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Review article

Effect of Korean Red Ginseng in chronic liver disease

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ABSTRACT

Chronic liver disease, one of the most common diseases, typically arises from nonalcoholic fatty liver disease, alcoholic liver disease, chronic viral hepatitis, or hepatocellular carcinoma. Therefore, there is a pressing need for improved treatment strategies. Korean Red Ginseng has been known to have positive effects on liver disease and liver function. In this paper, we summarize the current knowledge on the beneficial effects of Korean Red Ginseng on chronic liver disease, a condition encompassing nonalcoholic fatty liver disease, alcoholic liver disease, chronic viral hepatitis, and hepatocellular carcinoma, as supported by experimental evaluation and clinical investigation.

1. Introduction

Liver diseases can be characterized as a global health burden; in particular, liver cirrhosis is the ninth leading cause of death in western nations [1]. Chronic liver disease (CLD) is one of the most common and deleterious conditions. CLD can be defined as a progressive destruction of the hepatic parenchyma over a period of greater than 6 mo, leading eventually to fibrosis and cirrhosis. The most common causes of CLD include excessive alcohol consumption and chronic viral hepatitis. While clinical presentation of CLD can appear gradual, CLD can ultimately lead to cirrhosis and potentially hepatocellular carcinoma (HCC). More recently, nonalcoholic fatty liver disease (NAFLD), a condition linked with obesity, dyslipidemia, and metabolic syndrome, has garnered attention as a concern globally [2,3]. CLD is most often caused by NAFLD, alcoholic liver disease, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, or HCC. Given the wide-reaching implications of CLD, there is a critical need for the identification of better CLD treatment strategies.

Korean Red Ginseng (KRG) is produced when fresh ginseng (*Panax ginseng*) undergoes steaming and drying, a process that purportedly leads to biochemical transformations in peptides, ginsenosides, polysaccharides, fatty acids, and polyacetylenic alcohols [4]. KRG and its associated ginsenosides have been implicated with various biological effects: immunologic benefits [5,6]; antineoplastic [7,8], neuroprotective [9], and hepatoprotective activities [10–13]; and antidiabetic [14], antistress [15], antiinflammatory [16], antihyperlipidemic [17], and antioxidative [17,18] properties.

KRG has also been associated with several beneficial effects on liver function and liver disease. First, it has been shown to have a hepatoprotective effect against acute and chronic liver injury caused by a variety of hepatotoxins, which may include hydrogen peroxide [19], alcohol [11,18,20–22], carbon tetrachloride [23], aflatoxin B1 [24,25], diethylnitrosamine [26], and viruses [13,27]. Second, KRG is associated with antiinflammatory and antioxidative effects in the context of NAFLD [10,28]. Thirdly, KRG has been linked with anticarcinogenic impact in animal models of HCC [26,29] and a hepatoprotective influence on HCC patients [27]. Lastly, KRG has been seen with beneficial effects on hepatic regeneration following liver operations such as liver transplantation and partial liver resection [30–32].

A number of experimental and clinical studies have been carried out to evaluate the beneficial effects of KRG in the context of CLD [10–12,21,26,27,29,33,34]. In this review, we summarize the current knowledge on the beneficial effects of KRG on CLD, a condition encompassing NAFLD, alcoholic liver disease, chronic viral hepatitis, and HCC.

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2. Korean Red Ginseng

Ginseng (*P. ginseng*) is a plant that has been traditionally cherished for more than 2,000 yr for its medicinal properties. KRG is a type of ginseng preparation and is produced by the steaming and drying of fresh ginseng [4]. Ginseng saponins are known to consist of triterpenoidal glycosides of dammarane which contain glucose, arabinose, xylose, or rhamnose [8]. A total of 35 ginsenosides have been successfully isolated from various strains of ginseng. The identified ginsenosides include 20(S)-ginsenoside-Rg3, ginsenoside-Rh2, Rs1, Rs2, Rs3, Rs4, and Rg5; notoginsenoside-R4 in the protopanaxadiol group; and 20(R)-ginsenoside-Rh1, ginsenoside-Rh4 and F4 in the protopanaxatriol group [8].

