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Short Review

# Effect of Korean Red Ginseng on metabolic syndrome

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ABSTRACT

Metabolic syndrome (MS) refers to a clustering of at least three of the following medical conditions: high blood pressure, abdominal obesity, hyperglycemia, low high-density lipoprotein level, and high serum triglycerides. MS is related to a wide range of diseases which includes obesity, diabetes, insulin resistance, cardiovascular disease, dyslipidemia, or non-alcoholic fatty liver disease. There remains an ongoing need for improved treatment strategies for MS. The most important risk factors are dietary pattern, genetics, old age, lack of exercise, disrupted biology, medication usage, and excessive alcohol consumption, but pathophysiology of MS has not been completely identified. Korean Red Ginseng (KRG) refers to steamed/dried ginseng, traditionally associated with beneficial effects such as anti-inflammation, anti-fatigue, anti-obesity, anti-oxidant, and anti-cancer effects. KRG has been often used in traditional medicine to treat multiple metabolic conditions. This paper summarizes the effects of KRG in MS and related diseases such as obesity, cardiovascular disease, insulin resistance, diabetes, dyslipidemia, or non-alcoholic fatty liver disease based on experimental research and clinical studies.


## 1. Introduction

Metabolic syndrome (MS) poses a major public-health challenge throughout the world. The prevalence of MS is about 35% and 24% among adults in the United States and in European countries, respectively [1]. MS is defined as the presence of three or more of the following traits: a) abdominal obesity with a waist circumference ≥40 inches in men and ≥35 inches in women; b) a triglyceride level ≥150 mg/dL; c) a high-density lipoprotein (HDL) cholesterol level ≤40 mg/dL in men or ≤50 mg/dL in women; d) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; or e) a fasting glucose ≥100 mg/dL [2].

*Abbreviations:* ACC, Acetyl-Coenzyme A carboxylase; ADP, adenosine diphosphate; AG, American ginseng extract; AGE, advanced glycation end product; Akt, protein kinase B; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AST, aspartate aminotransferase; BMI, body mass index; C/EBPα, CCAAT/enhancer-binding protein alpha; COX-2, cyclooxygenase-2; CPT, current perception threshold; CPT-1, carnitine palmitoyl transferase 1; CRP, C-reactive protein; CVD, Cardiovascular disease; DBP, diastolic blood pressure; DEN, diethyl nitrosamine; EAT, epididymis adipose tissue; EF, ejection fraction; FABP4, fatty acid binding protein 4; FAS, Fatty acid synthase; FFA, free fatty acid; FR, fine root concentration; FS, fractional shortening; GBHT, ginseng-plus-Bai-Hu-Tang; GLUT, glucose transporter type; GPx, glutathione peroxidase; GS, ginsenoside; GST, glutathione S-transferase; GST-P, glutathione S-transferase placental form; GTT, glucose tolerance test; HbA1c, glycosylated hemoglobin; HCC, hepatocellular carcinoma; HCEF-RG, hypotensive components-enriched fraction of red ginseng; HDL, high-density lipoprotein; HFD, High fat diet; HOMA-IR, homeostasis model assessment of insulin resistance index; I.P., intraperitoneal injection; IL, interleukin; iNOS, inducible nitric oxide synthase; IR, insulin resistance; ITT, insulin tolerance test; KRG, Korean Red Ginseng; LDL, low-density lipoprotein; Lex, lower extremities; LPL, lipoprotein lipase; MDA, malondialdehyde; MMP, Matrix metallopeptidases; MS, Metabolic syndrome; NAFLD, Non-alcoholic fatty liver disease; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cell, Natural killer cell; NMDA-NR1, N-methyl-D-aspartate NR1; NO, nitric oxide; NRF1, Nuclear respiratory factor 1; Nrf2, Nuclear factor erythroid 2-related factor 2; OLETF rat, Otsuka Long-Evans Tokushima fatty rat; PCG-1α, PPAR-γ coactivator-1α; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptors; PPD, protopanaxadiol; PPT, protopanaxatriol; REKRG, Rg3-enriched KRG; Rg3-KGE, Rg3-enriched KRG extract; ROS, Reactive oxygen species; SBP, systolic blood pressure; SCD, Stearoyl-Coenzyme A desaturase; SHR, spontaneously hypertensive rat; SREBP-1C, Sterol regulatory element-binding protein 1; STAT5, Signal transducer and activator of transcription 5; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; t-BHP, tert-butyl hyperoxide; TC, total cholesterol; TG, triglyceride; tGST, total glutathione; TNF, tumor necrosis factor; UCP, Mitochondrial uncoupling proteins; VLDL, very low-density lipoprotein.

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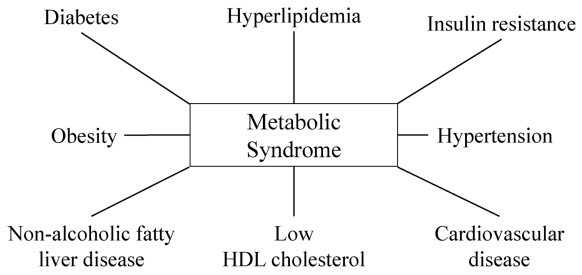


**Fig. 1.** Metabolic syndrome associated diseases.

Korean Red Ginseng (KRG) comes from the roots of *Panax ginseng* Meyer; first, the roots undergo a steam and dry process. This step purportedly enhances the ginseng's biological activity *via* chemical transformation, involving the production of certain metabolites [3]. KRG has often been used in traditional medicine in order to treat a number of metabolic conditions. The various ginsenosides which are the major constituents of ginseng have been demonstrated to have physiological and pharmacological activities which includes anti-inflammation and anti-cancer properties [4]. Moreover, a number of studies have suggested that KRG may have a beneficial effect on both acute and chronic liver disease [5]. KRG has been used to commonly to treat MS-related diseases in Korea [6]. This review establishes an overview of therapeutic potential of KRG in the context of metabolic syndrome and related diseases.

