkers for verifying such effects. Limitations and future considerations of studying red ginseng were been discussed. Although further clinical studies are warranted, red ginseng appears to be beneficial for attenuating disease-associated symptoms via its antioxidant activities, as well as for preventing oxidative stress-associated chronic diseases.

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1. Introduction

Panax ginseng Meyer root has been considered as a medicinal plant in Eastern countries for thousands of years, and has been widely used for its health promotion in various disease conditions [1]. *Panax ginseng* can be classified by its processing methods and include fresh ginseng, white ginseng (air-dried), red ginseng (steamed), and sun ginseng. Notably, red ginseng, which is harvested at 6 yr, steamed, and then further dried, is well known for its elevated content of ginsenosides, which are bioactive compounds [2,3]. Red ginseng also exhibits various biological activities against chronic diseases, such as diabetes mellitus, cancer, and cardiovascular disease [4,5].

Red ginseng is composed of saponin (generally known as ginsenosides) and nonsaponin, including polysaccharides. The main active components in red ginseng are ginsenosides containing triterpene and sugar moieties [3]. Ginsenosides can be divided into three groups depending on their structures: (1) the panaxadiol group, including Rb1, Rb2, Rb3, Rc, Rd, Rg3, and Rh2; (2) the panaxatriol group, including Re, Rf, Rg1, Rg2, and Rh1; and (3) the oleanolic acid group, including Ro, as shown in Fig. 1 [1]. The amount of ginsenosides vary according to harvest time, storage

condition, and processing methods [1]. Although there are other *Panax* species, such as *Panax notoginseng*, *Panax japonicus*, *Panax quinquefolius*, *Panax pseudoginseng*, and *Panax vietnamensis* as shown in Table 1, this review focuses on the biological activities of *Panax ginseng*.

2. Significance of proper determination of antioxidant activity

Certain levels of reactive oxygen species (ROS), such as superoxide, hydroxyl radical, and hydrogen peroxide, are necessary for crucial roles in differentiation, proliferation, and regulation of signal transduction in cells. ROS are constantly produced from mitochondria via the respiratory chain and the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, and can be eliminated by enzymatic and non-enzymatic ROS scavenging factors, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), thioredoxin, and NF-E2-related factor 2 (Nrf 2)-mediated expression of heme oxygenase 1 (HO-1), resulting in redox homeostasis [6,7]. However, impaired redox homeostasis results in excessive ROS, which is associated with the progression of several chronic

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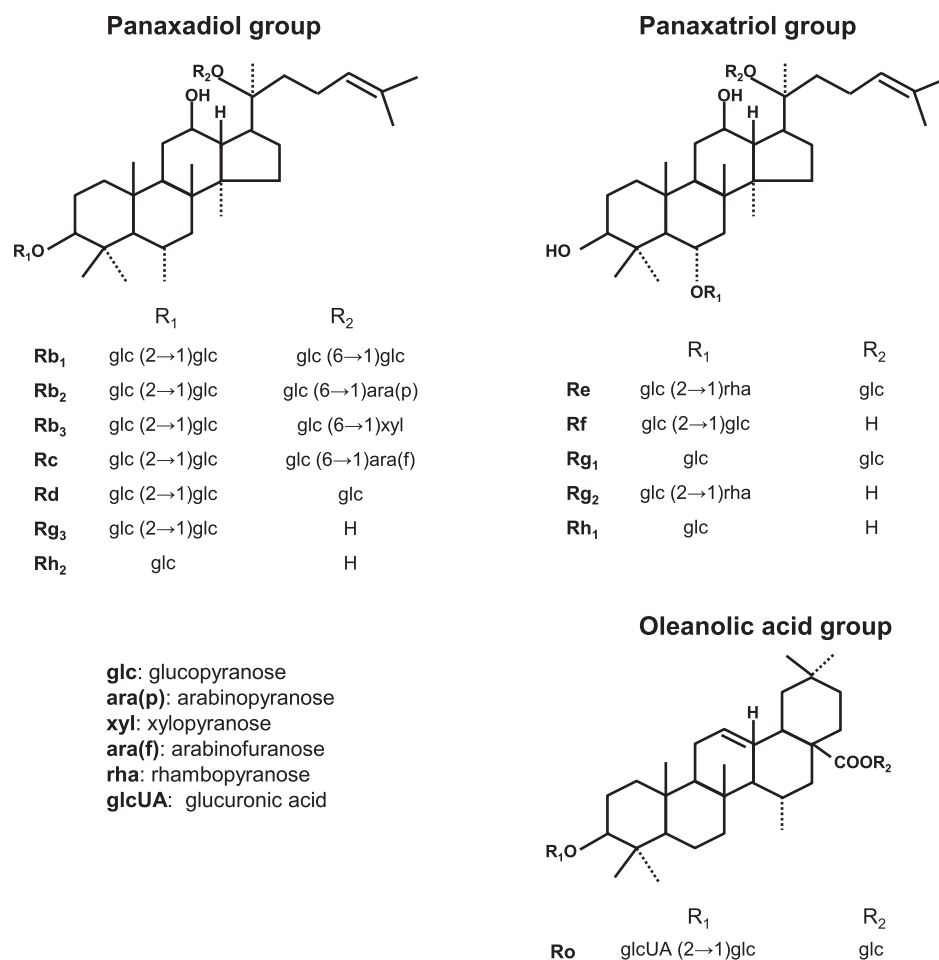