Ginsenoside Rg3 and Rg2 constitute major components of KRG. By contrast, ginsenoside Rb1 and Rg1 form the chief components of white ginseng [18,35–37]. Ginsenoside Rg3's chemopreventive activity has been well documented, particularly against several cancer cell lines and tumors, which include melanoma [38], colorectal cancer [39–42], ovarian cancer [43,44], prostate cancer [45], breast cancer [46], lung cancer [47,48], and HCC [49]. More recently, ginsenoside Rg3 at 25–200 μg/mL has been demonstrated to have antiproliferative effects on hepatic cancer cells (SMMC-7721, Hep1-6, and HepG2). In addition, it has been associated with inhibitory effects on hepatocellular tumor growth, which is induced by prevention of proliferation and induction of apoptosis, as seen in *in vivo* experiments [49,50]. In addition, ginsenoside Rg3 and its metabolite ginsenoside Rh2 have been demonstrated to have general hepatoprotective effects, particularly against hepatotoxins [51]. Further, oral administration of ginsenoside Rg3 to tert-butyl hydroperoxide-induced mice has revealed the inhibitory effects of ginsenosides on the increase of alanine transaminase (ALT) and aspartate transaminase (AST) levels. In addition, ginsenoside Rh2 has been shown to have potent preventive effects on hepatotoxicity in an experiment involving tert-butyl hydroperoxide-induced mice [51]. However, the mechanism of hepatoprotective activities of KRG and its associated ginsenosides including ginsenoside Rg3 and ginsenoside Rh2 is not elucidated definitely. Several mechanisms of attenuating the damage to hepatocytes including inhibition of cytotoxicity [51], inhibition of oxidative damage [18], and antiinflammatory effect by reducing proinflammatory cytokines [28] have been suggested by experimental and clinical studies, and these complicated mechanisms can simultaneously affect the hepatoprotection.

Ginsenoisde Rg2 has a role in inhibiting hepatic glucose production in HepG2 cells; this is achieved by the activation of the AMP-activated protein kinase pathway [52]. Rg2 serves to increase DNA repair, a mechanism by which it protects cells against ultraviolet B-induced genotoxicity; it may also bring about this effect by the modulation of protein levels involved in the p53 signaling pathway [53]. In addition, ginsenoside Rg2 has been implicated to have neuroprotective benefits against glutamate-induced neurotoxicity, which are the result of mechanisms related to antiapoptosis and antioxidation. Furthermore, because ginsenoside Rg2 has an inhibitory effect against the formation of Abeta1-40, ginsenoside Rg2 should be considered as a potential area of exploration for treatment of Alzheimer's disease [54]. Finally, ginsenoside Rg2 has been associated with protective effects against hypoxia-induced neuronal damage in the hippocampus. It has been suggested that this observation is related to the antiapoptotic function of ginsenoside Rg2, in addition to the roles of the compounds in the elimination of free radicals, blockage of calcium over-influx into neuronal cells, and the stimulation of antioxidative enzymes which serve to attenuate the damages caused by anoxia [55].

3. Non-alcoholic fatty liver disease

Fatty liver is defined as the condition in which more than 5% of liver's mass consists of triglycerides accumulated in hepatocytes. Fatty liver can be further classified into either alcoholic or nonalcoholic [56]. NAFLD and nonalcoholic steatohepatitis are associated with obesity, insulin resistance, and metabolic syndrome [57]. In particular, NAFLD is known to be the most prevalent cause of liver function abnormalities globally [58]. An understanding of the pathogenesis of NAFLD is integral to effectively prevent and treat NAFLD. It is known that oxidative stress induces increase in lipid peroxidation, eventually causing hepatocyte injury associated with NAFLD [59]. Further, recent studies have suggested that natural killer (NK) cells, by promoting antifibrotic effects and inducing hepatic satellite cell cycle arrest and apoptosis, may have a crucial role in the pathogenesis of NAFLD [60].