## 2. Metabolic syndrome

Since Gerald Reaven first characterized syndrome X, now known as metabolic syndrome, in 1988, risk factors such as hyperglycemia, hypertension, insulin resistance, decreased HDL cholesterol, and elevated very low-density lipoprotein (VLDL) and triglycerides have been studied for their role in various metabolic diseases [7]. It has been hypothesized that insulin resistance plays an integral role in the development of MS with visceral obesity, for which the waist phenotype is a central component [8]. However, the precise mechanism underlying of MS has remained obscure.

Ultimately, the importance of understanding the pathogenesis is that it may help identify people at high risk of MS-driven diseases including obesity, hyperlipidemia, type 2 diabetes and hypertension (Fig. 1) [9]. Obesity is characterized by an energy imbalance phenotype induced by an increase in ratio of calorie intake to energy expenditure. The prevalence of obesity in the adult has dramatically increased in the male population, and the related metabolic disorders which include atherosclerosis, dyslipidemia, and type 2 diabetes have become global health problems [10]. An excess of visceral fat accumulation can be considered a physical manifestation of the inability of subcutaneous fat tissue to sufficiently serve as an 'energy sink' when an individual has to manage a caloric surplus due to an excess in caloric intake and/or reduction in energy expenditure [11]. In obese people, the increased amount of adipose tissue is associated with increased release of glycerol, various hormones, pro-inflammatory cytokines, non-esterified fatty acids, glycerol, all of which may contribute to increased insulin resistance [12]. Plasma levels of C-reactive protein, an inflammatory marker of higher risk of myocardial infarction, are found to rise in patients with visceral obesity [13]. In addition, macrophage infiltration of adipose tissue plays a central role in the inflammatory signaling pathway [14]. Alteration of fatty acid metabolism and endocrine function caused by increase in visceral adipose tissue play a central role in the pathophysiology of MS.

Type 2 diabetes is a metabolic disorder, and is driven by insulin resistance and pancreatic β-cell dysfunction resulting from unresolved hyperglycemia [15]. When pancreatic β-cell dysfunction accompanies insulin resistance, the ability to control blood glucose levels is severely compromised. It can be said, then, β-cell dysfunction plays a key role when risk and the development of type 2 diabetes is to be defined [16]. The most widely accepted hypothesis to explain the development of MS centers around the problem of insulin resistance. Insulin resistance has traditionally been defined as the presence of a high glucose levels. However, postprandial hyperinsulinemia is known to occur even before fasting hyperinsulinemia is seen [17]. It is known that the excess of circulating fatty acids significantly contributes to the development of insulin resistance. Albumin-bound free fatty acids in plasma are mainly sourced from triglyceride stores in adipose tissues. In addition, fatty acids are produced via the lipoprotein lipase-catalyzed lipolysis of triglyceride-rich lipoproteins [18].

Across the globe, cardiovascular disease (CVD) stands as the leading cause of death. Per World Health Organization, CVD accounted for 30 percent of all deaths in the year 2005. Although often considered a disease that largely affects developed countries, the incidence in the developing world is increasing as well [19]. CVD most often results from vascular dysfunction as a consequence of atherosclerosis, thrombosis, or hypertension, all of which serve to compromise organ function. CVD includes a variety of diseases such as heart failure, peripheral vascular disease, coronary artery disease, and dyslipidemia [20]. Atherogenic dyslipidemia is characterized by increased levels of plasma triglycerides, increased number of small LDL (low density lipoprotein) particles, and reduced levels of HDL cholesterol levels [21]. Dyslipidemia has been reported to be the most common complication of MS and type 2 diabetes.

Though non-alcoholic fatty liver disease (NAFLD) is not a diagnostic criterion for MS, NAFLD and MS share risk factors and MS-related phenotypes such as obesity, diabetes, dyslipidemia, and hypertension. Genes related to blood pressure, triglycerides, glucose, insulin resistance, and low high-density lipoprotein regulate the progression of hepatic steatosis [22]. NAFLD, a spectrum of diseases encompassing steatosis, steatohepatitis, liver fibrosis and cirrhosis, is also the most frequent cause of liver function abnormalities worldwide [23]. NAFLD is intimately associated with insulin resistance, obesity, and MS [24].

## 3. Korean Red Ginseng

Korean ginseng (*Panax ginseng* Meyer) is one of the oldest and often used herbal remedies in traditional Asian medicine. KRG is a type of ginseng produced by the steaming and drying fresh ginseng to improve its therapeutic activities [25]. Saponins, major component of KRG, consist of triterpenoid glycosides of dammarane containing glucose, arabinose, xylose, or rhamnose [26]. Approximately, 150 ginsenoside saponins have been identified and are classified as Rb1, Rb2, Rc, Rd, Re, Rg1, and Rg3. Thirty-five ginsenosides have been extracted from fresh, white, or red ginseng. These include 20 (S)-ginsenoside-Rg3, ginsenoside-Rh2, Rs1, Rs2, Rs3, Rs4, and Rg5, in addition to notoginsenoside-R4 in the protopanaxadiol group, and 20(R)-ginsenoside-Rh1, ginsenoside-Rh4 and F4 in the protopanaxatriol group (Fig. 2) [26]. Ginsenosides Rg3 and Rg2 constitute the major components of KRG, whereas ginsenoside Rb1 and Rg1 constitute the major components of white ginseng [27].