Fig. 1. Structures of ginsenosides. Ginsenosides of *Panax ginseng* are classified into three groups according to their structures: panaxadiol, panaxatriol, and oleanolic acid groups.

diseases, such as diabetes, cancer, Alzheimer's disease, and cardiovascular diseases [8]. For these reasons, reducing oxidative stress by increased antioxidant intake is an attractive strategy for the prevention of such chronic diseases [9].

Proper biomarkers for oxidative stress validate the efficacy of red ginseng for evaluating the risk of chronic diseases. ROS determination in cells can be achieved by treatment with 2',7'-dichlorofluorescein diacetate (DCF-DA). Oxidized DCF-DA is changed to 2',7'-dichlorofluorescein, which appears under fluorescence examination and can be detected by a microscope, flow cytometry, or microplate reader [10]. Oxidative modification of macromolecules (DNA, lipids, proteins, and carbohydrates) are used to assess levels of oxidative stress, because of the short-lived nature of ROS. Oxidation of the eighth guanine of DNA can be detected by 8-hydroxydeoxyguanosine (8-OHdG) in serum, urine, and tissue [11]. Additionally, phosphorylation of a histone H2A

variant (H2AX) at Ser19 [12,13] can be determined by immunoblotting and immunohistochemistry in tissues as a novel biomarker for DNA damage by estimating the number of double-strand breaks. Comet assays (single-cell gel electrophoresis) also have been used for determination of DNA damage [14], which is closely related to cancer incidence [15].

Isoprostanes (IsoPs) and malondialdehyde (MDA) are by-products of lipid peroxidation from arachidonic acid and polyunsaturated fatty acid (PUFA), respectively [16]. Measurement of IsoPs in the plasma and urine can be performed by LC-MS, GC-MS, radioimmunoassay, and enzyme-linked immunosorbance assays (ELISA). MDA levels can be quantified through a reaction with thiobarbituric acid (TBA), resulting in an MDA-TBA adduct that appears as colored end products. This process is known as a TBA-reacting substances (TBARS) assay [17]. Additionally, oxidized low-density lipoprotein (oxLDL) is associated with oxidative stress [16], and 4-hydroxy-2-nonenal (HNE) can be produced by oxygen attack on ω -6-PUFA, which can make adducts with other macromolecules [18]. The HNE forms a Michael adduct with Cys, Lys, and His residues on proteins, and these adducts serve as advanced lipoxidation/glycation end products that are closely associated with various chronic diseases, such as cardiovascular diseases, chronic obstructive pulmonary diseases, and neurodegenerative diseases [16,18,19]. The advanced glycation end products can bind to their receptors, resulting in promotion of inflammatory factor production, which in turn produces oxidative stress and irreversible