Several studies have implicated the beneficial effect of KRG on NAFLD [10,34]. In a preclinical study involving a rat model of NAFLD [10], KRG and urushiol were evaluated for their antioxidative and immunological properties. Forty-five rats were divided into the following four dietary groups during 2 mo of experiment: NAFLD (chew), urushiol [chew + urushiol (0.5 mg/kg/d)], KRG [chew + KRG (200 mg/kg/d)], and ursodeoxycholic acid [chew + ursodeoxycholic acid (15 mg/kg/d)]. A number of evaluations were carried out for the liver and serum which included liver function, NK cell activity, pathology, lipid profiles, and antioxidant. In KRG and urushiol groups, it was discovered that the level of serum triglycerides [$(302.0 \pm 70.4$ and $275.2 \pm 63.8)$ vs. 527.7 ± 153.3 mg/dL] was lower in comparison with that of the NAFLD group ($p < 0.05$). The levels of high density lipoprotein-cholesterol [liver tissue: $(4.8 \pm 0.2$ and $4.8 \pm 0.5)$ vs. 4.2 ± 0.2 mg/g] and NK cell activity [$(3{,}485 \pm 910$ and $3{,}559 \pm 910)$ vs. $2{,}486 \pm 619$ counts] were found to be significantly elevated compared to those of the NAFLD group ($p < 0.001$). In the NAFLD group, only two rats were observed with inflammatory neutrophil infiltration. These results suggest that oral KRG or urushiol administration for 2 mo leads to the improvement of lipid profiles, stimulation of NK cell activity, and the inhibition of steatohepatitis in NAFLD rats.

Recently, a prospective randomized clinical trial was conducted to evaluate the antifatigue and antiinflammatory effects of KRG in the context of NAFLD patients [34]. In the KRG group, a significant decrease in the levels of serum ALT, AST, and gamma-glutamyl transpeptidase (γ-GT) were found. By contrast, the levels of serum adiponectin, which is a biomarker for metabolic syndrome, were elevated in the KRG group, a finding that suggests that KRG should be considered for the treatment of fatty liver disease [34]. Table 1 summarizes the effects of KRG on NAFLD.

4. Alcoholic liver disease

Alcoholic liver disease is known to be the leading cause of liver-related deaths globally. The wide spectrum of chronic alcohol-related conditions encompasses steatosis, cirrhosis, steatohepatitis, and HCC. While alcoholic liver disease has a clearly known cause, the mechanisms through which alcohol consumption mediates the pathogenesis of alcoholic liver disease are not well understood and an area of ongoing exploration. The major influences of alcohol on the liver include increase in *de novo* lipogenesis, inhibition of mitochondrial fatty acid β-oxidation, and decrease in very low-density lipoprotein secretion by the liver [61]. Additionally, the activations of proinflammatory cytokines, toll-like receptor-4-mediated signaling pathway, and the reactive oxygen species induced by endotoxins (lipopolysaccharide) are also known to be integral components in the pathogenesis of alcoholic liver disease [62].

Table 1
Effect of Korean Red Ginseng on nonalcoholic fatty liver disease (NAFLD)

Study	Condition	Treatment	Compound	Serum/plasma	Liver	
Otsuka Long Evans Tokushima fatty (OLETF) rats (age 6 wk)	NAFLD model 10 mo	Korean Red Ginseng (200 mg/kg/d) 2 mo	Ginsenoside -Rg1 (2.481), -Rb1 (5.481), -Rg3(s) (0.197), -Re (2.975), -Rc (2.248), -Rb2 (2.175), -Rb (0.566) mg/g	Triglyceride ↓ Natural killer cell activity ↑	HDL-cholesterol ↑	[10]
Human	AST ≥ 50 U/L or ALT ≥ 50U/L, and fatty liver, BMI ≥ 25 kg/m^2	KRG capsule (3,000 mg/d) 3 wk	Ginsenosides Rg1 + Rb1 6.0 mg/g	Total bilirubin ↓ Cholesterol ↓ Adiponectin ↑		[28]

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; HDL, high density lipoprotein; KRG, Korean Red Ginseng; NAFLD, nonalcoholic fatty liver disease.

Many studies have evaluated the potential beneficial effects of KRG on alcoholic liver disease [11,18,20–22]. In a preclinical study involving rats [22], KRG extract's effect on liver damage induced by short-term and long-term alcohol treatment was evaluated. While serum γ-GT activity and the concentration of malondialdehyde are significantly increased by short-term and long-term alcohol treatment, pretreatment with KRG extract resulted in unchanged activity of γ-GT. In addition, KRG treatment was also successful in maintaining normal levels of malondialdehyde concentration in the context of short-term ethanol ingestion, suggesting that KRG may be effective in normalizing the metabolism of alcohol under the conditions of short-term ingestion. However, it was found that pretreatment with KRG did not restrict the increase in serum γ-GT activity resulting from long-term alcohol treatment [22].

