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Review article

The antioxidant activities of Korean Red Ginseng (*Panax ginseng*) and ginsenosides: A systemic review through *in vivo* and clinical trials

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ABSTRACT

A wide range of studies have steadily pointed out the relation of oxidative stress to the primary and secondary causes of human disease and aging. As such, there have been multiple misconceptions about oxidative stress. Most of reactive oxygen species (ROS) generated from chronic diseases cause oxidative damage to cell membrane lipids and proteins. ROS production is increased by abnormal stimulation inside and outside in the body, and even though ROS are generated in cells in response to abnormal metabolic processes such as disease, it does not mean that they directly contribute to the pathogenesis of a disease. Therefore, the focus of treatment should not be on ROS production itself but on the prevention and treatment of diseases linked to ROS production, including types 1 and 2 diabetes, cancer, heart disease, schizophrenia, Parkinson's disease, and Alzheimer's disease. In this regard, Korean Red Ginseng (KRG) has been traditionally utilized to help prevent and treat diseases such as diabetes, cancer, inflammation, nervous system diseases, cardiovascular disease, and hyperlipidemia. Therefore, this review was intended to summarize *in vivo* animal and human clinical studies on the antioxidant activities of KRG and its components, ginsenosides.

1. Introduction

Oxidative stress is attributed to oxidation-reduction reactions in cells - a concept first presented in 1985, with approximately 150,000 relevant articles posted on PubMed. The human body, by itself, is constantly exposed to various types of free radicals such as reactive oxygen species (ROS). The unpaired electrons of reactive oxygen species cause the oxidation of cellular components [1]. Such oxidative stress affects the pathogenesis of a wide range of diseases, including dementia, diabetes, rheumatoid arthritis, and degenerative motor nervous system diseases [2]. Meanwhile, antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione-S-transferases (GSTs), alleviate the oxidative damage, reducing the possibility of the development of various diseases [3]. About this, others have reported that the intake of antioxidants can help alleviate symptoms of disease [4] (Table 1).

Ginseng has been traditionally used in Asia including Korea, China, and Japan for thousands of years not only as a nutritional tonic but also a medicine for various diseases such as immune disease, liver disease, and cancer. Moreover, multiple effects of ginseng have been scientifically proven through *in vitro, in vivo* and clinical research. Ginseng could be classified into fresh ginseng, white ginseng, and red ginseng. Korean Red Ginseng (KRG) has been manufactured in Korea for over a thousand years and used as a valuable medicinal ingredient for medical treatment in Asian countries such as Korea, China, and Japan. Recent clinical studies have revealed the KRG normalized the various antioxidant markers, thus suppressing intracellular oxidative stress [5]. In this review, we summarized the antioxidant activities of KRG, based on an animal and a human study.

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Table 1
Overview of antioxidatant effects in various diseases.