Rg3, Rg1, Rd, and Rh2 have undergone investigation most extensively [28], and ginsenoside Rg3 in particular have been evaluated for its chemopreventive activity against a number of cancerous cell lines, including melanoma [29], colorectal cancer [30], ovarian cancer [31], prostate cancer [32], breast cancer [33], lung cancer [34], and HCC [35]. In a recent study, ginsenoside Rg3

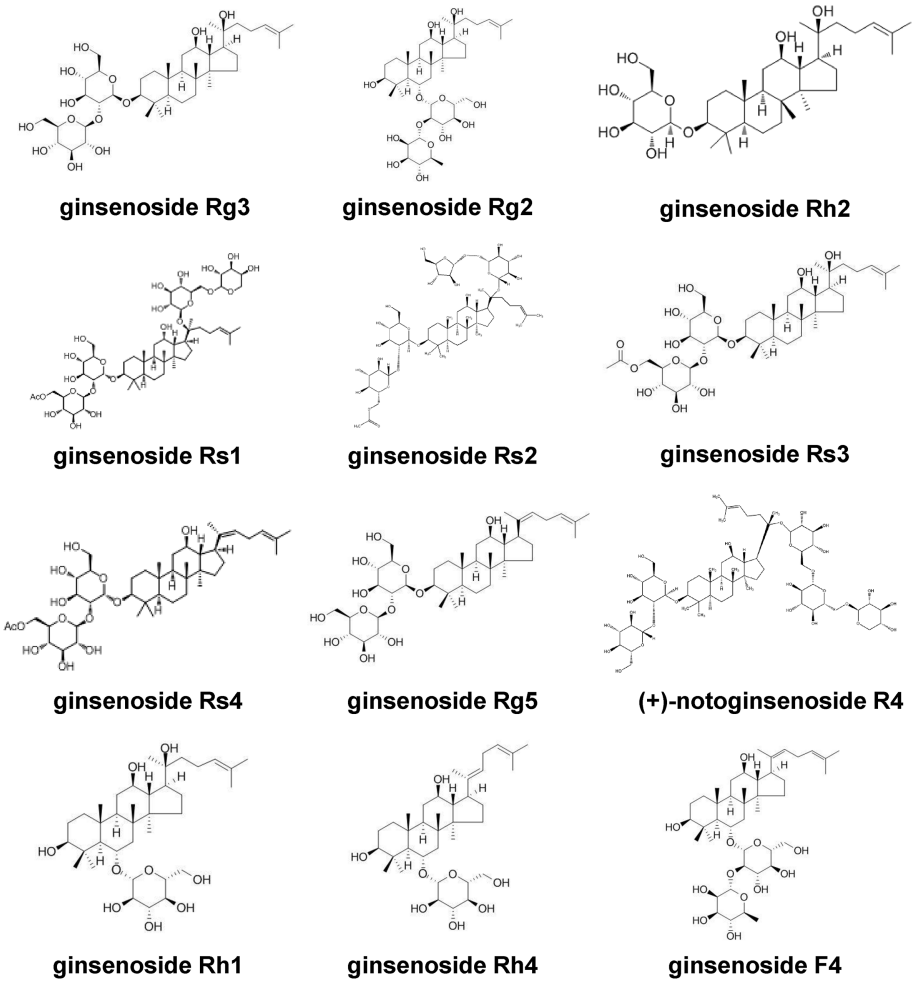


**Fig. 2.** The constituent parts of Korean Red Ginseng.

was shown to have significant anti-proliferative effects on liver cancer cells and inhibitory effects on *in vivo* HCC growth by preventing proliferation and inducing apoptosis [35]. In addition, ginsenoside Rg3 and its metabolite ginsenoside Rh2 was shown to have beneficial roles in general hepato-protection against hepatotoxins [36]. In tert-butyl hydroperoxide (t-BHP)-induced mice, orally administered ginsenoside Rg3 was shown to inhibit an increase in alanine transaminase and aspartate transaminase, and ginsenoside Rh2 was shown to potently prevent hepatotoxicity in t-BHP-induced liver damage model in mice [36]. Ginsenoside Rg2 significantly inhibits liver glucose production in HepG2 cells via activation of AMP-activated protein kinase pathway [37].

## 4. Metabolic syndrome and Korean Red Ginseng

KRG has been historically used as a folk remedy for the prevention and amelioration of various conditions associated with aging-related MS disorders, which include obesity, dyslipidemia, diabetes, and cardiovascular disease [38]. As growing number of studies have characterized the therapeutic effects of ginseng on the endocrine, central nervous, immune, and cardiovascular systems [39]. *P. quinquefolius* has been demonstrated to improve metabolic syndrome by regulating sugar and lipid metabolism, energy homeostasis, and lipoprotein secretion particularly in disease-prone states [40]. Treatment with fermented red ginseng significantly suppressed elevation of body weight, liver weight, epididymal fat weight, adipocyte size, and high-fat diet (HFD) induced fatty liver. Moreover, fermented red ginseng consumption had a significant impact in alleviating metabolic disturbances of hyperlipidemia and hypertension [41]. These results indicate that fermented red ginseng have great potential to ameliorate obesity, dyslipidemia, hypertension, and fatty liver.