In research utilizing mouse models of alcoholic liver disease [11], the effectiveness of uroshiol, KRG, and probiotics (*Lactobacillus rhamnosus* R0011 and *Lactobacillus acidophilus* R0052) was studied. Toll-like receptor-4 levels were found to be lower in the KRG, uroshiol, and probiotic groups in comparison to those of the alcohol group (0.37 ± 0.06 ng/mL, 0.39 ± 0.12 ng/mL, and 0.33 ± 0.07 ng/mL, respectively, vs. 0.88 ± 0.31 ng/mL; $p < 0.05$). It was revealed that the interleukin-1β levels in liver tissues decreased among mice that received probiotics or KRG; tumor necrosis factor-α levels in liver tissue were associated with a decline in the KRG group. By contrast, the pathological findings revealed a significant reduction of alcohol-induced steatosis following KRG and urushiol treatments. Because these agents have been demonstrated to boost immune system function, they should be considered as possible treatments for alcoholic liver disease [11].

The hepatoprotective effect of KRG was also assessed for both mice undergoing ethanol diet and ethanol-treated hepatocytes [20]. Treatment with KRG was associated with attenuated levels of ethanol-induced cytochrome P450 2E1, 4-hydroxynonenal, and nitrotyrosine. KRG also restored the ethanol-induced decreased phosphorylation of adenosine monophosphate-activated protein kinase. Further, KRG noticeably inhibited accumulation of fat in ethanol-treated hepatocytes, a finding that correlates with a decrease in sterol regulatory element-binding protein-1 and increases in sirtuin 1 and peroxisome proliferator-activated receptor-α expression. It should be noted that ginsenosides Rb2 and Rd, but

Table 2
Effect of Korean Red Ginseng on alcoholic liver disease (ALD)

Study	Condition	Treatment	Compound	Serum/plasma	Liver	
Mouse hepatocytes (TIB-73)	EtOH 1% (v/v)	KRG (100 μg/mL)	Ginsenoside -Rg1 (0.52), -Rb1 (4.03), -Rg3(s) (2.89), -Re (1.18), -Rc (1.98), -Rb2 (1.97), -Rd (1.51) mg/g		Cell viability ↓ LDH ↓ AST ↓ ROS ↓ p-ERK ↓ p-JNK ↓	[18]
C57BL/6 (age 6 wk)	Liebere-DeCarli liquid diet containing 10% (v/v) alcohol 6 wk after KRG	KRG (200 mg/kg/d) 4 wk	Ginsenoside -Rg1 (2.481), -Rb1 (5.481), -Rg3(s) (0.197), -Re (2.975), -Rc (2.248), -Rb2 (2.175), -Rb (0.566) mg/g		TNF-α ↓ IL-1β ↓ TLR4 ↓ Grade of steatosis ↓	[11]
C57BL/6	Liebere-DeCarli liquid diet containing 5% (v/v) alcohol 4 wk with KRG extract	KRG extract (500 mg/kg) 4 wk	Ginsenoside -Rb1, -Rb2, -Rd 36% of total weight	ALT ↓ AST ↓	Triglyceride ↓ SREBP-1 ↓ FAS ↓ ACC ↓ Sirt1 ↑ PPARα ↑	[20]
Sprague-Dawley rats (age 7 wk)	Liebere-DeCarli liquid diet containing 5% (v/v) alcohol 6 wk with KRG	KRG (250 mg/kg) 6 wk	Ginsenoside -Rb1 (10.32), -Rc (4.11), -Rb2 (3.95), -Rg1 (2.58), -Rg3 (1.62), -Rf (1.29), -Rd (1.07), -Rg2 (1.00), -Rh1 (0.71), -Re (0.11) mg/g	Free fatty acid ↓	Fat mass ↓ Triglyceride ↓ Total cholesterol ↓ p-AMPK/AMPK ↓ p-ACC/ACC ↓ SREBP-1c ↓ HSL ↓ Adiponectin ↑ Leptin ↓	[21]
Sprague-Dawley rats (age 5 wk)	Liebere-DeCarli liquid diet containing 5% (v/v) alcohol 6 wk with KRG extract	KRG extract (10 g/L) 6 wk	Moisture 36%, solid volume 64%, ash 2.5%, total fat 0.05%, total crude saponin 70 mg/g, and total ginsenosides 20 mg/g	ALT ↑ Malondialdehydes ↓		[22]