Table 1
Origins of *Panax* species

<i>Panax</i> species	Origin (habitat)
<i>Panax ginseng</i>	Korea, China, Japan
<i>Panax notoginseng</i>	China
<i>Panax japonicus</i>	Japan
<i>Panax quinquefolius</i>	Southern Canada, United States
<i>Panax pseudoginseng</i>	Nepal and eastern Himalayas
<i>Panax vietnamensis</i>	Vietnam

cellular dysfunction [20]. Additionally, protein modifications, such as nitrotyrosine and S-glutathionylation, can also be used as biomarkers for oxidative stress [16] (Fig. 2).

The antioxidant activity of red ginseng has been studied for several decades. Red ginseng water extracts were shown to scavenge free radicals, such as 1,1-diphenyl-2-picrylhydrazyl, hydroxyl, superoxide, and carbon-centered radical *in vitro* [21]. Additionally, red ginseng water extract decreased ROS-induced bacterial plasmid DNA-strand breaks *in vitro* [22]. The antioxidant function of red ginseng has been suggested for health benefits.

3. Assessment of antioxidant activities of red ginseng in cells

Due to the feasibility of diverse approaches, the antioxidant activities of red ginseng have been studied extensively in cells (Table 2). Red ginseng has a protective effect against cisplatin-induced ototoxicity [23], and pretreatment with red ginseng extract (2.5 mg/mL, major constituents: Rb1, Rg1) before inducing ototoxicity by cisplatin-attenuated apoptosis in HOI-OC1 auditory cells inhibited ROS production. Additionally, treatment with red ginseng extract (0.5 mg/mL) upregulated Nrf-induced HO-1 in polychlorinated biphenyl (PCB) 126-treated PC12 rat pheochromocytoma cells [24]. Red ginseng also rescues cells from oxidative stress by increasing the concentration of antioxidant enzymes, such as SOD, CAT, and GPx in hydrogen peroxide-treated HepG2 hepatoma cells, indicating cytoprotective effects in the liver [25]. Oxidative stress occurs following ethanol treatment in hepatocytes, leading to severe liver damage. Red ginseng (1–1,000 µg/mL) and its ginsenosides (Rg3 and Rh2 at 1–30 µg/mL) mitigated to the hepatocytic injury by increasing its antioxidant capacity [26]. The

underlying mechanism of antioxidant activities associated with red ginseng is due to the downregulation of ROS-stimulated mitogen-activated protein kinase (MAPK) and Akt pathways [24–26]. When ROS was induced by hydrogen peroxide, the saponin fraction of red ginseng (50–100 µg/mL) significantly decreased ROS detected by DCF-DA assay and MDA levels, as well as improved antioxidant enzyme activities. It was suggested that saponin in red ginseng prevents oxidative stress-induced hepatic diseases, and that the effects were stronger as compared with those of white ginseng extract [27]. Additionally, red ginseng extract (1 mg/mL) eliminated arachidonic acid + iron-induced oxidative stress in hepatocytes from diverse origins, including HepG2 (human), H4IIE (rat), and AML12 (mouse) cells. The inhibition of LKB1/AMP-activated protein kinases (AMPK) was reported to be a major mechanism associated with red ginseng antioxidant activity [28].

Studies of red ginseng in the area of neurodegenerative diseases have grown rapidly. Red ginseng water extract (0.3–3 mg/mL) blocked ROS generation and neuronal apoptosis, which was stimulated by glutamate, *N*-methyl-D-aspartate, or β-amyloid in rat cortical cells. These results implied the potential of red ginseng to aid in the prevention of neuronal diseases [29]. Additionally, red ginseng extract (0.01–1 mg/mL; major constituents: Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, and Rg3) was reported to have a neuroprotective effect on primary rat hippocampal neurons, where toxicity was induced by kainite, a glutamate analogue [30].