Subject type	State	Main Antioxidant effects of KRG	Type of Ginseng	Ref.
Animal (*in vivo*)	**Normal**	lipid peroxidation↓, oxygen free radical↓, CAT↑, GPx↑	G-Rb1 and G-Rg1	[7]
		lipid peroxidation↓, oxygen radical scavenging activity↑, MDA↓, CAT↑, GPx↑	G-Rb1 and G-Rg1	[8]
		Lipid peroxidation↓, DPPH radical scavenging activity↓	ginsenosides	[9]
		MDA↓, SOD↓, CAT↓, GR↑	total saponin	[10]
		SOD↑, H_2O_2↑, CAT↑, MDA↓	red ginseng	[11]
	Liver disease	oxygen radical scavenging activity↑	Korean red ginseng	[14]
		ALT↓, AST↓, ALP↓, urea↓, creatinine↓, uric acid↓, glucose↓, NO↓	ginseng	[15]
		lipid peroxidation↓	Korean ginseng	[16]
		ALT↓, AST↓, SDH↓, γ-GT↓, ALP↓, LDH↓, CYT P_{450}↓	Korean red ginseng	[17]
		SOD↑, CAT↑, GPx↑, serum 8-hydroxy-20-deoxyguanosine↓, AST↓, LDH↓	ginseng extracts	[19]
		SOD↑, CAT↑, lipid peroxidation↓	white and red ginseng extracts	[20]
		ALT↓, AST↓, MDA↓, SOD↑, CAT↑, GPx↑	Korean red ginseng	[21]
		ALT↓, AST↓, ALP↓, MDA↓, SOD↑, CAT↑, GPx↑	Panax ginseng	[22]
		lipid peroxidation↓, GSH↑, GST↑, GPx↑	Korean red ginseng	[23]
		acetaldehyde↓, γ-glutamylcysteine synthetase↑, GSH↑, GST↑, ALDH↑	Korean red ginseng	[25]
	Diabetes	GSH↑, MDA↓	Korean red ginseng	[27]
		blood glucose↓	wild ginseng	[28]
		blood glucose↓, t-cholesterol↓, triglyceride↓, MDA↓, GSH↑	G-Re	[29]
		ROS↓	ginseng extract	[30]
	Kidney disease	SOD↑, CAT↑, GPx↑, MDA↓, urea nitrogen↓, creatinine↓	G-Rd	[32]
		SOD↑, CAT↑, MDA↓	G-Rd	[33]
	Nerve disorder	GPx↑, MDA↓	Korean red ginseng	[41]
		MDA↓	Korean red ginseng	[42]
		ROS↓,	G-Rb2	[43]
		GSH↑, SOD↑	G-Rg1	[44]
	Vascular disease	MDA↓, SOD↑, CAT↑, GPx↑	Korean red ginseng	[45]
		SOD↑, CAT↑, GPx↑, MDA↓	Korean red ginseng	[46]
	Aging	GSH↑, GPx↑, GR↑, GSSG↓	G-Rd	[48]
		SOD↑, CAT↑, serum albumin↑, MDA↓	G-Rb2	[49]
		SOD↑, CAT↑, H_2O_2↓, MDA↓	ginsenoside	[50]
		MDA↓, AST↓, ALT↓, BUN↓, creatinine↓, SOD↑, CAT↑, GPx↑, GR↑, GST↑, GSH↑	Panax ginseng	[51]
		MDA↓, SOD↑, CAT↑, GPx↑, GR↑, GST↑	Korean red ginseng	[52]
	Others	SOD↑, CAT↑, peroxidase↑, lipid peroxidation↓	red ginseng extracts	[53]
		SOD↑, CAT↑, GPx↑, GSH↑, MDA↓	ginseng components	[54]
		MDA↓, GPx↑	white ginseng and red ginseng	[55]
		GR↑, CAT↑, GST↑	total saponins	[56]
Human (Clinics)	**Normal**	SOD↑, CAT↑, MDA↓, exercise time↑	Panax ginseng	[57]
		t-cholesterol↓, triglyceride↓, LDL↓, MDA↓, SOD↑, CAT↑	Panax ginseng	[58]
		ROS↓, MDA↓, GSH↑, GR↑	Panax ginseng	[59]
	Underlying diseases	8-hydroxydeoxyguanosine↓, carbonyl contents↓	Red ginseng	[60]
		SOD↑	Korean red ginseng	[61]
	Exercise stress	MDA↓	Red ginseng	[63]
		SOD↑, CAT↑, MDA↓	Red ginseng	[64]
		SOD↑, CAT↑, MDA↓	Red Panax ginseng	[65]