### 4.1. Obesity

KRG was shown to improve obesity and dyslipidemia in HFD-fed mice, and it has been hypothesized that such effect was associated with downregulation of adipogenesis-related genes [10]. Body weight and adipose tissue mass of the mice treated with ginseng were found to be lower than those of control HFD-fed mice [42]. Ginseng was also demonstrated to inhibit adipocyte hypertrophy in HFD-fed obese mice. It was found that the adipocytes were significantly reduced in ginseng-treated mice when compared to the untreated HFD-fed mice, with the ginseng-treated mice being associated with-reduction in adipose tissue mass and body weight gain. The new formation of adipose tissue is heavily dependent upon the continuation of angiogenesis [43] and different angiogenesis inhibitors were associated with reduced adipose tissue mass as well as body weight [44], strongly suggesting that angiogenesis plays an integral role in adipose tissue growth. Ginseng with its anti-angiogenic effects may be able to achieve its targeted fat reduction due to the fact that angiogenesis inhibitors primarily

**Table 1**
Effect of Korean Red Ginseng on obesity

| Type | Study | Condition | Treatment | Results | Ref |
|---|---|---|---|---|---|
| Animal | C57BL/6J | HFD induced obesity | KRG extract | Adipogenesis-related genes ↓ (SREBP-1C, PPARγ, FAS, SCD1, and ACC1) | [10] |
| | OLETF rat (age 10 weeks) | Diabetes | KRG oral gavage (200 mg/kg day) 40 weeks | Fatty acid oxidation↑, peroxisome proliferator−activated receptor−γ coactivator−1α↑, nuclear respiratory factor−1↑, cytochrome c↑, cytochrome c oxidase−4↑, and glucose transporter 4↑, AMPK↑, weight↓, visceral fat↓ | [3] |
| | Sprague-Dawley rats | HFD induced obese insulin resistant model | KRG oral gavage (200 mg/kg day) 18 weeks | Fat mass reduction↓, insulin sensitivity↑, insulin signal↑, phosphorylation of Akt and GLUT4↑ | [45] |
| | C57BL/6J | HFD | 0.5%/5% KRG 8 weeks | Body weight and adipose tissue mass↓, angiogenic factors↓ | [46] |
| Human | Fifty obese women | Obesity BMI ≥25 kg/m$^2$ | KRG, 6 g/day | weight↓, BMI↓, waist-hip ratio↓, daily food intake↓, Korean version of obesity-related quality of life scale↓ | [52] |
| | 68 participants | BMI ≥23 kg/m$^2$ | KRG, 6 g/day | No effect | [53] |
| | 60 subjects | Metabolic syndrome | KRG 4.5 g/day 12 weeks | No effect | [54] |
| | 10 obese middle-aged Korean women | Obesity BMI ≥25 kg/m$^2$ | KRG 4 g/day 8 weeks | weight↓, BMI↓ | [55] |

HFD, high fat diet; KRG, Korean Red Ginseng; OLETF rat, Otsuka Long-Evans Tokushima fatty rat; SREBP-1C, Sterol regulatory element-binding protein 1; PPARγ, Peroxisome proliferator-activated receptor gamma; FAS, Fatty acid synthase; SCD1, Stearoyl-Coenzyme A desaturase 1; ACC1, Acetyl-Coenzyme A carboxylase 1; AMPK, AMP-activated protein kinase; GLUT4, Glucose transporter type 4; BMI, body mass index.

**Table 2**
Effect of Korean Red Ginseng on type 2 diabetes and insulin resistance

| Type | Study | Condition | Treatment | Results | Ref |
|---|---|---|---|---|---|
| Animal | C57BL/6 (age 6 weeks) | HFD | Ginsenoside Rg3 I.P. (1 mg/kg/day) 8 weeks | weight↓, GTT↓, ITT↓, pAkt↑, blood FFA↓, pro-inflammatory cytokine (TNF-α, IL-1β)↓ in white fat tissue, TG↓, pSTAT5↓, PPARγ↓ | [60] |
| | OLETF rat | Type 2 diabetes | KRG (200 and 400 mg/kg/day) 180 days | weight↓, plasma glucose level↓, EF and FS level↑, MDA↓, GPx activity↑ | [61] |
| | C57BL/KsJ db/db (age 4 weeks) | Type 2 diabetes mellitus | KRG powder oral gavage (100 mg/kg/day) 12 weeks | Fasting glucose level↓, HbA1c↓, insulin↓, LDL cholesterol↓, mitochondria DNA copy number↑, inflammatory marker (IL-6, COX-2, CRP)↓ | [62] |
| | Wister rat | 50 mg/kg STZ I.P. induced diabetes | Ginsenoside 20(S)-Rg3 oral gavage (5, 10 and 20 mg/kg/day) | Water intake and urine excretion level↓, serum glucose and serum glycosylated protein level↓, protein expressions related to the oxidative stress-induced damage (NK-κBp65, COX-2, iNOS, and 3-nitrotyrosine)of renal tissue↓, NMDA-NR1↓ | [47] |
| | B6.V-Lepob, 'ob/ob' (age 24 weeks) | Leptin knock-out induced obesity and diabetes | KRG extract (0.5%, 1% containing in drinking water) 16 weeks | Weight↓, blood glucose level↓, serum contents (triglycerides, total cholesterol, free fatty acids)↓, expressions of IR, LPL, and GLUT1 in muscle↑, expression of IR and LPL in liver↑ | [73] |
| Human | 70 patients | Type 2 diabetes | KRG extract tablet 3 g/day 24 weeks | Fasting insulin level↓, HOMA-IR↓, CPT of Lex↓ | [74] |
| | 60 patients | Type 2 diabetes (fasting glucose ≥126 mg/dL) | KRG capsule 5 g/day 12 weeks | Serum glucose and whole blood glucose↓, C-peptide↓, HOMA-IR↓, insulin↓ | [75] |