Helicobacter pylori has been studied as a causative bacteria that increases the risk of gastritis by triggering inflammation cascades. *H. pylori*-associated inflammation causes oxidative stress by recruiting neutrophils and macrophages to an infection site. Red ginseng extract (1–100 µg/mL; major constituents: Rb1, Rb2, Rc, Rd,

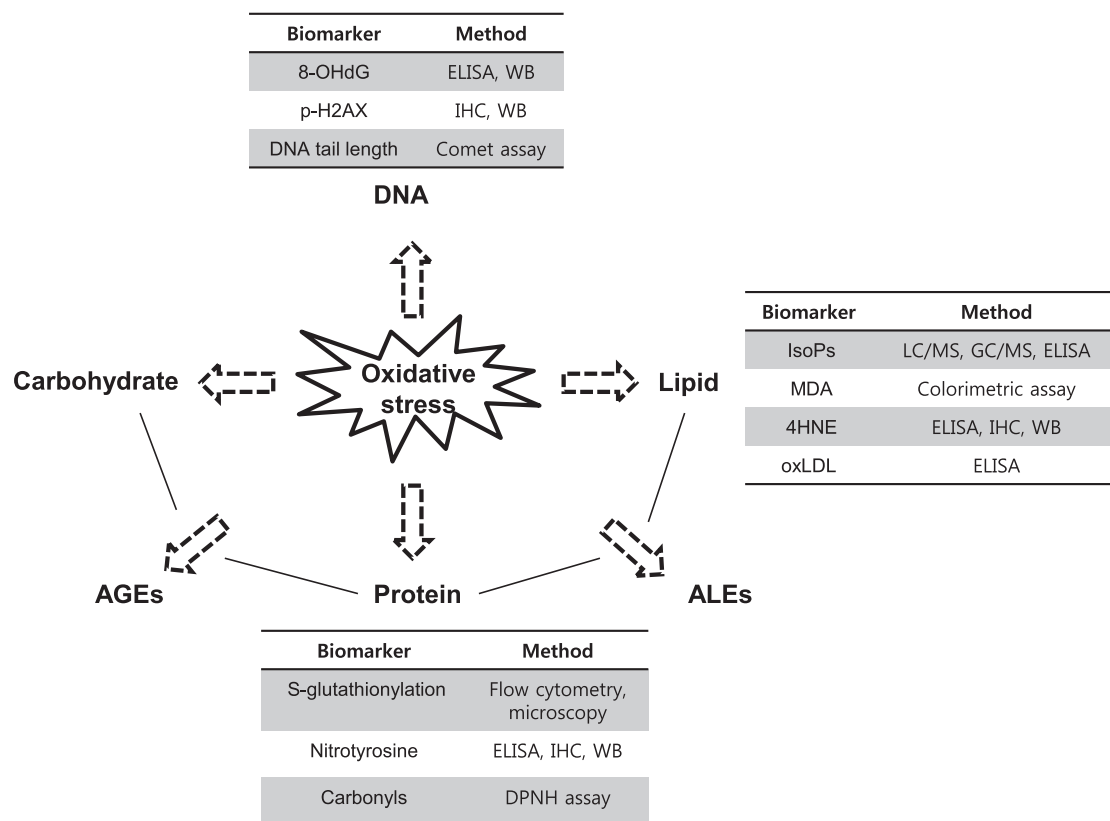


Fig. 2. Biomarkers for oxidative stress and their analytical methods. 4HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxydeoxyguanosine; AGEs, advanced glycation end products; ALEs, advanced lipoxidation end products; DPNH, 2,4-dinitrophenyl-hydrazine; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; IsoPs, isoprostanes; MDA, malondialdehyde; oxLDL, oxidized low-density lipoprotein; WB, western blot.

