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].

Keywords: Panax ginseng; Metabolic syndrome; Insulin resistance; Non-alcoholic fatty liver disease
Korean Red Ginseng (KRG) comes from the roots of <i>Panax ginseng</i> 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 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 phenomenon 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]. Atrogeneric 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 (<i>Panax ginseng</i> 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, R1, R2, 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...
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 hepatoprotection 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

| 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     |                  | Diabetes                      | KRG oral gavage (200 mg/kg day)    | Fatty acid oxidation †, peroxisome proliferator—activated receptor—γ coactivator—1†, 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) | Fat mass reduction †, insulin sensitivity †, insulin signal †, phosphorylation of Akt and GLUT4† | [45] |
| 40 weeks      |                  |                               | 40 weeks                           |                                                                         |      |
| C57BL/6J      |                  | High fat diet                 | KRG extract                        | Body weight and adipose tissue mass †, angiogenic factors †, weight † | [46] |
| OLETF rat     |                  | Otsuka Long-Evans Tokushima fatty rat | KRG, 6 g/day                       | weight †, BMI †, waist-hip ratio †, daily food intake †, Korean version of obesity-related quality of life † | [52] |
| 8 weeks       |                  |                               |                                    |                                                                         |      |
| Fifty obese women |                | Obesity                       | KRG, 6 g/day                       | weight †, BMI †, waist-hip ratio †, daily food intake †, Korean version of obesity-related quality of life † | [52] |
| BMI ≥25 kg/m² |                  |                               |                                    |                                                                         |      |
| 68 participants |                | Obesity                       | KRG, 6 g/day                       | weight †, BMI †, waist-hip ratio †, daily food intake †, Korean version of obesity-related quality of life † | [52] |
| BMI ≥25 kg/m² |                  |                               |                                    |                                                                         |      |
| 60 subjects   |                  | Metabolic syndrome            | KRG                               | No effect †                                                              | [53] |
| 8 weeks       |                  |                               |                                    |                                                                         |      |
| 10 obese middle-aged |       | Obesity                       | KRG                               | No effect †                                                              | [54] |
| Korean women  |                  |                               |                                    |                                                                         |      |
| BMI ≥25 kg/m² |                  |                               |                                    |                                                                         |      |
| 4 g/day 8 weeks |                |                               |                                    |                                                                         |      |
| S.J. Yoon et al / Effect of Korean red ginseng on metabolic syndrome | | | | | |