HFD, high fat diet; KRG, Korean Red Ginseng; GTT, glucose tolerance test; ITT, insulin tolerance test; pAkt, phosphatidyl protein kinase B; FFA, free fatty acid; TNF, tumor necrosis factor; IL, interleukin; TG, triglyceride; pSTAT5, phosphatidyl signal transducer and activator of transcription 5; PPARγ, peroxisome proliferator-activated receptors-gamma; OLETF rat, Otsuka Long-Evans Tokushima fatty rat; EF, ejection fraction; FS, fractional shortening; MDA, malondialdehyde; GPx, glutathione peroxidase; HbA1c, glycosylated hemoglobin; LDL, low density lipoprotein; COX-2, cyclooxygenase-2; CRP, C-reactive protein; STZ, streptozotocin; I.P., intraperitoneal injection; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS, inducible nitric oxide synthase; NMDA-NR1, N-methyl-D-aspartate NR1; IR, insulin resistance; LPL, lipoprotein lipase; GLUT1, Glucose transporter type 1; HOMA-IR, homeostasis model assessment of insulin resistance index; CPT, current perception threshold; Lex, lower extremities.

target growing or newly formed vessels. Similar findings were seen in Zucker diabetic fatty rats which were given a regimen that contains 1% ginseng root extract and in Sprague–Dawley rats/Otsuka Long-Evans Tokushima fatty rats which were administered HFD with ginseng (200 mg/kg, oral); no significant disparity in food consumption was observed between ginseng-treated and untreated rats [45]. Considering the inhibitory effect of ginseng on angiogenesis and adipose tissue increase, ginseng should be examined further for its potential to improve human obesity and its associated disorders [46].

In a study involving obese mice, Rg3 derived from red ginseng upregulated the expressions of GLUT4 glucose transporter and insulin receptor substrate 1, resulting in increased muscular glucose uptake [47]. Also, KRG has been reported to increase the expressions of PPAR-$\gamma$ coactivator-1$\alpha$ (PGC-1$\alpha$), nuclear respiratory factor 1 (NRF 1), cytochrome c, and cytochrome c oxidase to promote mitochondrial biogenesis and fatty acid oxidation in skeletal muscle and cultured C2C12 cells [48]. In a previous study, ginsenoside Rg3-stimulated glucose uptake was shown to occur via PI3K-dependent pathway [49]. Protopanaxatriol, a major constituent of ginseng, inhibited the rosiglitazone-supported adipocyte differentiation of 3T3-L1 cells through the repression of lipogenesis-related gene expression [50].

In a systematic review, a priori subgroup analyses revealed meaningful association between the different treatments and the body mass index (BMI) ($\beta = -0.95$ mmHg, 95% CI $= -1.56, -0.34$, $P = 0.007$) [51]. In a previous trial, KRG was shown to improve the BMI and scores in an obesity-related quality of life scale in the CT genotype of the G protein beta 3 gene on blood sugar test in the Trp64/Arg genotype of the beta 3 adrenergic receptor gene [52]. In contrast, KRG did not significantly improve insulin sensitivity over time and did not ameliorate the insulin sensitivity for obese subjects without accompanying hypertension or diabetes [53]. In context of subjects with MS, KRG had no effects on lipid profile, oxidized low density lipoprotein, lipid profile, fasting blood sugar levels, or arterial hardness [54]. Another study suggested that ginseng was associated with an effect on weight loss and the gut microbiota and that its anti-obesity effects were different depending on the composition of the gut microbiota before the ginseng is administered [55]. Furthermore, other research has demonstrated that KRG might bring about reduced weight gain [3]. Although the precise mechanism through which KRG exerts its beneficial effects on energy metabolism remains unclear, one explanation may be that KRG activates adenosine monophosphate-activated protein kinase [3] and reduces food intake or appetite [56]. Therefore, KRG appears to have the potential to play an important role in the treatment of metabolic syndrome.

In summary, ginseng and ginsenosides not only curb appetite and lower energy input in the gut, but also downregulate lipid synthesis and upregulate energy consumption in both the liver and skeletal muscle through the activated AMPK pathway (Table 1). There is growing evidence supporting the hypothesis that ginseng brings about an anti-obesity effect in humans. Additional studies and verification through longitudinal human studies are necessary to fully characterize the anti-obesity effects of ginseng.

### *4.2. Insulin resistance and diabetes*

KRG has been often employed as folk medicine in the treatment of diabetes, because it has been reported to not only improve insulin resistance but also have anti-hyperlipidemic effects (Table 2) [57,58]. The anti-diabetic properties of KRG are not merely dictated by the content of ginsenosides but the synergistic interplay between different non-saponin fractions and fractions of ginsenosides [4].