Table 2
List of studies showing antioxidant activity of red ginseng in cells

Disease model	Inducer	Cell line	Red ginseng type	Antioxidant biomarker	Ref
Ototoxicity	Cisplatin	HEI-OC1 (mouse auditory cell)	Red ginseng water extract	DCF ↓	23
Pheochromocytoma	PCB126	PC12 cell (rat adrenal gland)	Red ginseng extract	DCF ↓ GCLC, SOD, catalase ↑ Nrf2, HO-1 ↑	24
Hepatic disease	H ₂ O ₂	HepG2 cell (human hepatoma cell)	Red ginseng essential oil	DCF ↓ SOD, GPx, CAT ↑	25
Hepatic disease	Ethanol	TIB-73 cell (mouse hepatocyte)	Red ginseng water extract	DCF ↓ TBARS ↓	26
Hepatic disease	H ₂ O ₂	HepG2 cell (human hepatoma cell)	Rg3, Rh2 Red ginseng methanol extract	DCF ↓ MDA ↓	27
Hepatic disease	AA+ iron	HepG2 cell (human hepatoma cell) H4IIE (rat hepatoma cell) AML12 (mouse hepatocyte)	Red ginseng extract	DCF ↓ GPx, GR, CAT, SOD ↑ GSH ↑	28
Neurodegenerative disease	Glutamate NMDA β-amyloid	Rat cortical cell	Red ginseng water extract	DCF ↓	29
Neurodegenerative disease		Hippocampal Neuronal cell	Red ginseng extract	DCF ↓	30
Gastritis	Helicobacter pylori	AGS (human gastric epithelial cell)	Red ginseng water extract	DCF ↓ NADPH oxidase activity ↓	31
Oral mucositis	Radiation	HaCaT (human keratinocytes)	Red ginseng water extract	DCF ↓	32
Vascular disease	Acrolein	HUVECs (human umbilical vein endothelial cells)	Red ginseng water extract	DCF ↓	33
Vascular disease	H ₂ O ₂	HUVECs (human umbilical vein endothelial cells)	Red ginseng water extract	TRX1 ↑ DCF ↓	34
Diabetes	Cytokine	MIN6N8 (mouse pancreatic β-cells)	Red ginseng extract	DCF ↓	35

AA, arachidonic acid; CAT, catalase; DCF, 2',7'-dichlorofluorescein; GCLC, glutamate cysteine ligase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; HO-1, heme oxygenase 1; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; NMDA, N-methyl-D-aspartate; PCB126, polychlorinated biphenyls; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reacting substances; TRX, thioredoxin reductase.

Re, Rf, Rg1, Rg2, Rg3, and Rh1) reduced expression of inflammatory factors by suppressing NADPH oxidase activity and Jak2/Stat3 in AGS human gastric epithelial cells [31]. Furthermore, treatment with red ginseng (10–50 µg/mL) was beneficial to enhancing cell survival under radiation exposure by inhibiting ROS generation and activation of the MAPK signaling pathways [32].

In an *in vitro* model of vascular diseases, red ginseng extract (0.5–2 mg/mL) exhibited a protective effect on oxidative stress-induced cell death in endothelial cells by upregulating thioredoxin reductase 1 and downregulating ROS generation, p38, and PKC-δ expression in endothelial cells damaged by α,β-unsaturated aldehyde acrolein and hydrogen peroxide [33,34].

Furthermore, red ginseng extract (0–100 µg/mL) was effective at inhibiting cytokine-induced cell death by downregulating apoptosis cascades and ROS production in MIN6N8 cells and pancreatic β cells. In particular, ginsenosides at low concentrations of 0.1–1.0 µg/mL were responsible for such activity, introducing the possibility for red ginseng use in diabetic treatments [35].

4. Assessment of antioxidant activities of red ginseng in animal models

Aging is closely related to oxidative stress and is related to physiological status [36]. Therefore, various red ginseng studies evaluated biomarkers of oxidative stress in young versus aged animals, as well as sexual dysfunction and kidney dysfunction (Table 3). Aged rats fed red ginseng water extract (200 mg/kg/d; major constituents: Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg3, and Rh1)

exhibited a significant reduction in oxidative stress as determined by MDA, as well as elevated concentration of antioxidant factors, such as SOD, CAT, GPx, glutathione reductase (GR), glutathione-S-transferase (GST), reduced glutathione, vitamin C, and vitamin E in various organs [37].