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

| Type          | Study            | Condition                     | Treatment                          | Results                                                                 | Ref  |
|---------------|------------------|-------------------------------|------------------------------------|-------------------------------------------------------------------------|------|
| Animal        | C57BL/6J         | HFD                           | Ginsenoside Rg3 IP (1 mg/kg/day)   | weight †, GTT †, ITT †, pAkt †, blood FFA †, pro-inflammatory cytokine (TNF-α, IL-1)†, in white fat tissue, TG †, pSTAT5 †, PPARγ †, weight †, plasma glucose level †, EF and FS level †, MDA †, GPx activity † | [60] |
| (age 6 weeks) |                  |                               | 8 weeks                           |                                                                         |      |
| OLETF rat     |                  | Type 2 diabetes               | KRG (200 and 400 mg/kg/day)        | Fasting glucose level †, HBAlc †, insulin †, LDL cholesterol †, mitochondria DNA copy number †, inflammatory marker (IL-6, COX-2, CRP)†, Water intake and urine excretion level †, serum glucose and serum glycosylated protein level †, protein expressions related to the oxidative stress-induced damage (NF-kBp65, COX-2, iNOS, and 3-nitrotyrosine) of renal tissue †, NMDA-NR1 † | [61] |
| (age 4 weeks) |                  |                               | 180 days                          |                                                                         |      |
| C57BL/KsJ db/db |                  | Type 2 diabetes mellitus      | KRG powder oral gavage (100 mg/kg/day) | Fasting glucose level †, HBAlc †, insulin †, LDL cholesterol †, mitochondria DNA copy number †, inflammatory marker (IL-6, COX-2, CRP)†, Water intake and urine excretion level †, serum glucose and serum glycosylated protein level †, protein expressions related to the oxidative stress-induced damage (NF-kBp65, COX-2, iNOS, and 3-nitrotyrosine) of renal tissue †, NMDA-NR1 † | [62] |
| (age 4 weeks) |                  |                               | 12 weeks                          |                                                                         |      |
| Wistar rat    |                  | Type 2 diabetes               | Ginsenoside 20(S)-Rg3 oral gavage (5, 10 and 20 mg/kg/day) | Fasting glucose level †, HBAlc †, insulin †, LDL cholesterol †, mitochondria DNA copy number †, inflammatory marker (IL-6, COX-2, CRP)†, Water intake and urine excretion level †, serum glucose and serum glycosylated protein level †, protein expressions related to the oxidative stress-induced damage (NF-kBp65, COX-2, iNOS, and 3-nitrotyrosine) of renal tissue †, NMDA-NR1 † | [63] |
| (age 4 weeks) |                  |                               | 180 days                          |                                                                         |      |
| B6.V-Leplp, 'ob/ob' |            | Type 2 diabetes              | KRG extract (0.5%, 1% containing in drinking water) | Fasting glucose level †, HBAlc †, insulin †, LDL cholesterol †, mitochondria DNA copy number †, inflammatory marker (IL-6, COX-2, CRP)†, Water intake and urine excretion level †, serum glucose and serum glycosylated protein level †, protein expressions related to the oxidative stress-induced damage (NF-kBp65, COX-2, iNOS, and 3-nitrotyrosine) of renal tissue †, NMDA-NR1 † | [64] |
| (age 24 weeks)|                  | obesity and diabetes          | 16 weeks                          |                                                                         |      |
| Human         | 70 patients      | Type 2 diabetes              | KRG extract tablet 3 g/day 24 weeks | Fasting insulin level †, HOMA-IR †, CPT of Lex †, Serum glucose and whole blood glucose †, C-peptide †, HOMA-IR †, insulin † | [74] |
| 60 patients   |                  | Type 2 diabetes (fasting glucose ≥126 mg/dL) | KRG capsule | Fasting insulin level †, HOMA-IR †, CPT of Lex †, 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; HbAlc, glycated hemoglobin; LDL, low density lipoprotein; COX-2, cyclooxygenase-2; CRP, C-reactive protein; STZ, streptozotocin; LP, 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-γ coactivator-1α (PGC-1α), 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) (β = –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 [5]. 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 synergic 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 STAT3-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 angiostatic 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) 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) 12 weeks | Central-systolic BP↓, end-systolic pressure ↓, area under the systolic/diastolic BP curve ↓ | [91] |
|           | 23 individuals             | BMI, 22 ± 0.6 kg/m² SBP/DBP, 113 ± 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) 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%) 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 Nude mouse (age 6 weeks) | HFD induced NAFLD and dyslipidemic Tumor xenograft with inoculated Huh-7 cells (5 × 10⁶) | KRG oral gavage 20(S)-ginsenoside Rg3 oral gavage (20 mg/kg/3 times a week) and doxorubicin IP (1 mg/kg/3 times a week) 21 days | Weight↓, liver inflammation (IL-1β, Ph-p38)↓, Rg3 + doxorubicin kill HCC cell line (HCC cell viability, tumor volume and tumor weight↓, LC3 protein↑) | [96] |
| Human     | 80 patients                | NAFLD patients (AST or ALT ≥50IU/L) | Silybum marianum (450m g/day) + KRG capsule (3 g/day) 3 weeks | Liver function test improved 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; LP, intra-peritoneal injection; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TNF, tumor necrosis factor.
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 F1α 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 ginsenose’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 ± 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 ± 70.4 vs. 527.7 ± 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 ± 0.2 vs. 4.2 ± 0.2 mg/g) and natural killer cells activity (3485 ± 910 vs. 2486 ± 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-38 [96]. Rg3 brought about lowering of incidence of postoperative liver failure and the reduction of the levels of TG, LDL, and TNF-α 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/m² or more. Furthermore, KRG when given to NAFLD patients resulted in improvement in the KRG group with a BMI of 25 kg/m² or more. Consequently, serum adiponectin levels, a biomarker of metabolic syndrome, were elevated in the KRG group, suggesting levels. Especially, the levels of ALT and anti-inflammatory 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.

Acknowledgements
This research was supported by Hallym University Research Fund, Korea National Research Foundation (NRF-2018M3A9F3020956 and NRF-2019R1I1A3A01060447), Basic Science Research Program (2020R1A6A1A03043026) through the NRF funded by the Ministry of Education, and Hallym University Research Fund 2018 (HURF-2018-67).

References
[1] Aguilar M, Bhuket T, Torres S, Liu B, Wong R. Prevalence of the metabolic syndrome in the United States, 2003–2012. JAMA 2015;313:1973–4.
[2] Nazara Otero CA, Pose Reino A, Pena Gonzalez E. [Metabolic syndrome: diagnosis and management. An update]. Clin Invest Arterioscler 2016;28:20–1.
[3] Lee HJ, Lee YH, Park SK, Kang ES, Kim HJ, Lee YC, Choi CS, Park SE, Ahn CW, Cha BS, et al. Korean red ginseng (Panax ginseng) improves insulin sensitivity and attenuates the development of diabetes in Otsuka Long-Evans Tokushima fatty rats. Metabolism 2009;58:1170–7.
[4] Park SJ, Nam J, Ahn CW, Kim Y. Anti-diabetic properties of different fractions of Korean red ginseng. J Ethnopharmacol 2019;236:220–30.
[5] Park TY, Hong M, Sung H, Kim S, Suk KT. Effect of Korean Red Ginseng in chronic liver disease. J Ginseng Res 2017;41:450–5.
Lee HU, Bae EA, Han MJ, Kim DH. Hepatoprotective effect of 20(S)-ginsenosides Rg3 and its metabolite 20(S)-ginsenoside Rb2 on tert-butyl hydroperoxide-induced liver injury. Biol Pharmaceut Bull 2008;31:1992–4.