Adipocyte hypertrophy has been often associated with a number of metabolic syndromes, which includes insulin resistance. Enlarged adipocytes are related to insulin resistance while smaller adipocytes are linked to insulin sensitivity [59]. Ginsenoside Rg3, which is linked to STAT5-PPAR gamma pathway, has been demonstrated to ameliorate both obesity-induced insulin resistance and lipotoxicity [60]. Therefore, it can be summarized that ginseng's ability to improve insulin resistance lies in its inhibition of adipocyte hypertrophy in obese animals. Another study proposed that KRG exerted significant anti-hyperglycemic and anti-oxidative effects in KRG-treated rats [61]. Twelve-week treatment with 100 mg/kg KRG resulted in improvements in fasting glucose, HbA1c, insulin, inflammatory markers (interleukin-6, cyclooxygenase-2, and C-reactive protein) and LDL cholesterol levels while increasing mitochondrial DNA copy number in db/db mice [62]. Rg3 was shown to bring about a protective effect against diabetes through the reduction of oxidative stress in a streptozotocin-induced diabetic renal damage model [47]. In addition, Rg3 exerted an antihyperglycemic effect in db/db mice by increasing glucagon-like peptide-1 release via the sweet taste receptor-mediated signal transduction pathway [63].

Studies have shown that ginseng also may have anti-angiogenic activities with the potential to serve as cancer chemoprevention [64]. Ginsenosides Rb1 and Rb3 downregulate an early step involved in angiogenesis in addition to lowering the chemoinvasion of endothelial cells; compound K which is a ginsenoside metabolite achieves its anti-angiogenic effects by the inhibition of the tube formation and migration of endothelial cells [65]. These findings demonstrate that ginseng through its angiosuppressive properties can significantly lower adipose tissue mass and body weight.

Adipose tissue is responsible for the production of various angiogenic factors and inhibitors that coordinate adipose angiogenesis. These angiogenic factors promoted the proliferation and differentiation of endothelial cells in the context of adipose tissue [66,67], whereas thrombospondin-1 inhibited angiogenesis *in vivo* and inhibited the proliferation and migration of cultured microvascular endothelial cells [68]. Adipocytes also produced matrix metalloproteinase (MMP) and inhibitors which were differentially expressed in fat tissue of obesity model mice [69,70]. The interplay between MMPs and their inhibitors is assumed to play an important role in developing and maintaining adipose tissue. It was also observed that the treatment of HFD-induced obese mice with ginseng reduced the production of vascular endothelial growth factor, but upregulated the levels of anti-angiogenic agents in fat tissues. Furthermore, ginseng brought down MMP-2 and MMP-9 mRNA levels but elevated the levels of tissue inhibitors of metalloproteinases. It appears that ginseng brings about a regulatory effect on genes associated with angiogenesis and MMPs in adipose tissues. What's more, MMP-2 and MMP-9 was found to indirectly enhance angiogenesis [71,72], which suggests that obesity is mediated by synergistic action between angiogenesis and MMPs. The expression levels of insulin receptor, lipoprotein lipase, and glucose transporters 1 and 4 in the liver and the muscle were elevated in KRG-treated groups when compared with the control group [73].

In a clinical study, administration of KRG to patients with diabetes for 24 week resulted in a large improvement in symptoms and metabolic parameters of neuropathy, particularly in those with a chronic condition [74]. Compared with placebo, KRG supplementation (5 g/day) have been associated with therapeutic benefits in controlling serum and whole blood glucose levels among patients with attenuated glucose tolerance or type 2 diabetes mellitus [75].

**Table 3**
Effect of Korean Red Ginseng on cardiovascular disease and dyslipidemia

| Type | Study | Condition | Treatment | Results | Ref |
|---|---|---|---|---|---|
| Animal | SHR | Hypertension | HCEF-RG or FR (500 and 1000 mg/kg/day)<br>8 weeks | Systolic and diastolic blood pressure↓, renin activity↓, angiotensin-1 converting enzyme inhibition and NO↑ | [76] |
| | SHR | Hypertension | KRG or REKRG jugular vein injection (3 mg/kg) | SBP and DBP↓, endothelial nitric oxide synthase phosphorylation levels in the aorta↑, nitric oxide production in plasma↑ | [78] |
| Human | 80 individuals | Type 2 diabetes and hypertension | AG and Rg3-KGE (1.5 g/day AG and 0.75 g/day Rg3-KGE)<br>12 weeks | Central-systolic BP↓, end-systolic pressure↓, area under the systolic/diastolic BP curve↓ | [91] |
| | 23 individuals | BMI, 22 ± 0.6 kg/m$^2$<br>SBP/DBP, 113 ± 3/70 ± 2 mmHg | Rg3-KGE (400 mg/twice with 7-day washout) | Augmentation index↓, central and brachial mean arterial pressure↓, central systolic and diastolic BP↓, brachial systolic and diastolic BP↓ | [92] |

SHR, spontaneously hypertensive rat; HCEF-RG, hypotensive components-enriched fraction of red ginseng; FR, fine root concentration; NO, nitric oxide; HFD, high fat diet; GBHT, ginseng-plus-Bai-Hu-Tang; EAT, epididymis adipose tissue; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; KRG, Korean Red Ginseng; REKRG, Rg3-enriched KRG; SBP, systolic blood pressure; DBP, diastolic blood pressure; AG, American ginseng extract; Rg3-KGE, Rg3 enriched Korean Red Ginseng extract; BMI, body mass index.