As male adults become older, one physical problem is sexual dysfunction. Red ginseng intake (200 mg/kg/d) in aged rats restored sexual function as estimated by enhancement of both sperm maturation and impaired testicular functions. The underlying mechanism for these alterations was revealed to be due to the antioxidant functions of red ginseng. Rats fed with red ginseng also displayed reduced MDA levels, while enzymatic and non-enzymatic antioxidants were elevated [38]. Other symptoms observed in aging rats was renal dysfunction; however one study showed that red ginseng treatment (200 mg/kg/d; major constituents: Rg1, Rb1, Rg3, Re, Rc, Rb2, and Rd) rescued oxidative-stress damaged renal tissue as detected by 8-OHdG and advanced glycation end-product levels [39]. As listed in Table 3, red ginseng oil (10–50 mg/kg/d)-fed mice exhibited improvements in carbon tetrachloride (CCl₄)-damaged liver tissue following upregulation of antioxidant capacity, as well as downregulation of the MAPK pathway [25]. Additionally, rats administered 250mg/kg/d red ginseng extract prior to injection of aflatoxin B₁ to induce hepatocyte damage showed decreased apoptosis levels in liver tissue and elevated antioxidant enzyme levels [40]. Red ginseng extract treatment (250–500 mg/kg/d) also relieved symptoms of fatty liver induced by chronic exposure to ethanol. In this study, lipid peroxidation as determined by 4-HNE and oxidative-protein

Table 3

List of studies showing antioxidant activity of red ginseng in animals (rodents)

Disease model	Inducer	Red ginseng type	Antioxidant biomarker	Ref
Aging	12-mo old	Red ginseng water extract	MDA ↓ SOD, CAT, GPx, GR, GST ↑ GSH, Vit C, Vit E ↑	37
Age-related male sexual dysfunction	12-mo old	Red ginseng water extract	MDA ↓ SOD, CAT, GPx, GR, GST ↑ GSH, Vit C, α -tocopherol ↑	38
Age-related renal injury	HFD, D-galactose	Red ginseng	8-OHdG ↓ AGE ↓	39
Hepatic disease	CCl ₄	Red ginseng essential oil	TBARS ↓ SOD, GPx, CAT ↑	25
Hepatic disease	Aflatoxin B ₁	Red ginseng extract	SOD, CAT, GPx ↑ MDA ↓	40
Alcoholic liver disease	Ethanol	Red ginseng water extract	4-HNE ↓ Nitrotyrosine ↓	41
Diabetes	Streptozotocin	Fermented red ginseng extract	GSH ↑ MDA ↓ SOD, CAT, GPx, GR ↑	42
Diabetes	Cyclosporine	Red ginseng water extract	8-OHdG ↓	43
Gastric ulcer	Hydrochloride/Ethanol indomethacin	Red ginseng powered extract containing drug	TBARS ↓	44
High intensive exercise	Treadmill for 3 wks	HRG	MDA ↓ SOD ↑	45
Arthritis	Murine type II collagen	Red ginseng saponin extract	MDA ↓ Nitrotyrosine ↓ SOD, GSH, CAT ↑	46
Skin cancer	7,12-dimethylbenz(a)anthracene Croton oil	Red ginseng hydroalcoholic extract	GSH, SOD, CAT, Vit C ↑ TBARS ↓	47

4HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxydeoxyguanosine; AA, arachidonic acid; AGE, advanced glycation end product; CAT, catalase; DCF, 2',7'-dichlorofluorescein; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; HFD, high-fat diet; HRG, high pressure-treated red ginseng; HO-1, heme oxygenase 1; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; NMDA, N-methyl-D-aspartate; PCB126, polychlorinated biphenyls; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reacting substances; TRX, thioredoxin reductase; Vit, vitamin.

modifications evaluated by nitrotyrosine were both decreased. Furthermore, AMPK/Sirt1 levels were reported to be involved in the observed decrease in oxidative stress [41].

Fermented red ginseng extract (100–200 mg/kg/d) treatment of diabetic rats exerted antioxidant effects, and red ginseng (0.2–0.4 mg/kg/d; major constituents: Rg1, Rb1, Rg3, Re, Rc, Rb2, Rd, Rf, Rh1, and Rg2) administration reduced cyclosporine-induced elevated 8-OHdG levels in mouse pancreas [42,43], indicating anti-diabetic effects.