Yuan HD, Kim do Y, Quan HY, Kim SJ, Jung MS, Chung SH. Ginsenoside Rg2 induces orphan nuclear receptor SHP gene expression and inactivates GSK3beta via AMP-activated protein kinase to inhibit hepatic glucose production in HepG2 human hepatic-biogenic liver cells. J Chin Pharmocol 2017:95:1046–57.

Yin J, Zhang H, Ye J. Traditional Chinese medicine in treatment of metabolic syndrome. Endocr Metab Disord Drug Targets 2008;8:99–111.

Liu JM, Yao Q, Chen C. Ginseng complications: an update on their molecular mechanisms and medical applications. Curr Vasch Pharmacol 2009;7:293–302.

Singh RK, Lui E, Wright D, Taylor A, Bakovic M. Alcohol extract of North American ginseng (Panax quinquefolius) reduces fatty liver, dyslipidemia, and other complications of metabolic syndrome in a mouse model. Can J Physiol Pharmacol 2017:95:1046–57.

Kho MC, Lee YJ, Park JH, Kim HY, Yoon JH, Ahn YM, Tan R, Park MC, Cha JD, Choi KM, et al. Fermented red ginseng potentiates improvement of metabolic dysfunction in metabolic syndrome rat models. Nutrients 2016;8.

Lijnen HR, Maquoi E, Hansen LB, Van Hoef B, Frederix L, Collen D. The matrix metalloproteinase inhibition impairs adipose tissue development in mice. Arterioscler Thromb Vasc Biol 2002;22:374–9.

Brakenhoff E, Cao R, Gao B, Angelin B, Cannon P, Parini C, Yao Y. Angiogenesis inhibitor, TNP-470, prevents diet-induced and genetic obesity in mice. Circ Res 2004;94:1579–88.

Lee YJ. Angiogenesis modulates adipogenesis and obesity. J Clin Invest 2011;127:2562–70.

Lee SH, Lee JH, Lee YH, Lee BW, Cha BS, Kang ES, Ahn CW, Park JS, Kim HJ, Lee EY, et al. Korean red ginseng (Panax ginseng) improves insulin sensitivity and reduces body weight in overweight and obese rats. Physiol Res 2012;61:161–72.

Lee H, Park D, Yoon M. Korean red ginseng (Panax ginseng) prevents obesity by inhibiting angiogenesis in high fat diet-induced obese C57BL/6J mice. Food Chem Toxicol 2013;53:402–8.

Kang KS, Yamabe N, Kim HY, Park JH, Yokozawa T. Therapeutic potential of 20(S)-ginsenoside Rg3 against streptozotocin-induced diabetic renal damage in rats. J Pharm Pharmacol 2008;59:266–72.

Li Z, Ji GE. Ginseng and obesity. J Ginseng Res 2018;42:1–8.

Lee OH, Lee HH, Kim JH, Lee BY. Effect of ginsenosides Rg3 and Re on glucose transport in mature 3T3-L1 adipocytes. Phytother Res 2011;25:768–73.

Zhang Y, Yu L, Cai W, Fan S, Feng L, Ji G, Huang C. Protopanaxatriol, a novel PPARGamma antagonist from Panax ginseng, alleviates steatosis in mice. Sci Rep 2014;4:7377.

Komishon AM, Shishtar E, Ha V, Sievenpiper JL, de Souza RJ, Jovanovski E, Ho HV, Duvnjak LS, Vukan V. The effect of ginseng (genus Panax) on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. J Hum Hypertens 2016:30:193–26.

Kwon DH, Bose S, Song MY, Lee MJ, Lim CY, Kwon BS, Kim HJ. Efficient of Korean red ginseng by single nucleotide polymorphism in obes women: randomized, double-blind, placebo-controlled trial. J Ginseng Res 2012;36:176–89.

Cho YH, Ahn SC, Lee SY, Jeong DW, Choi EJ, Kim YJ, Lee JG, Lee YH, Shin BC. Effect of Korean red ginseng on insulin sensitivity in non-diabetic healthy overweight and obese adults. Asia Pac J Clin Nutr 2013;22:235–41.