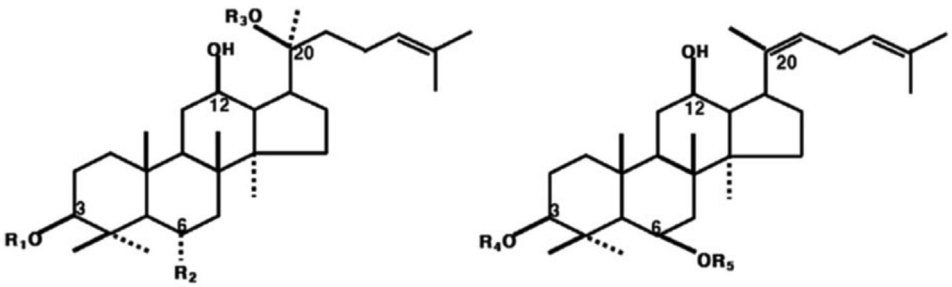
Abbreviation: superoxide dismutase (SOD), Catalase (CAT), malondialdehyde (MDA), 2,2-diphenyl-1-picrylhydrazyl (DPPH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), Glutathione disulfide (GSSG), glutathione (GSH), Aldehyde dehydrogenase (ALDH), low density lipoprotein (LDL), blood urine nitrogen (BUN), sorbitol dehydrogenase (SDH), Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), lactate dehydrogenase (LDH), reactive oxygen species (ROS), γ-GT (γ-Glutamyltransferase).

2. Free radicals and diseases

For the last 50 years, it has been known that free radical contributes to the development of diseases. When superoxide (O_2^-) is produced in cells and tissues, it can cause disease through harmful toxicity regardless of the cause. It is known that cytotoxic factor O_2^-, which is the cause of disease, is generated by the activation of granulocytes or macrophages, the decreased SOD activity and the abnormal intracellular metabolism. These free radicals induce intracellular lipid peroxidation, thereby resulting in the pathogenesis of a disease. In other words, increased intracellular lipid peroxidation is mainly known to be responsible for the development of various diseases from free radical-mediated toxicity to cell death [6].

3. Evaluation of KRG efficacy in animal study

Until now, about 200 ginsenosides have been known, including major ginsenosides (Rb1, Rb2, Rc, Rd, Re and Rg1, etc.) and minor ginsenosides (Rg3, Rh1 and Rh2, etc.). These ginsenosides are classified into two important groups such as protopanaxadiol (PPD) and protopanaxatriol (PPT), which have a four-ring hydrophobic steroid backbone with sugar but differ in the carbohydrate at C3, C6 and C20 positions (Fig. 1).



Protopanaxadiol(PPD) **Protopanaxatriol(PPT)**

Fig. 1. Chemical structures of gensenosides. Ginsenosides are classified into protopanaxadiol(PPD) and protopanaxatriol(PPT) with different groups at C3, C6, and C20.

An animal model subject to artificially induced oxidative stress was used to evaluate antioxidant activity in animals. When oxidative stress is artificially induced in animals, it causes various pathological conditions, such as hepatotoxicity, diabetes, and kidney disease. In addition, some studies have examined the antioxidant activities of KRG in healthy animals as well as animals exposed to oxidative stress. The experiments using animals according to the above criteria are explained as follows.

3.1. Antioxidant activities of KRG in healthy animal

The following studies have discussed the antioxidant activities of ginseng and ginsenosides in healthy animals. Zhang et al reported that when ginsenoside Rb1 was administered to rats and mice, lipid peroxidation in the brain was reduced, oxygen free radicals were removed, and the CAT and GPx activities increased [7]. According to Deng et al, the administration of ginsenoside to rats for three days inhibited the lipid peroxidation of rat liver and brain microsomes. In addition, it was reported that ginsenoside-Rb1 removed oxygen free radicals, inhibited the formation of malondialdehyde (MDA), and increased the CAT and GPx activities in the liver [8]. Jung et al also revealed that when ginsenosdies were bioconverted by the *Lactobacillus plantarum* KCCM11613P, fermented red ginseng exerted the antioxidant effect [9]. Kim et al showed that the intraperitoneal injection of ginseng total saponin (TS) in mice for five days resulted in a significant decrease in the total free radical and the MDA [10]. According to Sung et al, when 50 mg/kg KRG extracts (water or alcohol extract), fat-soluble fraction, TS, protopanaxadiol (PD) and protopanaxatriol (PT), were orally administered to ICR mice for 15 days, SOD activity increased the most in the fat-soluble extract-administered groups, followed by PD and the alcohol extract-administered groups [11].