**Table 4**
Effect of Korean Red Ginseng on non-alcoholic fatty liver disease

| Type | Study | Condition | Treatment | Results | Ref |
|---|---|---|---|---|---|
| Animal | OLETF rat | Insulin resistance and NAFLD | Normal chow diet with KRG (200 mg/kg/day)<br>2 months | Serum TG level↓, HDL-cholesterol and NK cell activity↑ | [94] |
| | Sprague-Dawley rats (age 4 weeks) | Hepatocarcinogenesis by the injection of DEN (200 mg/kg) | KRG diet (0.5, 1, or 2%)<br>10 weeks | GST-P positive foci are and number↓, TBARS↓, tGSH and glutathione-related enzymes (GST, GPx)↑, cytochrome P450 signaling pathway gene expression (Cyp2c6, Cyp2e1, Cyp3a9, and Mgst1)↓ | [95] |
| | db/db mouse and C57BL/6 | HFD induced NAFLD and dyslipidemic | KRG oral gavage | Weight↓, liver inflammation (IL-1β, Ph-p38)↓ | [96] |
| | Nude mouse (age 6 weeks) | Tumor xenograft with inoculated Huh-7 cells (5 × 10$^6$) | 20(S)-ginsenoside Rg3 oral gavage (20 mg/kg/3 times a week) and doxorubicin I.P. (1 mg/kg/3 times a week)<br>21 days | Rg3 + doxorubicin kill HCC cell line (HCC cell viability, tumor volume and tumor weight↓, LC3 protein↑) | [98] |
| Human | 80 patients | NAFLD patients (AST or ALT ≥50IU/L) | Silybum marianum (450m g/day) + KRG capsule (3 g/day)<br>3 weeks | Liver function test improved<br>TNF-α↓, significant difference in change of adiponectin level with placebo group, fatigue score↓ | [99] |

OLETF rat, Otsuka Long-Evans Tokushima Fatty rat; NAFLD, non-alcoholic fatty liver disease; KRG, Korean Red Ginseng; TG, triglyceride; HDL, high density lipoprotein; NK cell, natural killer cell; DEN, diethylnitrosamine; GST-P, glutathione S-transferase placental form; TBARS, thiobarbituric acid reactive substances; tGST, total glutathione; GST, glutathione S-transferase; GPx, glutathione peroxidase; IL, interleukin; Ph-p38, phospho-p38; I.P., intraperitoneal injection; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TNF, tumor necrosis factor.

**Table 5**
Effect of ginsenosides on metabolic syndrome

| Ginsenoside | GS Type | Known roles in metabolic syndrome | Ref |
|---|---|---|---|
| Ginsenoside F4 | PPT | (In cardiovascular disease) Effect on ADP and collagen-induced platelet aggregation | [102] |
| Ginsenoside Rg2 | PPT | (In NAFLD) body weight↓, hepatic steatosis↓, glucose tolerance and insulin sensitivity↑ | [103] |
| Ginsenoside Rg3 | PPD | (In NAFLD) Inflammation cytokine (IL-1β, p-p38)↓<br>(In obesity) Lipogenesis protein (PPARγ, C/EBPα, FABP4, ACC, FAS, and perilipin)↓ in adipose tissue/GLUT4, PPARγ, and AMPK phosphorylation↑ in skeletal muscle<br>(In diabetes) Oxidative stress↓, body weight↓, AGE formation↓, PPARγ expression↑ by AMPK phosphorylation<br>(In hypertension) Reduction of blood pressure and blood vessel wall thickness, renin activity and angiotensin-I level↓ | [104] |
| Ginsenoside Rg5 | PPD | (In diabetes) Lipid accumulation and insulin resistance↓, insulin secretion and glycogen storage↑ | [105] |
| Ginsenoside Rh1 | PPT | (In obesity) Body weight gain and fat accumulation↓, improve insulin resistance and glucose intolerance | [106] |
| Ginsenoside Rh2 | PPD | (In obesity) PPARγ↓, and AMPK, UCP-2, and CPT-1 activation in 3T3-L1 adipocyte | [107] |
| Ginsenoside Rh4 | PPT | (In diabetes) GLUT4, PPARα, and PPARγ regulate in muscle and liver | [108] |
| Ginsenoside Rs1 | PPD | No reference | – |
| Ginsenoside Rs2 | PPD | No reference | – |
| Ginsenoside Rs3 | PPD | No reference | – |
| Ginsenoside Rs4 | PPD | No reference | – |
| (+)-notoginsenoside R4 | PPD | No reference | – |

GS, ginsenoside; PPD, protopanaxadiol; PPT, protopanaxatriol; ADP, adenosine diphosphate; NAFLD, Non-alcoholic fatty liver disease; p-p38, phosphor-p38; PPARγ, peroxisome proliferator-activated receptor gamma; C/EBPα, CCAAT/enhancer-binding protein alpha; FABP4, fatty acid binding protein 4; ACC, acetyl-Coenzyme A carboxylase; FAS, fatty acid synthase; GLUT4, glucose transporter type 4; AMPK, AMP-activated protein kinase; AGE, advanced glycation end product; UCP-2, mitochondrial uncoupling protein 2; CPT-1, carnitine palmitoyl transferase 1; PPARα, peroxisome proliferator-activated receptor alpha.

### *4.3. Cardiovascular disease and dyslipidemia*

Ginseng has been also traditionally used for addressing cardiovascular risk factors including hypertension and hypercholesterolemia (Table 3). In a hypertensive rat model, Rg3 was shown to not only significantly reduce renin activity but also curb blood pressure [76]. Ginseng with Bai-Hu-Tang, a Chinese formula widely used in traditional medicine, had protective effects against HFD-induced body weight gain, hyperlipidemia, and hyperglycemia [77]. In another study, mice treated with Rg3 exhibited lowering of blood pressure and reduction of vascular wall thickness [78].