Paek JH, Park YJ, Lee HH, Hong DH, Na HY, Lee JH, Park HS, Jum YJ. Effect of Korean red ginseng on cardiovascular risks in subjects with metabolic syndrome: a double-blind randomized controlled study. Korean J Fam Med 2012;33:190–5.

Song MY, Kim BS, Kim H. Influence of Panax ginseng on obesity and gut microbiota in obese middle-aged Korean women. J Ginseng Res 2014;38:106–15.

Hasan-Ranjbar S, Nayeji N, Larijani B, Abdollahi M. A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. World J Gastroenterol 2009;15:3073.

Kim K, Kim HY. Korean red ginseng stimulates insulin release from isolated rat pancreatic islets. J Ethnopharmacol 2008;120:190–5.

Luo JZ, Luo L. Ginseng on hyperglycemia: effects and mechanisms. Evid Based Complement Alternat Med 2009;6:423–7.

Jeong S, Yoon M. Fenofibrate inhibits adipocyte hypertrophy and insulin resistance by activating adipose PPARGamma in high fat diet-induced obese mice. Exp Mol Med 2009;41:397.

Lee JB, Yoon SJ, Lee SH, Lee MS, Jung H, Kim TD, Yoon SR, Choi I, Kim IS, Chung SW, et al. Ginsenoside Rg3 ameliorated HFID-induced hepatic steatosis through downregulacion of STATs-PPARGamma. J Endocrinol 2017;235:223–35.

Hossain MA, Lee D, Kim B, Kang CW, Kim NS, Kim JH. Korean Red Ginseng attenuates type 2 diabetic cardiovascular dysfunction in Otsuka Long-Evans Tokushima Fatty rats. J Ginseng Res 2020;44:308–11.

Park JK, Shin JY, Cho AR, Cho MR, Lee YJ. Korean red ginseng protects against mitochondrial damage and intracellular inflammation in an animal model of type 2 diabetes mellitus. J Med Food 2018;21:544–50.

Kim YJ, Zhang D, Yang DC. Biosynthesis and biotechnological production of ginsenosides. Biotechnol Adv 2015;33:717–35.

Sato K, Mochizuki M, Sakai I, Yoo YM, Sumakawa K, Azuma I. Inhibition of tumor angiogenesis and metastasis by a saponin of Panax ginseng, ginsenoside-Rb2. Biol Pharmaceut Bull 1994;17:635–9.
Red ginseng (Panax Ginseng) and American ginseng (Panax Quinquefolius) administration in individuals with hypertension and type 2 diabetes: a randomized controlled trial. Complement Ther Med 2020;49:102338.

Jovanovski E, Bateman EA, Bhardwaj J, Fairgrieve C, Muscalo I, Jenkins AL, Vuksan V. Effect of Rg3-enriched Korean red ginseng (Panax ginseng) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial. J Am Soc Hypertens 2014;8:537–41.

Hernandez-Garcia D, Granado-Serrano AB, Martin-Gari M, Naudi A, Serrano JC. Efficacy of Panax ginseng supplementation on blood lipid profile. A meta-analysis and systematic review of clinical randomized trials. J Ethnopharmacol 2019;243:112090.

Hong SH, Suk KT, Choi SH, Lee JW, Sung HT, Kim CH, Kim EJ, Kim MJ, Han SH, Kim MY, et al. Anti-oxidant and natural killer cell activity of Korean red ginseng (Panax ginseng) and urushiol (Rhus vernicifera Stokes) on non-alcoholic fatty liver disease of rat. Food Chem Toxicol 2013;55:586–91.

Kim H, Hong MK, Choi H, Moon HS, Lee HJ. Chemopreventive effects of Korean red ginseng extract on rat hepatocarcinogenesis. J Cancer 2015;6:1–8.

Kim JC, Jeon JY, Yang WS, Kim CH, Eom DW. Combined amelioration of ginsenoside (Rg1, Rb1, and Rg3)–enriched Korean red ginseng and probiotic lactobacillus on non-alcoholic fatty liver disease. Curr Pharmaceut Biotechnol 2019;20:222–31.

Nan B, Liu YL, You Y, Li WC, Fan JJ, Wang YS, Piao CH, Hu DL, Lu GJ, Wang YH. Protective effects of enhanced minor ginsenosides in Lactobacillus fermentum KP–3–fermented ginseng in mice fed a high fat diet. Food Funct 2018;9:6020–8.

Kim DG, Jung KH, Lee DG, Yoon JH, Choi KS, Kwon SW, Shen HM, Morgan MJ, Hong SS, Kim YS. 20(S)–Ginsenoside Rg3 is a novel inhibitor of autophagy and sensitizes hepatocellular carcinoma to doxorubicin. Oncotarget 2014;5:4438–51.