ACC, adenoid cystic carcinoma; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; AST, aspartate transaminase; ERK, extracellular signal-regulated kinases; FAS, fatty acid synthase; HSL, hormone sensitive lipase; IL, interleukin; JNK, Jun N-terminal kinase; KRG, Korean Red Ginseng; LDH, lactate dehydrogenase; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding proteins; TLR, toll-like receptor; TNF, tumor necrosis factor.

Table 3
Effect of Korean Red Ginseng on chronic viral hepatitis

Study	Condition	Treatment	Compound	Serum/plasma	
Human	Hepatic C virus Diagnosed with cirrhotic liver disease	KRG extract capsule (600 mg/d) 11 wk	Ginsenosides -Rg3, -Rh2, -Rs1, or -Rs2, -Rs3, -Rs4, -Rg5, -Rg2, -Rh1, -Rh4, -F4, notoginsenoside-R4, 20-O-(β-D-glucopyranosyl)-20(S)-protopanaxadiol (IH-901)	ALT↓ Direct Bilirubin↑ HCV IU/mL↓	[27]

ALT, alanine transaminase; KRG, Korean Red Ginseng.

not ginsenoside Rb1, were associated with the inhibition of fat accumulation in hepatocytes. These results suggest that, in both *in vivo* and *in vitro*, KRG and its ginsenoside components are effective in inhibiting liver injury and alcoholic steatosis through the activation of adenosine monophosphate-activated protein kinase/sirtuin 1. All in all, KRG should be considered as a potential treatment for alcoholic liver disease. Table 2 summarizes the effects of KRG on alcoholic liver disease.

5. Chronic hepatitis B and chronic hepatitis C

HBV and HCV infections are known to be a major global problem [63]. The clinical manifestations of HBV and HCV infections are varied; these include acute or fulminant hepatitis and various forms of chronic pathologies which encompass chronic hepatitis, cirrhosis, and HCC. There is a shortage of literature that assesses the potential of KRG as a treatment option for chronic hepatitis B and C infections [27]. In a clinical study [27], a number of treatment strategies, which did not involve KRG administration, were shown to be ineffective in normalizing liver enzymes or decreasing viral loads. By contrast, KRG administration has been associated with significant improvement in liver function and decrease of the alpha fetoprotein levels. Furthermore, HCV patients of both sexes who took KRG capsules at a dose of 600 mg/d presented with a significant decrease in viral loads when compared with control HCV patients. Table 3 summarizes the effects of KRG on chronic viral hepatitis.

6. Hepatocellular carcinoma

HCC is the most common primary liver cancer in a number of countries; it now constitutes the second most prevalent cause of cancer death worldwide [64–66]. HCC is most common in regions where chronic HBV infection is highly widespread. HCC is increasingly a major problem, even in the Western world, due to the following factors: migration of people from HBV-endemic regions; HCV infection; alcoholic cirrhosis; and nonalcoholic obesity-related steatohepatitis [67,68].

A number of studies have evaluated the correlation between KRG and HCC [7,27,29,69]. In an epidemiologic study [7], it was seen that patients who consumed KRG were associated with lower risk (OR; 0.20, 95% CI 0.08–0.50) of cancer compared with those who did not consume KRG. Further, it was noted that patients who incorporated ginseng into their diet benefitted from a lower risk of liver cancer (OR; 0.48 95% CI 0.33–0.70) compared with those who did not.

In a preclinical study [69], carcinogenesis was induced by various chemical carcinogens, and KRG was evaluated for its anti-carcinogenic effects. Newborn ICR mice were administered KRG by the oral route; urethane, aflatoxin B1, and 9,10-dimethyl-1,2-benzanthracene (DMBA) were injected to the subscapular region within 24 h of birth. In aflatoxin B1-treated mice that also received ginseng, decreases in the incidence of hepatoma were noted when the mice were sacrificed 56 wk after birth (75%) ($p < 0.05$). This finding demonstrates that the extended administration of KRG extract effectively inhibits both the incidence of hepatoma and the proliferation of tumors induced by DMBA, urethane, and aflatoxin B1.