3.2. Inhibition of oxidative damage by KRG of hepatotoxicity

The production of ROS plays a vital role in damage to the liver and the beginning of liver fibrosis. In addition, ROS stimulates the production of profibrogenic mediators in Kupffer cells and circulating inflammatory cells, directly activates hepatic stellate cells, and thus causes hepatic fibrosis [12]. Carbon tetrachloride (CCl_4) is experimentally used to induce liver fibrosis. Depending on the dose and duration, the effects of CCl_4 on hepatocytes can histologically range from fibrosis to death of liver tissue to liver cancer [13]. In this regard, Wee et al reported that when oxidative damage was induced with CCl_4 after administering KRG to rats, the necrosis of hepatocytes was significantly inhibited, and the removal of oxygen radicals from serum was significantly increased [14]. Moreover, El Denshary et al found that when KRG was administered to rats causing liver toxicity with CCl_4, the liver toxicity was alleviated in the KRG-administered group [15]. According to Kim et al, after administering panaxydol, panaxynol, and panaxatriol, which are polyacetylene compounds isolated from ginseng to rats inducing hepatotoxicity with CCl_4, the formation of lipoperoxides in the liver and the release of lactate dehydrogenase (LDH) were suppressed. In particular, panaxynol was reported to reduce the level of lipid peroxidation in the serum [16]. Also, Lee et al found that when hepatotoxicity was induced with CCl_4 and D-galactosamine after administrating KRG, the KRG pretreatment had the effect of inhibiting the activities of alanine aminotransferase (ALT), aspartate transaminase (AST), succinate dehydrogenase (SDH), γ-Glutamyl Transpeptidase (GT), Alkaline phosphatase (ALP), LDH, and cytochrome CYT P450 (microsomal enzyme system) in rats. In addition, the KRG pretreatment also suppressed the lipid peroxide content but increased the GSH content, the GST and the GR activities [17].

Acetaminophen (APAP), a widely antipyretic-analgesic agent, is known to be safe for medical purpose, but it can also damage the liver when taken in excess, to acute liver failure and death [18]. In a study by Saba et al, when 500 mg/kg KRG were administered to rats with oxidative stress with APAP for 7 days, the liver SOD, CAT and GPx activities were increased in the KRG group, while the levels of 8-hydroxy-2′-deoxyguanosine, AST, and LDH were decreased [19]. In addition, Seong et al reported that when acute liver failure was triggered by APAP, the SOD and CAT activities were increased, with the decreased lipid peroxide content in KRG group [20]. Moreover, Kim et al showed that when 250 mg/kg KRG was administered to rats for 4 weeks and then hepatotoxicity was induced with Aflatoxin B1, the serum ALT, AST, and MDA levels were decreased, while the SOD, CAT, and GPx activities were increased [21]. According to Abdelfattah-Hassan et al, the administration of 100 mg/kg KRG for 2 weeks to rats with hepatotoxicity induced by cyclophosphamide (CPh) led to a reduction in AST, ALT and ALP levels but an increase in the SOD, GPx, and CAT activities along with the decreased MDA level in liver tissues, all of which show the antioxidant activities of KRG [22]. In a study by Kim et al, hepatocarcinogenesis was induced by the diethylnitrosamine (DEN), following administering KRG to rats for 10 weeks. As a result, low levels of lipid peroxidation were observed in the 0.5% and 1% KRG groups, and the level of total GSH, the cytosolic GST and GPx activities were increased in 1% KRG group [23]. Alcohol promotes ROS production in the liver through many interferes with the body's defense mechanisms. Also, alcohol also facilitates the activity of the cytochrome P450, that contributes to ROS production [24]. In this regard, Lee et al found that after the administration of alcohol, the treatment of KRG improved the liver functions [25]. These results suggest that the KRG enhances the

effect of enzymes in breaking down alcohol and thus is effective in alleviating hepatotoxicity.