Gastric ulcers can be induced by oral administration of hydrochloride in ethanol or indomethacin in mice. Red ginseng treatment (30–300 mg/kg/d) with these drugs resulted in a decrease in ulcer area and TBARS [44]. Interestingly, high temperature- and high pressure-treated red ginseng (100 mg/kg/d)-fed mice ameliorated exercise-induced oxidative stress as compared with commercial red ginseng extracts (100 mg/kg/d) [45].

When saponin was fractionated from red-ginseng crude extract and administered to mice with arthritis, the red ginseng saponin extract (10 mg/kg/d; major constituents: Rg3, Rk1, and Rg5) reduced not only inflammatory factors, but also lipid peroxidation and nitrotyrosine levels. Additionally, the recovery of antioxidant enzymes in the liver and kidney that had been damaged by oxidative stress was also observed [46]. Furthermore, red ginseng (25 mg/kg/d; major constituents: Rb1 and Rg1) reduced incidence of skin cancer induced by 7,12-dimethylbenz(a)anthracene and croton oil through antioxidant mechanisms [47].

5. Assessment of antioxidant activities of red ginseng in humans

Biomarkers that were utilized to determine antioxidant activities of red ginseng in humans are listed in Table 4. Three grams of red ginseng per day and 6 g/d of red ginseng were randomly

allocated to healthy participants for 8 wk along with a placebo. The participants that ingested red ginseng displayed elevated levels of antioxidant enzymes that were greater than the placebo group, along with decreased levels of DNA damage (detected by alkaline comet assay) and lipid peroxidation (detected as oxLDL levels) [48].

Reduced estrogen levels in postmenopausal women are associated with high-risk of cardiovascular diseases. Postmenopausal women who ingested 3 g/d of red ginseng for 12 wk displayed higher concentrations of antioxidant enzymes relative to the placebo group. Furthermore, serum MDA levels were also reduced, although ingestion of red ginseng had no effect on serum 8-OHdG levels [49].

6. Limitations and perspectives

There have been limited studies on the antioxidant activity of red ginseng in humans. Although ginseng has been regarded as safe [50,51], several studies warned about adverse effects of red ginseng, including allergies and toxicity to the heart, kidney, liver, and reproductive organs [52]. Additionally, depending on the processing method, the amount and type of ginsenosides vary. Therefore, application of red ginseng in humans requires

Table 4

List of studies showing antioxidant activity of red ginseng in humans

Participants	Red ginseng type	Antioxidant Biomarker	Ref
Healthy participants	Capsule containing red ginseng	SOD, CAT, GPx ↑ DNA tail length ↓ oxLDL ↓	48
Postmenopausal women	Capsule containing red ginseng	SOD ↑ MDA ↓	49

CAT, catalase; GPx, glutathione peroxidase; MDA, malondialdehyde; oxLDL, oxidized low-density lipoprotein; SOD, superoxide dismutase.

development of a standard processing method and various other controlled conditions, such as proper daily dose duration and accurate determination of patient health status. As previously described, red ginseng is produced through a process of steaming and drying of white ginseng, resulting in improved stability and elevated ginsenoside content [53]. Despite its reported health benefits, studies on red ginseng are still limited in Asia, in contrast to worldwide studies on white ginseng. Therefore, further studies on the efficacy of red ginseng in Western countries and direct comparison with white ginseng regarding their reported functions are necessary.

In summary, red ginseng and ginsenosides, the major bioactive constituents in red ginseng, have biological functions ameliorating various disease symptoms via antioxidant mechanisms in cells and animals (especially in rodents). Although, there are limitations with respect to human studies on the effect of red ginseng, ingestion of red ginseng has also been shown to improve antioxidant activities in humans determined by various biomarkers of oxidative stress. Taken together, ingestion of red ginseng can be a preventive strategy against oxidative stress associated chronic diseases.

Conflicts of interest

None declared.

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