Cardiac ischemia can result in myocardial injury which is associated with the production of ROS; it has been shown that treatment with ginseng in this context helps restore coronary blood flow [79]. Ginsenosides Rg2 and Rh1 were also associated with minimizing the damage on erythrocyte brought by oxidation [80]. The energy metabolism and protective effects of mitochondria were observe to be regulated via polysaccharides of *P. ginseng* [81]. The antioxidant effects of ginseng were facilitated through Nrf2 and increase in the levels of the antioxidant enzymes glutathione peroxidase and superoxide dismutase [82,83]. Ginsenosides' ability to prevent myocardial reperfusion injury hinges on its upregulation of 6-keto-prostaglandin F1$\alpha$ production and downregulation of lipid peroxidation [84]. In addition, ginseng can stimulate nitric oxide production, thereby preventing ROS toxicity. Homocysteine and human immunodeficiency virus protease inhibitors are responsible for endothelial dysfunction; ginsenoside Rb1 and other ginsenosides were demonstrated to block this effect via inhibition of ROS production [85,86]. Ginsenoside Re, a potent antioxidant, brings about a protective effect for cardiomyocytes against oxidant-mediated injury. This process is partially mediated by the ginsenoside's scavenging properties of radicals, especially against H2O2 and hydroxyl radicals. Ginsenoside Re which constitutes the major constituent in ginseng extract, may have an integral role in antioxidant activity, specifically improving cardiomyocyte survival and enhancing contractile function during ischemic and reperfusion events [87,88]. These results are suggestive of ginsenoside Re's antioxidant functions, which serve to protect cardiomyocytes from oxidative damage caused by exogenous and endogenous oxidants; these protective effects can be largely attributed to scavenging of the H2O2 and hydroxyl radicals. *P. notoginseng* saponins caused an enhanced vasodilation response to nitric oxide and a reduction of blood pressure, both of which contributed to protection against vascular dysfunction in murine model [89].

Two studies described in a systematic review showed the positive effect of KRG compared with placebo in reducing blood pressure [90]. In a recent randomized controlled trial suggested that a reduction in central systolic blood pressure ($-4.69 \pm 2.24$ mmHg, $p = 0.04$) was observed with the coadministration of Rg3-KRG and American ginseng relative to the control at 12 weeks [91]. In addition, Rg3-KRG extract was shown to acutely decrease central and peripheral arterial pressures in healthy individuals [92]. Another clinical trial also demonstrated that *P. ginseng* extract improved blood lipid profile largely through a decrease in total and LDL-cholesterol levels [93].

Regarding the effect of KRG on cardiovascular disease and dyslipidemia, KRG can be used to improve the heart function and dyslipidemia in patients with MS. However, additional long-term clinical trials are necessary to fully elucidate the benefits of KRG on cardiovascular disease and dyslipidemia.

### *4.4. Nonalcoholic fatty liver disease*

KRG has been studied as a potential therapeutic option for NAFLD. A number of studies have suggested the benefit of KRG administration in NAFLD (Table 4) [94,95]. In a preclinical study [94], serum triglycerides level ($302.0 \pm 70.4$ vs. $527.7 \pm 153.3$ mg/dL) was found to be reduced in the KRG-administered group when compared with NAFLD group ($p < 0.05$). In addition, HDL-cholesterol levels (liver tissue, $4.8 \pm 0.2$ vs. $4.2 \pm 0.2$ mg/g) and natural killer cells activity ($3485 \pm 910$ vs. $2486 \pm 619$ counts) were elevated when compared to the NAFLD group ($p < 0.001$). In dyslipidemic db/db mice, combination of Rg3 and probiotics improved NAFLD symptoms, which involved a reduction of liver inflammation via downregulation of cytokines such as IL-1β and phospho-p38 [96]. Rg3 brought about lowering of incidence of post-operative liver failure and the reduction of the levels of TG, LDL, and TNF-$\alpha$ levels in HFD-fed mice [97]. KRG inhibited the production of

proteins that are linked to lipogenesis and adipogenesis in HCC [98].

A recent prospective randomized clinical trial evaluated the anti-inflammatory and anti-fatigue effects of KRG in individuals with NAFLD [99]. The biochemical parameters including AST, ALT, and γ-GT were significantly decreased in patients treated with KRG. Especially, the levels of ALT and γ-GT showed more noticeable improvement in the KRG group with a BMI of 25 kg/m$^2$ or more. Furthermore, KRG when given to NAFLD patients resulted in reduction of TNF-α serum levels and increase in adiponectin serum levels. Consequently, serum adiponectin levels, a biomarker of metabolic syndrome, were elevated in the KRG group, suggesting that KRG can be effective in treating fatty liver disease [99]. KRG may have the potential to play an essential role in the treatment of metabolic syndrome. However, further clinical trials are required to confirm these promising findings [100].

## 5. Conclusion

KRG and its primary ginsenosides are associated various beneficial effects in MS-related phenotypes and risk factors, such as obesity, CVD, insulin resistance, dyslipidemia, and NAFLD (Table 5). The detailed molecular mechanisms which underlie the promising effects of KRG and its primary ginsenosides are yet to be fully elucidated. Moreover, additional well designed clinical trials are needed to demonstrate both the safety and efficacy of KRG and its primary ginsenosides for the wider clinical application [101].

## Each author's contribution

Sang Jun Yoon: analysis and interpretation of the data, collection and assembly of data, drafting of the article. Ki Tae Suk: conception and design, critical revision of the article for important intellectual content, final approval of the article. Other authors: analysis and interpretation of the data

## Conflicts of interest

The authors declare that there is no conflict of interest, including relevant financial interests, activities, relationships, affiliations, and any other conflict of interest as explicitly and implicitly expressed in the Editorial Policies for Authors.

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