3.3. Inhibition of oxidative damage by KRG in diabetes

Oxidative stress plays a critical role in the development of diabetes complications related to microvessels and coronary vessels. Meanwhile, diabetes mellitus triggers excessive mitochondrial peroxide production in vascular endothelial cells and the myocardium, which leads to the activation of the main pathways involved in the pathogenesis of complications [26]. In relation to this, Ryu et al reported that when 30 mg/kg KRG were administered to rats with streptozotocin (STZ)-induced diabetes mellitus (NIDDM) for 30 days, the GSH and MDA levels were decreased close to those of the normal group [27]. Furthermore, Jung et al found that the administration of 40–200 mg/kg KRG to STZ-induced diabetic rats for 4 weeks resulted in a decrease in the blood glucose levels [28]. According to Cho et al, when 5, 10, and 20 mg/kg KRG extracts were administered to streptozotocin-induced diabetic rats for 2 weeks, the blood glucose, total cholesterol, triglyceride levels, and MDA content decreased, while the GSH level was increased [29]. In addition, Lim et al revealed that 4 week administration of KRG to tacrolimus (Tac)-induced diabetes mice exhibited the decreased formation of autophagosomes, the inhibition of lysosomal degradation, and an increase in beta cell viability and insulin secretion. In addition, they found that the mitochondrial dysfunction caused by Tac was improved in the KRG group, thereby reducing ROS production [30].

3.4. Inhibition of oxidative damage on kidney disease

It is known that the oxidative stress level is high in patients with chronic disease or hypertension caused by age, diabetes, and kidney disease [31]. Yokozawa et al reported that the oral administration of ginsenoside-Rd (1 and 5 mg/kg) to rats with ischemia-induced kidney injury resulted in an increases in the SOD, CAT and GPx activities. In contrast, the MDA, urea nitrogen, and creatinine concentrations in serum and kidney tissue were decreased [32]. In addition, it was found that 30-day oral administration of ginsenoside-Rd to rats with cisplatin-induced acute renal failure resulted in an increase in the SOD and CAT activities, with the decreased MDA levels in serum and renal tissue [33].

3.5. Inhibition of oxidative damage by KRG in neurological disorders

The central nervous system is particularly susceptible to oxidative damage because it has a high rate of oxygen utilization [34]. An animal model with paraquat-induced oxidative stress is often used to induce neurotoxicity. Paraquat is a nonselective herbicide widely used in North America and can cause fatal reactions in both animals and humans after acute exposure because of its high toxicity [35]. Exposure to paraquat increases cellular ROS production in the mitochondria, thus causing oxidative stress [36]. Previous studies have reported that there is a strong correlation between the degree of exposure to pesticide and the development of Parkinson's disease [37–39], and animal models used in recent studies also showed the neurotoxicity of paraquat [40]. With respect to paraquat-treated mice after the injection of the KRG fraction extract, the levels of hydrogen peroxide and MDA in tissues were decreased whereas the GPx activity was increased [41]. On the other hand, Hamid et al reported that when KRG were administered to rat with heat-induced oxidative stress, oxidative stress via BDNF and ER-β upregulation in the brain was decreased [42]. According to Kim et al, when Mongolian gerbils were treated with ginsenoside-Rb2 for neuroprotective effect, ginsenoside-Rb2 has decreased the cell damaged by the ischemic injury [43]. In addition, Chen et al showed that three-day administration of 5, 10, and 20 mg/kg KRG extracts resulted in an increase in the total SOD activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced Parkinson's disease mouse model [44].