In another preclinical study [29], rats that underwent diethylnitrosamine-induced hepatocarcinogenesis were administered KRG to evaluate its chemopreventive activity. A reduction in the production of thiobarbituric acid reactive substances was found in rats treated with diets of 0.5% and 1% of KRG. The supplementation of 1% KRG in the rats' diet also significantly increased the levels of total glutathione (tGSH) and activity of glutathione-related enzymes, which includes cytosolic glutathione S-transferase and glutathione peroxidase. cDNA microarray demonstrated that there was a downregulation in the expression of genes involved in xenobiotic metabolism via the cytochrome P450 signaling pathway

Table 4
Effect of Korean Red Ginseng on hepatocellular carcinoma (HCC)

Study	Condition	Treatment	Compound	Serum/plasma	Liver	
ICR mice	9,10-Dimethyl-1,2-benzanthracene (DMBA), urethane, and aflatoxin B1 were injected 24 h after birth after 6 wk KRG	Korean Red Ginseng extract power was dissolved in tap water (1 mg/mL) 3 wk	Ginsenoside -Rh1, -Rh2, -Rg3 -Rg5		Hepatoma ↓	[69]
Sprague-Dawley rats (age 4 wk)	Diethylnitrosamine (DEN) injection (200 mg/kg) after KRG 10 wk	1% KRG extract diet 10 wk	Ginsenoside (20) mg/g		Glutathione S-transferase placental form positive foci (GST-P+foci) ↓ Thiobarbituric acid ↓ Total GSH ↑ GST ↑ Cytochrome P450 ↓	[29]
Human	Hepatocellular carcinoma Abdominal computed tomography	KRG extract capsule (900 mg/d) 11 wk	Ginsenosides -Rg3, -Rh2, -Rs1, or -Rs2, -Rs3, -Rs4, -Rg5, -Rg2, -Rh1, -Rh4, -F4, notoginsenoside-R4, 20-O-(β-D-glucopyranosyl)-20(S)-protopanaxadiol (IH-901)	Alpha-fetoprotein ↑		[27]

GT, glutathione S-transferase; KRG, Korean Red Ginseng.

(*Cyp2c6*, *Cyp2e1*, *Cyp3a9*, and *Mgst1*) in the 1% KRG-treated group; this result was not observed in the diethylnitrosamine-control group. The chemopreventive effects of KRG can be summarized as follows: (1) a decrease in lipid peroxidation; (2) an increase in tGSH content and GSH-dependent enzyme activities; and (3) a decrease in the expression profile of genes involved in the cytochrome P450 signaling pathway. All in all, these results reveal that KRG should be considered as a potential therapeutic agent against hepatocarcinogenesis.

In a clinical study that enrolled 26 Egyptian patients with HCC [27], the therapeutic effect of KRG extract was evaluated. The liver functions of these patients were assessed at 6 wk and 11 wk following oral KRG administration; a significant decrease in the serum ALT and AST levels were found in patients who received KRG, but not in the control group. Furthermore, it was revealed that the oral administration of KRG extract resulted in elevated serum albumin levels after 6 wk of administration. These findings suggest that KRG may have therapeutic effects in the context of HCC. The effects of KRG on HCC are summarized in Table 4.

7. Conclusion

KRG and its primary ginsenosides appear to have an array of beneficial effects in the context of CLD, a condition that encompasses NAFLD, alcoholic liver disease, chronic viral hepatitis, and HCC. However, studies have yet to elucidate the precise molecular mechanisms that underlie the hepatoprotective activities of KRG and its associated ginsenosides. For wider clinical application of KRG, the efficacy and safety of KRG and its primary ginsenosides would need to be demonstrated through further clinical studies.

Conflicts of interest

The authors declare that there is no conflicts 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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Author contributions

Tae Young Park, Meegun Hong, Hotaik Sung, Sangyeol Kim: analysis and interpretation of the data, collection and assembly of data, and drafting of the article. Ki Tae Suk: conception and design, critical revision of the article for important intellectual content, and final approval of the article.

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