3.6. Inhibition of oxidative damage by KRG in vascular disease

Ban et al reported that the administration of 100 mg/kg KRG extracts to the middle cerebral artery occlusion/reperfusion (MCAO/R) rat model for 7 days resulted in a decrease in lipid peroxidation levels but an increase in the GPx, SOD, and CAT activities [45]. Moreover, Lim et al found that when KRG extracts were administered to male pigs for 9 days, with myocardial infarction induced with isoproterenol, the SOD, CAT, and GPx levels were increased, while the MDA level was decreased [46].

3.7. Inhibition of oxidative damage by KRG in aging

ROS-mediated damage to mitochondrial DNA (mtDNA) is one of the main causes of aging. Oxidative damage affects the replication and translation of mtDNA and triggers mitochondrial dysfunction, consequently promoting ROS production and damage to mtDNA [47]. Yokozawa et al reported that one-month administration of 5 mg/kg ginsenoside-Rd to mice of accelerated cellular senescence led to an increase in the GSH content but a decrease in the GSSG content, in conjunction with increased GPx and GR activities [48]. According to Oh et al, the five-day injection of ginsenoside Rb2 to the senescence-accelerated mice (SAM-R/1) contributed to an increase in the SOD activities, CAT activities and the blood albumin but a decrease in the MDA content [49]. Kim et al showed that the oral administration of TS, PD, PT, ginsenoside-Rd, and compound K to 40-week-old mice resulted in an increased SOD and CAT activities [50]. A study of Ramesh et al showed a decrease in MDA level, AST, ALT, blood urine nitrogen and creatinine in the KRG-treated aged rats. In addition, it was revealed that KRG contributed to an increase not only in the amounts of SOD, CAT, GPx, GR and GST in the heart and lungs, but also in the GSH, vitamins C and E contents in the liver and kidney [51]. Kopalli et al also suggested that the MDA level was decreased when 200 mg/kg KRG water extract was administered to the aged rat model [52].

3.8. Other antioxidative effects by KRG

Besides, there are various ways of inducing oxidative stress in animals. Kim et al reported that the administration of KRG extracts to ICR mice with oxidative stress caused by systematic irradiation of γ-rays showed that the SOD, CAT and GPx activities were increased, whereas the lipid peroxide content was suppressed compared to the control group [53]. Kim et al found that the administration of ginseng components to ICR mice, followed by systematic γ-ray irradiation, resulted in the increases of the survival for 30 days, an increase in the SOD, CAT, and GPx activities and the GSH content level in the KRG-treated group [54]. In addition, Jeon et al showed that when ginseng extract was orally administered, the MDA content was decreased and the GPx activity was increased in high-fat diet-fed mice for 4 weeks [55]. Song et al also reported that the two-time administration of total saponin from red ginseng led to an increase in the GR, CAT and GST activities in the liver of pregnant rats [56].

4. Clinical trials

Several clinical studies have been conducted to evaluate the antioxidant activities of KRG in humans. Some human clinical studies have been carried out targeting healthy adult subjects or exercise-induced oxidative stress. In addition, others have evaluated the antioxidant activities of KRG in unhealthy subjects with oxidative stress induced by various causes in their bodies.

4.1. Antioxidant efficacy of KRG in healthy humans

According to Kim et al, when healthy males ingested 2 g of KRG extracts, 3 times a day for 8 weeks, the CAT and SOD activities were increased while the MDA level was decreased [57]. Kim et al reported that when young males ingested 6 g/day of KRG extracts for 8 weeks, the total cholesterol, triglyceride, and MDA levels were decreased, whereas the SOD and CAT activities were increased [58]. In addition, Kim et al suggested that when 82 healthy subjects (21 males and 61 females) ingested 1 or 2 g/day of KRG for 4 weeks, the ROS and MDA levels were significantly decreased in the blood, while the total GSH content and the GR activity were ameliorated in KRG group [59].

4.2. Antioxidant efficacy of KRG in adults with underlying disease

Unhealthy people, including cigarette smokers and patients with underlying conditions, usually are more susceptible to diseases than to healthy people. The antioxidant activities of KRG were evaluated on subjects with oxidative stress. Lee et al reported that when the smokers ingested 1.8 g of KRG daily for 4 weeks, the 8-hydroxydeoxyguanosine (8-OHdG) and carbonyl contents were decreased (8-OHdG: 31.7 % and carbonyl content: 21.3 %) [60]. According to Seo et al, when 45- to 60-year-old women experiencing menopause ingested 3 g/day of KRG for 12 weeks, the serum SOD activity was increased significantly [61].

4.3. Efficacy of KRG against the generation of free radicals during exercise

The oxygen demand of skeletal muscle increases during exercise, which triggers rapid changes in the blood flow to various organs. Such physiological changes that occur during exercise increases the production of free radicals, resulting in oxidative damage to different biomolecules in body [62]. Choi et al found that when young and elderly females ingested 2.7 g/day of KRG for 12 weeks, the MDA level in blood significantly was decreased following the course of exercise. This indicates that KRG intake has an antioxidant effect of removing accumulated lipoperoxides and inhibiting the formation of lipoperoxides on the elderly as well as young adults [63]. In a study by Lee et al, when 14 healthy young females ingested 3 g/day of KRG while exercising on a treadmill for 8 weeks, the SOD and CAT activities were significantly increased and the MDA concentration was decreased in the KRG intake group than the placebo group. Especially, the SOD and CAT activities were significantly increased and the MDA concentration was significantly decreased at that point in fourth and eighth weeks of KRG ingestion. Therefore, for harmful action of free radicals produced during exercise, KRG protects the body by inhibiting the generation of lipoperoxides and improving the activity of antioxidant enzymes (SOD and CAT) [64]. Park et al showed that when 18 male patients with non−insulin-dependent diabetes ingested 3 g/day of KRG for 12 weeks and performed aerobic exercises, the SOD and CAT activities significantly were increased, but the MDA level was decreased. This indicated that the intake of KRG during aerobic exercises by patients with diabetes could lead to positive improvement in antioxidant enzymatic changes [65].

5. Conclusion

Oxidative stress is the result of an imbalance between ROS production and antioxidant ability in the body. It can impair a series of cellular functions and thus cause various pathological conditions such as aging, cancer, and neurodegenerative diseases [66]. To respond to such oxidative stress, enzymatic antioxidant and nonenzymatic antioxidant systems have been developed in the body. Also, the ingestion of antioxidants can be another way of preventing oxidative stress. As KRG has a wide range of pharmacological effects and medical applications, it has an attractive attention from many researchers all around the world. This review paper is intended to summarize the results of recent studies in regard to the antioxidant activities of KRG and to describe its efficacy against various diseases in animals and human. For this purpose, we examined a wide range of researches to evaluate antioxidant activities based on animals and clinical researches. KRG is well known as substance with antioxidant activities, and many researches have been done to assess the antioxidant activities on the efficacy of KRG. In particular, clinical studies have been carried out with healthy subjects for the oxidative stress through exercise to determine the effect of KRG. In each situation, KRG normalized the biomarkers associated with oxidative stress. Specifically, KRG contributed to an increase in the activities of antioxidant enzymes SOD, CAT, and GPx, but a decrease in the level of MDA, a lipid oxidation marker. In the hepatotoxicity model, the administration of KRG reduced the indicators such as ALT, AST and ALP. Although there are many experimental results for antioxidant activities of KRG, *in vivo* studies can be applied to humans in the field of antioxidant, and out of these animal studies, some have been verified on human studies. Until now, the main reasons for the problem of ginseng research are that the absorption of ginsenosides, a component of KRG, are not clearly suggested and many ginsenosides can induce the synergistic effects in different pathways. Therefore, more clinical research on human subjects need to be carried out.

In conclusion, more studies for how antioxidant roles of KRG can be increased need to be conducted. Accordingly, extensive and in-depth researches of various ginsenosides focused on antioxidant activities will provide new insights into the clinical therapeutic applications of KRG.

Conflicts of Interest

The authors have declared no conflict of interest

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